Journal of Molecular and Genetic Medicine

Malagù et al., J Mol Genet Med 2019, 13:1
DOI: 10.4172/1747-0862.1000411

Review Article Open Access

State of The Art in Clinical Management of Channelopathies and Risk of Sudden Cardiac Death

Malagù M[1]*, Balla C[1], Gualandi F[2], Vitali F[1], Selvatici R[2], Ferlini A[2], Zaraket F[1], Del Franco A[1], Cimaglia P[3], Squeri A[3], Ferrari R[3] and Bertini M[1]

[1]*Cardiology Unit, Azienda Ospedaliero-Universitaria di Ferrara, Italy*
[2]*Medical Genetics Logistic Unit, Azienda Ospedaliero-Universitaria di Ferrara, Italy*
[3]*Maria Cecilia Hospital, GVM Care & Research, Cotignola, Italy*

Abstract

Major arrhythmias and sudden cardiac death in young and apparently healthy people are usually the first manifestation of cardiac channelopathies (CC). CC include long QT syndrome, short QT syndrome, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia. Identification and proper management of these diseases is a challenge for the clinical cardiologists, which could benefit from collaboration with geneticists and other physicians due to relevant genetic, molecular, biologic and psychologic implications. Medical awareness of these issues is growing fast as clinical research provides continue update. In this paper, we provide a comprehensive review of CC. The genes associated with CC and their relative role are here illustrated and summarized

Keywords: Cardiac death; Tachycardia; Gene-by-gene; Genetic heterogeneity

Introduction

Sudden cardiac death (SCD) involves 1.4-6.7 per 100000 person-years, provoking about 1100-9000 deaths per year in Europe and 800-6200 in the USA [1,2]. Coronary artery disease and heart failure are the principal causes of SCD that occurs in old patients. However, SCD often occurs in young and previously healthy individuals as result of channelopathies and cardiomyopathies which may present ventricular arrhythmias (VA).

Channelopathies are subdolous and elusive as they are not associated to structural heart abnormality and their identification before a malignant event is not easy. Even autopsy may not find the cause of a large number of sudden deaths, leaving from 2 to 54% of unexplained cases [3]. In recent years, scientific interest about channelopathies has grown with a parallel improvement in the understanding, prevention and treatment of SCD. Notably, advance in genetic research allowed to identify several genes associated to channelopathies, many others still remaining unknown (Table 1) [2].

Clinical management of these conditions is a challenge for the physician. The first manifestation is often sudden death in young and previously healthy individuals and our knowledge on the subject is still incomplete. This partially explains why clinical trials are rare and involve small number of subjects. Diagnosis before clinical manifestations is possible but limited to relatives of patients with established disease. Here we summarize the existing evidence in the hope that it would help to optimize the clinical management of patients with suspected or confirmed channelopathy.

Literature Review

Genetic testing

Clinical guidelines for arrhythmias and SCD management recommend genetic testing as part of the diagnostic workflow, with different levels of recommendation in different channelopathies. The main aim is to identify the causative mutation in affected patients and to provide screening for relatives at risk and clinical surveillance for mutated subjects [2]. To this end, the "gene-by-gene" approach, based on standard Sanger sequencing, has been replaced by the "multi-gene panels" (or even whole exomes) thanks to the "next-generation sequencing (NGS)" technologies. This later approach, which is faster and cheaper, is appropriate for the study of channelopathies at least for five reasons:

i) The high genetic heterogeneity of these cardiac diseases with multiple genes to be identified to reach a high diagnostic sensitivity,

ii) The frequent occurrence of multiple mutations in different genes in the same subject (often with a negative prognostic value),

iii) The increasing evidence of a great overlap between different channelopathies and even cardiomyopathies, for the genes involved,

iv) The emerging role of "modifiers" (genetic factors other than the primary disease-associated mutation that can modify the risk for disease-related morbidity and mortality) and v) the large number of patients still uncharacterized after screening of known genes, suggesting the existence of novel genes awaiting identification. With the introduction of NGS, the cost per base of sequencing has substantially dropped respect to the traditional Sanger methodology, and low/middle throughput sequencers are available on the market, suitable for diagnostic procedures [4].

As a counterpart of highly sensitive, faster and cheaper analyses, simultaneous sequencing of a large number of genes (or exomes) generates variable sets of nucleotide "variants" that need to be classified for their pathogenic role and distinct from benign polymorphisms. Interpretation of genetic findings is not straightforward, complementary investigations are often necessary, based on the interrogation of databases, the use of bioinformatics for prediction of pathogenicity and the segregation analysis of variants within

***Corresponding author:** Dr. Michele Malagù, Cardiology Unit, Azienda Ospedaliero-Universitaria di Ferrara, Via Aldo Moro 8, 44124 Cona, Ferrara, Italy, Tel: +39 532 236269; E-mail: mlgmhl1@unife.it

Received February 25, 2019; **Accepted** March 11, 2019; **Published** March 18, 2019

Citation: Malagù M, Balla C, Gualandi F, Vitali F, Selvatici R, et al. (2019) State of The Art in Clinical Management of Channelopathies and Risk of Sudden Cardiac Death. J Mol Genet Med 13: 411 doi:10.4172/1747-0862.1000411

families. Functional data assessing the biophysical consequences of a specific mutation, are extremely useful for decision-making but rarely available. A common instance is the identification of novel variants of uncertain significance (VUS), in sporadic cases or in families with low penetrance and in the absence of functional information. This situation generates uncertainties with psychological implication for patients and relevant ethical issues related to the appropriateness of searching for the identified variants in healthy relatives, especially if of minor age.

In this scenario, a multidisciplinary team with cardiologists, geneticists, molecular biologists and psychologists is probably the most successful approach to provide optimal counselling and clinical management to patients and families [5].

Long QT syndrome

Two are the main characteristics of the long QT syndrome (LQTS): prolongation of the QT interval on the electrocardiogram (ECG) and life-threatening VA. Although LQTS is congenital, a similar acquired condition may occur, as well as, in some patients with acquired LQTS a supposed "*forme fruste*" of congenital LQTS may remain clinically silent until exposure to a particular drug or trigger.

The prevalence of LQTS has been estimated in 1 over 5000-20000 individuals but it is known that 10-15% of LQTS gene carriers have a normal corrected QT (QTc) duration [6]. As natural history, in untreated patients SCD has an annual incidence of 0.33-0.9% and syncope 5% [7]. VA usually occurs in childhood and early adulthood or – in case of female patients – in the postpartum and during menses [8].

In 2015, three diagnostic criteria were proposed by the European Society of Cardiology: A QTc ≥ 480 msec, a LQTS risk score >3 (as described in 1993 LQTS Diagnostic Criteria, Table 2) and a positive genetic analysis. In patients with unexplained syncope and QTc ≥ 460 msec, LQTS diagnosis should be considered class of recommendation IIa (Figure 1) [2].

The pathogenetic basis involves alterations in ion flow with early afterdepolarization and imbalance in the sympathetic tone. In particular, the QT interval may be prolonged as result of a reduction of outward Na^+ current or increasing of inner Ca^{2+} current, interfering with the delayed outward rectifier K^+ current. The cause may lie in gene mutations or acquired conditions such as electrolyte abnormalities (hypokalemia, hypomagnesemia, hypocalcemia), metabolic disorders (hypothyroidism, liquid protein diets, anorexia nervosa), bradyarrhythmias, drugs (antiarrhythmics, antimalarials, antifunginals, antibiotics, ranolazine, ivabradine, antidepressants and psychotropic drugs, analgesics, antineoplastics), myocardial ischemia, intracranial disease and HIV infection. A reduced sympathetic activity of the right stellate ganglion or an increased activity of the left stellate ganglion may lead to increased sympathetic tone of the heart and QT prolongation. Adrenaline causes dispersion of repolarization and sympathetic stimulation induces a reduction of the refractory period leading to re-entry and arrythmias.

In congenital LQTS, also known as "catecholamine-dependent", VA are typically triggered by an increased adrenergic activity. In the acquired form, also defined "pause-dependent", LQTS is induced by bradycardia or a sequence of interchange long-short RR intervals [9].

Considering the congenital types of LQTS, two patterns of inheritance were described the autosomal dominant Romano-Ward syndrome (RWS), with a prevalence of 1:2000-1:5000, and the autosomal recessive Jervell Lange-Nielsen syndrome (JLNS), with a prevalence of 1:400000-1:1000000 [10]. Implicated genes are described in Table 1. The inheritance pattern is related to the phenotype [11]. JLNS is typically associated with deafness. To date, at least thirteen types of congenital LQTS have been identified, being KCNQ1 (LQTS type 1 - LQT1, 30-35% of cases), KCNH2 (LQTS type 2 - LQT2, 25-40% of cases) and SCN5A (LQTS type 3 - LQT3, 5-10%) the most frequent among the other 10 types, which generally account for less than 5% of cases (Table 1) [12].

The presence of a confirmed pathogenic mutation is a diagnostic criterion for LQTS, irrespective of QTc duration. Genetic testing for LQTS genes is available in specialized centres. It is important a judicious use of genetic testing confined to individuals with a strong clinical suspicion of LQTS based on clinical history and ECG findings, asymptomatic individuals with unexplained QTc prolongation (>500 msec), relatives of patients with identified LQTS mutations [12]. Genetic basis for LQTS are identified in 75-80% of patients, as well as 10-40% of genotype-positive individuals have no QTc prolongation and are classified as "normal QT" or "concealed" LQTS [13]. It is necessary to underline that a negative analysis does not exclude LQTS. Risk stratification for LQTS is based upon both genotype and phenotype (Figure 2) [4,14,15].

Triggers for VA typically differ among genotypes: LQT1 patients usually suffer cardiac events during physical exercise, in particular swimming, while LQT2 during emotional stress or exposure to loud noise (alarm clock, phone ring) and LQT3 during night sleep.

Although the absence of structural heart disease, recent data suggest that LQTS may be an electromechanical disorder, rather than a merely electrical problem. A prolonged myocardial contraction and mechanical dispersion both longitudinally and trasmurally have been documented at echocardiography [16]. Furthermore, magnetic resonance imaging showed a regional dispersion in contraction duration (mainly cardiac apex) with preserved systolic function and a reduced diastolic function [17].

All patients should avoid drugs that prolong the QT interval or reduce serum potassium and magnesium (Drugs list: https://www.crediblemeds.org/pdftemp/pdf/CompositeList.pdf). Competitive sports should be avoided, in particular for LQT1 patients and swimming. Avoidance of exposure to sudden noises for LQT2 patients should be encouraged. Careful maintenance of normal potassium level is important especially for LQT2 patients, which are the most susceptible category to LQTS-triggered cardiac events in case of hypokalemia [2].

In case of genotypically confirmed LQTS, genetic counselling of family members should be considered. Currently, LQTS therapy has two different targets: Reduction of adrenergic tone and prevention of VA. In this setting, β-blockage with propranolol or nadolol is indicated in all patients. Response to β-blockers may vary according to genotype. In LQT1, therapy is effective against exercise-induced events but less or ineffective during sleep or arousal [18]. In LQT2, in which the trigger is acoustic stimulation, a significant risk reduction has been observed with nadolol [19]. In LQT3, mexiletine, flecainide or ranolazine has also been used in addition to β-blockers.

Survivors of a cardiac arrest have a high risk of recurrences, even on medical therapy (14% within 5 years), thus, implantable cardioverter-defibrillator (ICD) implantation in secondary prevention is strongly recommended [2]. ICD is strongly recommended also in patients who experience syncope or VA. In primary prevention, ICD could be considered in asymptomatic carriers of a pathogenic mutation

Genes	Locus	Gene Name	Gene Product	Function	Disease/s	Frequency in phenotype	Inheritance
SCN5A	3p21	Sodium channel protein type 5 subunit α	α subunit fast Na^+ channel	Depolarizing inward sodium current	BrS1	20-30%	AD
					LQT3	5-10%	AD
SCN1B	19q13.1	Sodium channel subunit β1	β1 subunit fast Na^+ channel	Depolarizing inward sodium current	BrS5	< 1%	AD
SCN3B	11q23.3	Sodium channel subunit β3	β3 subunit fast Na^+ channel	Depolarizing inward sodium current	BrS7	< 1%	AD
SCN4B	11q23.3	Sodium channel subunit β4	β4 subunit fast Na^+ channel	Depolarizing inward sodium current	LQT10	< 0.1%	AD
KCND3	1p13.3	Potassium-voltage-gated channel subfamily D member 3	α subunit transient outward potassium channel Ito	Repolarizing outward potassium current	BrS11	< 1%	AD
KCNE1	21q22.12	Potassium-voltage gated channel subfamily E member 1	β subunit slowly activating potassium delayed rectifier IKs	Repolarizing outward potassium current	LQT5	< 1%	AD
KCNE2	21q22.12	Potassium-voltage gated channel subfamily E member 2	β subunit rapidly activating potassium delayed rectifier IKr	Repolarizing outward potassium current	LQT6	< 1%	AD
KCNE3	11q13.4	Potassium voltage-gated channel subfamily E member 3	β subunit transient outward potassium channel Ito and slowly potassium delayed rectifier IKs	Repolarizing outward potassium current	BrS6	< 1%	AD
KCNE5	Xp22.3	Potassium voltage-gated channel accessory subunit 5	β subunit transient outward potassium channel Ito	Repolarizing outward potassium current	BrS15	1%	X-L
KCNH2	7q36.1	Potassium voltage-gated channel subfamily H member 2	α subunit rapidly activating potassium delayed rectifier IKr	Repolarizing outward potassium current	LQT2	38%	AD
					SQT1	-	AD
KCNQ1	11p15.5	Potassium voltage-gated channel subfamily KQT member 1	α subunit slowly activating potassium delayed rectifier IKs	Repolarizing outward potassium current	LQT1	46%	AD
					SQT2	-	AD
KCNJ2	17q24.3	Potassium voltage-gated channel 2 subfamily J member 2	α subunit inwardly rectifying potassium channel Ik1	Repolarizing outward potassium current	LQT7	< 1%	AD
					SQT3	-	AD
KCNJ5	11q24	Potassium channel 4 subfamily J, member 5	α subunit G protein-activated inwardly-rectifying potassium channel IKACh	Repolarizing outward potassium current	LQT13	-	AD
KCNJ8	12p11.23	Potassium channel 8, subfamily J, member 5	α subunit ATP-sensitive inwardly-rectifying potassium channel IKATP	Repolarizing outward potassium current	BrS9	< 1%	AD
CACNA1C	12p13.3	Calcium channel subunit α1c	α subunit voltage dependent L-type calcium channel	Depolarizing inward slow calcium current	BrS3	2-12%	AD
					LQT8	< 1%	AD
					SQT4		AD
CACNB2	10p12	Calcium channel subunit β2	β subunit voltage dependent L-type calcium channel	Depolarizing inward slow calcium current	BrS4	2-12%	AD
					SQT5		AD
CACNA2D1	7q21-22	Calcium channel subunit α2/δ1	α2/δ1 subunit voltage dependent L-type calcium channel	Depolarizing inward slow calcium current	BrS10	2-12%	AD
					LQT8	< 1%	AD
					SQT6		AD
GPD1L	3p22.3	Glycerol-3-phosphate dehydrogenase 1-like protein	Inward sodium channel interacting protein	expression of Na^+ channel on the cell surface	BrS2	< 1%	AD
RANGRF(MOG1)	17p13.1	Ran guanine nucleotide release factor	Inward sodium channel interacting protein	expression of Na^+ channel on the cell surface	BrS12	< 1%	AD
SLMAP	3p21.2-p14.3	Sarcolemmal-associated protein	Inward sodium channel interacting protein	intracellular trafficking of Na^+ channel	BrS13	-	AD
SNTA1	20q11.2	α1 syntrophin	Inward sodium channel interacting protein	scaffolding protein involved in macromolecular complexes controlling the function of Na^+ channel	LQT12	< 0.1%	AD
CAV3	3p25	Caveolin-3	Inward sodium channel interacting protein	major scaffolding protein present in caveolae in the heart	LQT9	< 1%	AD
ANK2	4q25-q27	Ankyrin-2	Sodium-potassium ATPase and sodium-calcium exchanger-associated interacting protein	targeting and stability of Na/Ca exchanger 1, Na/K ATPase, and InsP3 receptor in cardiomyocytes	LQT4	< 1%	AD
AKAP9	7q21-q22	A-kinase anchor protein	Slowly potassium delayed rectifier IKs interacting protein	involved in macromolecular complexes controlling phosphorylation Iks channel	LQT11	< 0.1%	AD

HCN4	15q24.1	Hyperpolarization-activated cyclic nucleotide-gated channel 4	Structural funny channels subunit	permeability to K^+ and Na^+ and hyperpolarization	BrS8	< 1%	AD
CALM1	17q25.1	Calmodulin 1	calcium-modulated protein	calcium-modulated protein regulating L-type calcium channel function	LQT14	-	AD
					CPVT5	< 1%	AD
CALM2	17q25.1	Calmodulin 2	calcium-modulated protein	calcium-modulated protein regulating L-type calcium channel function	LQT15	-	AD
RYR2	1q43	Ryanodine receptor 2	α subunit	Ca^{2+}-releasing channel of the sarcoplasmic reticulum	CPVT1	50-55%	AD
CASQ2	1p13.1	Calsequestrin-2	isoform 2 of calsequestrin	buffering Ca^{2+} ions of the sarcoplasmic reticulum	CPVT2	2-5%	AR
TRDN	6q22.31	Triadin	sarcoplasmic reticulum protein related to the ryanodine receptor	buffering Ca^{2+} ions of the sarcoplasmic reticulum (cooperate with CASq2)	CPVT4	-	AR

Note: BrS: Brugada Syndrome; LQT: long QT; SQT: short QT; CPVT: Catecholaminergic Polymorphic Ventricular Tachycardia

Table 1: Genes implicated in cardiac channelopathies.

	1993 LQTS Diagnostic Criteria	Points
ECG findings	**QTc (Bazett's formula)**	
	≥480 msec	**3**
	460-470 msec	**2**
	≤450 msec (in male)	**1**
	Torsade de pointes	**2**
	T-wave alternans	**1**
	Notched T wave in three leads	**1**
	Low heart rate for age	**0.5**
Clinical history	**Syncope**	
	With Stress	**2**
	Without Stress	**1**
	Congenital deafness	**0.5**
Family history	Family members with definite LQTS	**1**
	Unexplained SCD below age 30 among immediate family members	**0.5**

Note: Scoring: ≤ 1 point associated with low probability; 2-3 with intermediate probability and ≥ 4 high probability of LQTS (Definite LQTS) [72].
LQTS: Long QT Syndrome; ECG: Electrocardiogram; SCD: Sudden Cardiac Death.

Table 2: The 1993 Diagnostic criteria for long QT syndrome.

in KCNH2 or SCN5A, in females with LQT2 in post-puberty and in patients with ECG signs of electrical instability (e.g. T-wave alternans), when the QTc is >500 msec and the genetic profile shows a high-risk (carriers of two mutations, including JLNS and Timothy syndrome).

Left cervicothoracic stellectomy is an option for non-responders to medical and device therapy, but randomized clinical trials are lacking [20]. It consists in the removal of the lower half of stellate ganglion (T1) and thoracic ganglia (T2-T4) of the left sympathetic chain with the preservation of the upper portion of T1 to avoid iatrogenic Horner's syndrome. This treatment should be considered in selected patients, such as arrhythmic storm despite medical therapy or when an ICD is contraindicated or refused. Stellectomy has also been proposed as "bridge to ICD" in very young patients at high risk [21].

Genotype-driven therapy is under investigation. This approach is tricky because of the large number of genes for few LQTS patients and the evidence that multiple mechanisms may lead to similar phenotypes [22]. As an example, being LQT3 associated with gain-of-function mutations in Na^+ channels, a Na^+ channel blocker has been suggested as genotype-specific therapy for these patients. Another possibility is to identify specific triggers for VA associated with specific genotypes, for example exercise-induced VA in specific LQT2 mutations which are known to benefit from β-blockers [23].

Short QT syndrome

The principal characteristic of short QT syndrome (SQTS) is an accelerated repolarization of cardiac myocytes, which constitutes a substrate at risk for VA.

According to the last European guidelines, a QTc ≤340 msec is diagnostic for SQTS whilst a QTc of 340-360 msec should be considered diagnostic only in presence of a pathogenic mutation, family history of SQTS, family history of SCD or survival from ventricular tachycardia/fibrillation (Figure 1) [2]. QT variation during exercise are lower in SQTS patients than in healthy subjects, therefore exercise test may be useful for the diagnosis of SQTS [24]. Electrophysiologic study (EPS) has been proposed to confirm diagnosis in subjects with borderline QT values, as patients with true SQTS have shorter ventricular refractory periods than normal subjects [25].

SQTS is considered a rare condition but newly recognized cases are emerging. It is still uncertain if the high lethality is real or due to under detection of the syndrome in asymptomatic patients.

The most recent findings report a >40% probability of cardiac arrest by the age of 40 [26]. Arrhythmias are also common and include atrial fibrillation, ventricular fibrillation, supraventricular tachycardia and polymorphic ventricular tachycardia [27].

Six ion channel genes are known to be mutated in SQTS with high penetrance, suggesting that different genotypes lead to different clinical manifestations [28]. SQTS-causing mutations affect the function of channels involved in cardiac repolarization with two different mechanisms. Some are mutations of K^+ channels causing a gain of function that enhance the outward current and shorten the action potential duration, others are mutations of Ca^{++} channels causing a loss of function that reduce the inward current and lead to a premature repolarization of the action potential [29].

No independent risk factors for malignant events have been recognized apart from syncope, and EPS is not useful in risk stratification for SCD [2]. No differences have been found at EPS between patients with a history of cardiac arrest or syncope and those without [26]. Equally, the risk of arrhythmias during competitive physical activity is unknown. The management of SQTS is still empirical and not supported by sufficient evidence.

In one study, different antiarrhythmic drugs have been tested, and results showed that hydroquinidine caused QT and refractory period prolongation, sotalol and ibutilide induced no changes of QT interval, while flecainide produced a slight QT increase mainly due to QRS prolongation [30]. A subsequent study involving 53 patients followed-up for 5 years showed a 4.9% event rate in untreated patients and no event in those taking hydroquinidine [31]. Hydroquinidine also prevented the induction of ventricular arrhythmias during EPS. In SQTS patients with HERG mutation, hydroquinidine normalized QT interval and effective refractory periods [31]. The effect of β-blockers varies depending on channel mutation, as carvedilol and metoprolol differ significantly in their inhibitory properties for the specific mutant HERG and KCNQ1 channels [32]. Ranolazine, vernakalant and ivabradine showed good results in experimental whole-heart models but have not been tested in a clinical setting [33,34].

ICD implantation in primary prevention should be considered individually, whether it is recommended in secondary prevention after an aborted SCD or documented sustained VA.

Brugada syndrome

Brugada syndrome (BrS) was first described in 1988 by Nava et al. but was popularized by the Brugada brothers who 4 years later described the same syndrome in eight patients [35,36]. It is a genetic disorder associated with SCD resulting from polymorphic VA in absence of structural heart disease.

The syndrome is inherited as a dominant trait and shows age- and sex-related penetrance, it is more common in men than women, with events at age 41±15 years (but it may occur at any age), at rest or sleep when vagal tone is high [37-39]. Prevalence ranges from 1-5/10000 in Europe to 12/10000 in Southeast Asia where it seems the most common cause of death in young male adults, particularly in Laos with 1 death per 1000 inhabitants/year [40,41].

Genetic abnormalities are found in about 35% of genotyped patients. So far about, 18 genes have been associated with BrS but three (*SCN5A, CACNA1c and CACNB2b*) individually account for >5% of genotypes (Table 2). A recent assessment by ClinGen resource (https://www.clinicalgenome.org/), has classified *SCN5A* as the unique confirmed BrS gene, the others being "disputed". Mutations of the α subunit of the Na^+ channels Nav 1.5 are strongly related with pathogenesis and poor prognosis in BrS [42]. *SCN5A* mutations associated to BrS are classically loss of function. [43]. Interestingly, mutations of *SCN5A* causing gain of function are associated with LQTS. The *CACNA1c* and *CACNB2b* genes encode the subunits of the L-type Ca^{++} channel and their mutations reduce inward current and are associated with the combined Brugada/short QT syndrome [44].

Undoubtedly, BrS shows a very complex inheritance in which "mutation load" role has been recently assessed [45]. The decreased inward positive currents (Na^+, Ca^{++}) on the K^+ transient outward current (Ito), varies across the myocardium layers, with loss of the action potential in the epicardium but not in the endocardium. This causes ST segment elevation and electrical heterogeneity of repolarization, that increase the risk of re-entry circuits and VA [46,47].

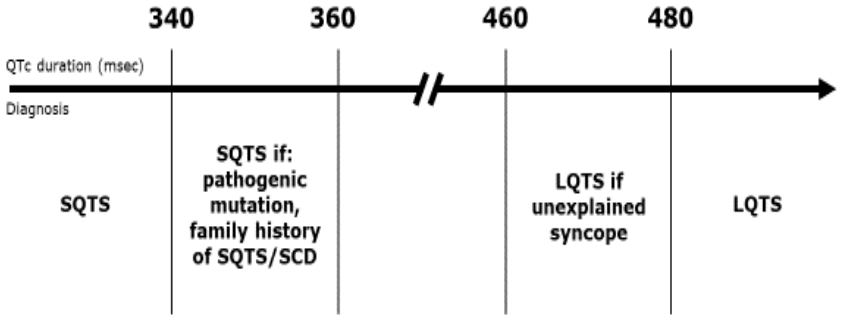
According to the latest consensus, only two ECG patterns are considered proper of BrS: type 1 is a coved ST-segment elevation ≥ 2 mm with concave or straight ST segment and negative T wave in the right precordial leads (V1-V3), whether type 2 combines previous patterns 2 (≥ 2 mm J-point elevation, ≥ 1 mm ST elevation, saddleback appearance, positive/biphasic T-wave) and 3 (saddleback or coved appearance but with ST elevation <1 mm) [48]. European Society of Cardiology consider only type 1 diagnostic for BrS, but it is debatable if a lonely ECG sign could be sufficient to define a clinical syndrome in the absence of signs and symptoms. Previous diagnostic recommendations required the presence of clinical features like syncope, documented arrhythmias or family history of SCD. In the latest guidelines, clinical factors remain important for risk stratification, but diagnosis is based only on ECG findings [2]. Fever, excessive alcohol intake and large meals are triggers that can unmask a type I ECG pattern and predispose to VA [49,50].

ECG recordings with V1 and V2 leads in 2nd , 3rd and 4th, intercostal space may increase the sensitivity and should be performed in any patient with suspected BrS [51]. The rationale for that is to place the lead closer to the right ventricular outflow tract, where the mutated ion channels are.

Flecainide, ajmaline, procainamide, disopyramide, propafenone and pilsicainide can be used to unmask suspicious but not diagnostic ECG patterns (e.g. for familial screening). A positive test result is ECG conversion to type 1 pattern [52]. However, prognostic significance of drug induced type 1 pattern is unclear [53]. Autonomic neurotransmitters like acetylcholine facilitate loss of the dome by suppressing ICa and/or enhancing potassium current, whereas β-adrenergic agonists such as isoprenaline and dobutamine restore the dome by enhancing Ica.

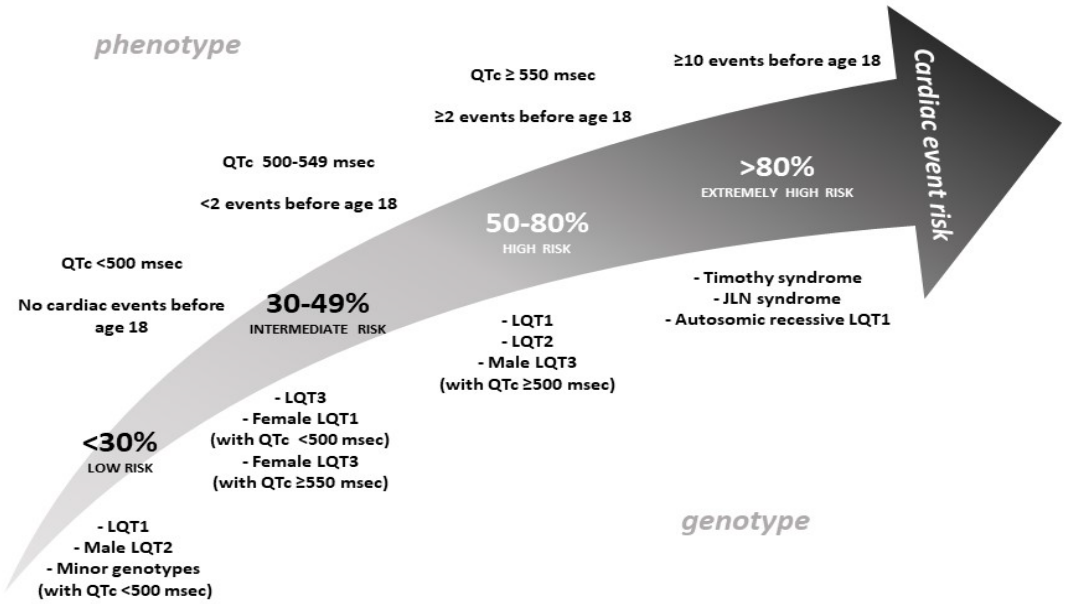
Once the diagnosis of BrS is established, lifestyle changes are mandatory: Avoidance of excessive alcohol intake, large meals and drugs that may induce a type 1 ECG (complete list available at http://www.brugadadrugs.org), but also prompt treatment of any fever with antipyretic drugs and family screening in first-degree relatives [54-56].

Risk stratification is the cornerstone of clinical management in order to prevent SCD in high risk individuals [57,58]. A recent meta-analysis revealed an incidence of events (VA, SCD or appropriate ICD therapy) of 13.5% per year in patients with a previous history of SCD, 3.2% per year in patients with syncope and 1% per year in asymptomatic patients (Figure 3) [59]. The only proven effective strategy for the prevention of SCD is the ICD, strongly recommended (class I) only for secondary prevention (patients who survived an aborted SCD or have documented spontaneous sustained VA). ICD implantation in primary prevention is suggested (class IIa) in patients with type 1 ECG pattern and history of syncope. EPS has been proposed for risk stratification, but its prognostic value has not been confirmed by clinical studies [60]. ICD implantation could be considered in patients with a spontaneous



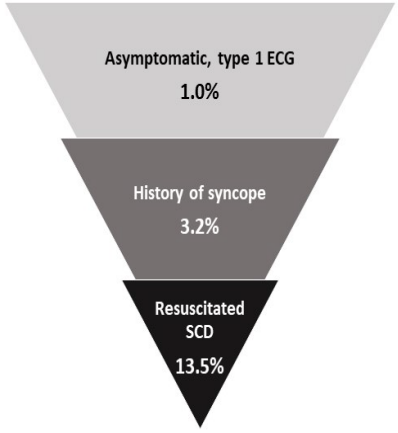
STQS: Short QT Syndrome; VT: Ventricular Tachycardia; VF: Ventricular Fibrillation; LQTS: Long QT Syndrom

Figure 1: QTc duration in the diagnosis of short and long QT syndrome.



LQTS: Long QT Syndrome; JLN: Jervell Lange-Nielsen

Figure 2: Phenotype- and genotype-based risk stratification of LQTS patients and their probability of suffering a first or recurrent cardiac event before the age of 40 in the absence of appropriate therapeutic interventions. Percentages are calculated based on the previously published probability of cardiac event (sudden cardiac death, ventricular arrhythmias, syncope or seizure) [4,15].



SCD: Sudden Cardiac Death; ICD: Implantable Cardioverter-Defibrillator; ECG: Electrocardiogram

Figure 3: Risk stratification for patients with Brugada syndrome. Rate of SCD, sustained ventricular arrhythmias or appropriate ICD intervention per year according to clinical history [59].

diagnostic type I ECG pattern, presenting VA during programmed ventricular stimulation (class IIb) [2]. A careful ICD programming is essential to avoid inappropriate shocks mostly due to sinus tachycardia and supraventricular tachyarrhythmias.

Pharmacological treatment is still under study, following the rationale that drugs that inhibit the Ito current or increase the Na^+ and Ca^{++} currents can be useful in reducing the impairment of the ionic currents during the cardiac action potential. Quinidine has been shown to prevent induction of ventricular fibrillation during programmed ventricular stimulation, so it has been proposed as preventive therapy and is used in patients with ICD and multiple shocks or when ICD implantation is contraindicated, but there are no data confirming its ability to reduce the risk of SCD. Isoproterenol, which increases the ICaL current, has proved to be useful for the treatment of electrical storms [61]. Epicardial catheter ablation over the anterior right ventricle outflow tract has been recently suggested to prevent electrical storms in patients with recurring episodes, but this approach require confirmation before entering general clinical practice [62].

Catecholaminergic polymorphic ventricular tachycardia

The principal characteristic of catecholaminergic polymorphic ventricular tachycardia (CPVT) is that VA are induced by adrenergic activation. Polymorphic (typically bidirectional) VA, syncope, and SCD occur in young individuals with structurally normal heart. The exact prevalence of this inherited disease is unknown, with estimates in the order of 1 on 10000 [63]. Mortality rate is 20% at 7 years [64].

Discussion

To date, two inheritance models of CPVT are known: an autosomal dominant form due to mutations on the gene encoding for a cardiac ryanodine receptor, RyR2 (65% of cases) and an autosomal recessive form associated to mutations in the gene for cardiac calsequestrin, CASQ2 (3-5%) [12]. Mutations in other genes have been associated with CPVT but their role is less clear [63]. The presence of a pathogenic mutation is sufficient to establish the diagnosis [2].

Due to pathogenetic role of catecholamines, clinical manifestations usually occur during physical activity or emotional stress, especially in the first decade of life [65]. No organic cardiopathy has been documented in patients with CPVT. Resting ECG and echocardiography are usually normal, but prolongation of the QTc interval has been described [66]. ECG during effort may be useful for the diagnosis: patients with CPVT typically develop ventricular ectopic beats which progressively increase in number and complexity to polymorphic of bidirectional tachycardia. Pharmacologic challenge with adrenaline has been proposed but its diagnostic role is limited [67].

Once the diagnosis has been established, lifestyle changes are recommended to avoid adrenergic-induced arrhythmias. Competitive sports, strenuous exercise and stressful environments are strongly discouraged. Pharmacological treatment is mainly based on β-blockers, which should be prescribed in all patients with a diagnosis of CPVT. Flecainide has been proved to be effective in clinical practice in preventing VA during exercise and reducing clinical events [68,69]. That is why flecainide is now recommended in patients treated with β-blockers who continue to experience syncope or VT, whether they are or not ICD recipients. A few studies involving small number of patients showed good results in reducing arrhythmias with left cardiac sympathetic denervation in patients with LQTS or CPVT [70,71]. Patients intolerant or with contraindication to β-blockers, as well as patients already treated with β-blockers and flecainide who continue to experience major arrhythmias, may be candidated to this surgical procedure. As in other channelopathies, for secondary prevention of cardiac arrest ICD implantation is mandatory unless refused or contraindicated [72].

Conclusion and Future Perspectives

Although recent acquisitions and advances in the field of cardiac channelopathies, many young and apparently healthy people all over the world are at risk of SCD. Identifications of these conditions before fatal events is crucial in order to adopt preventive measures, but unfortunately, we are still far from this goal. Imaging techniques play a limited role due to the absence of structural abnormalities. Genetic and molecular analysis have a key role, which is likely to further increase in the future, and cardiologists should expand their knowledge and interest to collaborate with geneticists, molecular biologists and psychologists as treatment of patients with established diagnosis and their families requires integration of all these different skills. The "cardiogenetic team" is likely to emerge soon as the best practice.

References

1. Eckart RE, Shry EA, Burke AP, McNear JA, Appel DA, et al. (2011) Sudden death in young adults: An autopsy-based series of a population undergoing active surveillance. J Am Coll Cardiol 58: 1254-1261.
2. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, et al. (2015) ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J 36: 2793-2867.
3. Mazzanti A, Rourke S, Ng K, Miceli C, Borio G, et al. (2014) The usual suspects in sudden cardiac death of the young: A focus on inherited arrhythmogenic diseases. Expert Rev Cardiovasc Ther 12: 499-519.
4. Malagù M (2018) Latest news and perspectives in cardiogenetics. G Ital Cardiol 19: 91-100.
5. Mogensen J (2015) The current role of next-generation DNA sequencing in routine care of patients with hereditary cardiovascular conditions: A viewpoint paper of the European Society of Cardiology working group on myocardial and pericardial diseases and members of the European Society of Human Genetics. Eur Heart J 36: 1367-1370.
6. Schwartz PJ, Stramba-Badiale M, Crotti L, Pedrazzini M, Besana A, et al. (2009) Prevalence of the congenital long-QT syndrome. Circulation 120: 1761-1777.
7. Moss AJ, Schwartz PJ, Crampton RS, Tzivoni D, Locati EH, et al. (1991) The long QT syndrome. Prospective longitudinal study of 328 families. Circulation 84: 1136-1144.
8. Buber J, Mathew J, Moss AJ, Hall WJ, Barsheshet A, et al. (1991) Risk of recurrent cardiac events after onset of menopause in women with congenital long-QT syndrome types 1 and 2. Circulation 123: 2784-2791.
9. Jackman WM, Friday KJ, Anderson JL, Aliot EM, Clark M, et al. (1988) The long QT syndromes: A critical review, new clinical observations and a unifying hypothesis. Prog Cardiovasc Dis 31: 115-172.
10. Jervell A (1957) Congenital deaf-mutism, functional heart disease with prolongation of the Q-T interval and sudden death. Am Heart J 54: 59-68.
11. Schwartz PJ, Periti M, Malliani A (1975) The long Q-T syndrome. Am Heart J 89: 378-390.
12. Ackerman M, Priori SG, Willems S, Berul C, Brugada R, et al. (2011) JHRS/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 13: 1077-1109.
13. Priori SG, Napolitano C, Schwartz PJ (1999) Low penetrance in the long-QT syndrome: Clinical impact. Circulation 99: 529-533.
14. Priori SG (2003) Risk stratification in the long-QT syndrome. N Engl J Med 348: 1866-1874.

15. Giudicessi JR (2013) Genotype- and phenotype-guided management of congenital long QT syndrome. Curr Probl Cardiol 38: 417-455.

16. Leren IS (2015) Cardiac mechanical alterations and genotype specific differences in subjects with long QT syndrome. JACC Cardiovasc Imaging 8: 501-510.

17. Arbelo E (2017) Another piece of the puzzle: Assessment of mechanical dispersion by magnetic resonance in long QT syndrome. Heart Rhythm 14: 1398-1399.

18. Goldenberg I (2008) Long QT Syndrome. Curr Probl Cardiol 33: 629-694.

19. Abu-Zeitone A (2014) Efficacy of different beta-blockers in the treatment of long QT syndrome. J Am Coll Cardiol 64: 1352-1358.

20. Schwartz PJ (1976) Effects of unilateral cardiac sympathetic denervation on the ventricular fibrillation threshold. Am J Cardiol 37: 1034-1040.

21. Collura CA, Johnson JN, Moir C, Ackerman MJ (2009) Left cardiac sympathetic denervation for the treatment of long QT syndrome and catecholaminergic polymorphic ventricular tachycardia using video-assisted thoracic surgery. Heart Rhythm 6: 752-759.

22. Ruan Y, Liu N, Napolitano C, Priori SG (2008) Therapeutic strategies for long-QT syndrome: Does the molecular substrate matter? Circ Arrhythm Electrophysiol 1: 290-297.

23. Kim JA, Lopes CM, Moss AJ, McNitt S, Barsheshet A, et al. (2010) Trigger-specific risk factors and response to therapy in long QT syndrome type 2. Heart Rhythm 7: 1797-1805.

24. Giustetto C, Scrocco C, Schimpf R, Maury P, Mazzanti A, et al. (2015) Usefulness of exercise test in the diagnosis of short QT syndrome. Europace 17: 628-634.

25. Rollin A, Gandjbakhch E, Giustetto C, Scrocco C, Fourcade C, et al. (2017) Shortening of the short refractory period in short QT syndrome. J Am Heart Assoc 6: E005684.

26. Mazzanti A, Kanthan A, Monteforte N, Memmi M, Bloise R, et al. (2014) Novel insight into the natural history of short QT syndrome. J Am Coll Cardiol 63: 1300-1308.

27. Villafane J, Atallah J, Gollob MH, Maury P, Wolpert C, et al. (2013) Long-term follow-up of a pediatric cohort with short QT syndrome. J Am Coll Cardiol 61: 1183-1191.

28. Harrell DT, Ashihara T, Ishikawa T, Tominaga I, Mazzanti A, et al. (2015) Genotype-dependent differences in age of manifestation and arrhythmia complications in short QT syndrome. Int J Cardiol 190: 393-402.

29. Abriel H, Rougier JS (2013) Beta-blockers in congenital short-QT syndrome as ion channel blockers. J Cardiovasc Electrophysiol 24: 1172-1174.

30. Gaita F, Giustetto C, Bianchi F, Schimpf R, Haissaguerre M, et al. (2004) Short QT syndrome: Pharmacological treatment. J Am Coll Cardiol 43: 1494-1499.

31. Giustetto C, Schimpf R, Mazzanti A, Scrocco C, Maury P, et al. (2011) Long-term follow-up of patients with short QT syndrome. J Am Coll Cardiol 58: 587-595.

32. Bodi I, Franke G, Pantulu ND, Wu K, Perez-Feliz S, et al. (2013) Differential effects of the beta-adrenoceptor blockers carvedilol and metoprolol on SQT1- and SQT2-mutant channels. J Cardiovasc Electrophysiol 24: 1163-1171.

33. Frommeyer G, Ellermann C, Dechering DG, Kochhäuser S, Bögeholz N, et al. (2016) Ranolazine and vernakalant prevent ventricular arrhythmias in an experimental whole-heart model of short QT syndrome. J Cardiovasc Electrophysiol 27: 1214-1219.

34. Frommeyer G, Weller J, Ellermann C, Kaese S, Kochhäuser S, et al. (2017) Antiarrhythmic properties of ivabradine in an experimental model of short-QT-syndrome. Clin Exp Pharmacol Physiol 44: 941-945.

35. Nava A, Martini B, Buja GF (1988) Early repolarization in the precordial right. ECG-VCG-electrophysiology correlations. G Ital Cardiol 1: 118.

36. Brugada P, Brugada J (1992) Right bundle branch block, persistent ST segment elevation and sudden cardiac death: A distinct clinical and electrocardiographic syndrome. A multicenter report. J Am Coll Cardiol 20: 1391-1396.

37. Bennett PB (1995) Molecular mechanism for an inherited cardiac arrhythmia. Nature 376: 683-685.

38. Benito B (2008) Gender differences in clinical manifestations of Brugada syndrome. J Am Coll Cardiol 52: 1567-1573.

39. Shimizu W (2007) Sex hormone and gender difference-role of testosterone on male predominance in Brugada syndrome. J Cardiovasc Electrophysiol 18: 415-421.

40. Kamakura S (2013) Epidemiology of Brugada syndrome in Japan and rest of the world. J Arrhythmia 29: 52-55.

41. Nademanee K, Veerakul G, Nimmannit S, Chaowakul V, Bhuripanyo K, et al. (1997) Arrhythmogenic marker for the sudden unexplained death syndrome in Thai men. Circulation 96: 2595-2600.

42. Sommariva E, Pappone C, Boneschi FM, Resta CD, Carbone MR, et al. (2013) Genetics can contribute to theprognosis of Brugada syndrome: A pilot model forrisk stratification. Eur J Hum Genet 21: 911-917.

43. Brugada R (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.

44. Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, et al. (2007) Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. Circulation, 115: 442-449.

45. Gualandi F, Zaraket F, Malagù M, Parmeggiani G, Trabanelli C, et al. (2017) Mutation load of multiple ion channel gene mutations in Brugada syndrome. Cardiol 137: 256-260.

46. Wilde AA, Postema PG, Di Diego JM, Viskin S, Morita H, et al. (2010) The pathophysiological mechanism underlying Brugada syndrome: Depolarization versus repolarization. J Mol Cell Cardiol 49: 543-553.

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

48. Brugada J, Campuzano O, Arbelo E, Sarquella-Brugada G, Brugada R (2018) Present status of Brugada syndrome, JACC state-of-the-art review. J Am Coll Cardiol 72: 1046-1059.

49. Kovacic JC, Kuchar DL (2004) Brugada pattern electrocardiographic changes associated with profound electrolyte disturbance. Pacing Clin Electrophysiol 27: 1020-1023.

50. Antzelevitch C, Brugada R (2002) Fever and Brugada syndrome. Pacing Clin Electrophysiol 25: 1537-1539.

51. Sangwatanaroj S, Prechawat S, Sunsaneewitayakul B, Sitthisook S, Tosukhowong P, et al. (2001) New electrocardiographic leads and the procainamide test for the detection of the Brugada sign in sudden unexplained death syndrome survivors and their relatives. Eur Heart J 22: 2290-2296.

52. Naseef A, Behr ER, Batchvarov VN (2015) Electrocardiographic methods for diagnosis and risk stratification in the Brugada syndrome. J Saudi Heart Assoc 27: 96-108.

53. Delise P, Allocca G, Sitta N, Migliore F, Dagradi F, et al. (2018) Cardiac arrest and Brugada syndrome: Is drug-induced type 1 ECG pattern always a marker of low risk? Int J Cardiol 254: 142-145.

54. Delise P, Marras E, Bocchino M (2006) Brugada-like electrocardiogram pattern: how to stratify the risk for sudden cardiac death. Is sports activity contraindicated? J Cardiovasc Med 7: 239-245.

55. Kamakura S (2009) Long-term prognosis of probands with Brugada-pattern ST-elevation in leads V1-V3. Circ Arrhythm Electrophysiol 2: 495-503.

56. Priori SG, Napolitano C, Gasparini M, Pappone C, Della Bella P, et al. (2002) Natural history of Brugada syndrome: Insights for risk stratification and management. Circulation 105: 1342-1347.

57. Morita H, Takenaka-Morita S, Fukushima-Kusano K, Kobayashi M, Nagase S, et al. (2003) Risk stratification for asymptomatic patients with Brugada syndrome. Circ J 67: 312-316.

58. Probst V (2010) Long-term prognosis of patients diagnosed with Brugada syndrome: Results from the FINGER Brugada Syndrome Registry. Circulation 121: 635-643.

59. Fauchier L, Isorni MA, Clementy N, Pierre B, Simeon E, et al. (2013) Prognostic value of programmed ventricular stimulation in Brugada syndrome according to clinical presentation: An updated meta-analysis of worldwide published data. Int J Cardiol 168: 3027-3029.

60. Priori SG (2012) Risk stratification in Brugada syndrome: Results of the PRELUDE (Programmed Electrical stimUlation preDictive valuE) registry. J Am Coll Cardiol 59: 37-45.

61. Maury P, Hocini M, Haissaguerre M (2005) Electrical storms in Brugada syndrome: Review of pharmacologic and ablative therapeutic options. Indian Pacing Electrophysiol J 5: 25-34.

62. Cortez-Dias N (2014) Epicardial ablation for prevention of ventricular fibrillation in a patient with Brugada syndrome. Rev Port Cardiol 33: 305 e1-305 e7.

63. Priori SG (2013) Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. Europace 15: 1389-1406.

64. Kawata H, Ohno S, Aiba T, Sakaguchi H, Miyazaki A, et al. (2016) Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) Associated with Ryanodine Receptor (RyR2) Gene Mutations - Long-Term Prognosis After Initiation of Medical Treatment. Circ J 80: 1907-1915.

65. Priori SG, Napolitano C, Memmi M, Colombi B, Drago F, et al. (2002) Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. Circulation 106: 69-74.

66. Del Franco A (2017) A clinical case of catecholaminergic polymorphic ventricular tachycardia: The clinical suspicious and the need of genetics. Cardiol 138: 69-72.

67. Marjamaa A, Hiippala A, Arrhenius B, Lahtinen AM, Kontula K, et al. (2012) Intravenous epinephrine infusion test in diagnosis of catecholaminergic polymorphic ventricular tachycardia. J Cardiovasc Electrophysiol 23: 194-199.

68. Kannankeril PJ, Moore JP, Cerrone M, Priori SG, Kertesz NJ, et al. (2017) Efficacy of Flecainide in the treatment of catecholaminergic polymorphic ventricular tachycardia: A randomized clinical trial. JAMA Cardiol 2: 759-766.

69. Pérez WF, Afonso JSH, Marco MG, Dorta EC, Acosta LA, et al. (2018) Flecainide reduces ventricular arrhythmias in patients with genotype RYR2-positive catecholaminergic polymorphic ventricular tachycardia. Rev Esp Cardiol 71: 185-191.

70. Nordkamp LR, Driessen AHG, Odero A, Blom NA, Koolbergen DR, et al. (2014) Left cardiac sympathetic denervation in the Netherlands for the treatment of inherited arrhythmia syndromes. Neth Heart J 22: 160-166.

71. Hofferberth SC, Cecchin F, Loberman D, Fynn-Thompson F (2014) Left thoracoscopic sympathectomy for cardiac denervation in patients with life-threatening ventricular arrhythmias. J Thorac Cardiovasc Surg 147: 404-409.

72. Schwartz PJ, Moss AJ, Vincent GM, Crampton RS (1993) Diagnostic criteria for the long QT syndrome. Circulation 88: 782-784.