Genetic arrhythmias

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The increasing interaction between molecular biology and clinical cardiology has allowed to demonstrate that mutations on the genes encoding cardiac ion channels or regulatory proteins can cause inherited arrhythmogenic disorders predisposing to sudden death in young individuals. These diseases are the long QT syndrome, the Brugada syndrome, the catecholaminergic polymorphic ventricular tachycardia, and the short QT syndrome. Since incomplete penetrance is present, genetic screening is pivotal to perform a correct diagnosis in mutation carriers who do not manifest phenotype, but are still at increased risk of cardiac events if left untreated.

All these syndromes show genetic heterogeneity and it is becoming evident that each genetic variant of the disease presents distinguishing clinical characteristics suggesting that genetics may be used for targeting risk stratification and treatment of these diseases. In this chapter, the molecular bases, the clinical features and the current therapeutic approach of these syndromes are presented.

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Introduction

The introduction of the recent accomplishments of molecular biology into clinical medicine has allowed to make very important advancements in the understanding of the pathophysiology of inherited diseases. As a practical consequence molecular diagnosis has progressively entered into practice and molecular data are used for risk stratification and therapy targeting. In the field of cardiac arrhythmias, several conditions that predispose to potentially lethal arrhythmias and sudden cardiac death (SCD) are caused by genetically transmitted diseases. The objective of this review is to discuss the most recent advancement in the understanding of inherited arrhythmogenic diseases, their molecular basis and to review the current recommendations for pharmacological and device treatment.

Long QT syndrome

Molecular bases. The long QT syndrome (LQTS) is an inherited disease characterized by a prolongation of the repolarization phase that could trigger life-threatening arrhythmias. Two patterns of transmission have been identified[1]: one autosomal recessive called Jervell-Lange-Nielsen syndrome that is characterized by congenital deafness, prolonged QT interval and increased susceptibility to cardiac arrhythmias and SCD and one autosomal dominant form, called Romano-Ward syndrome, that presents the same cardiac phenotype as the recessive form, but is not associated with deafness. In the early '90s Keating and colleagues[1] discovered the first genes responsible for LQTS: since all genes encoded for subunits of cardiac ion channels, these authors proposed that LQTS is a cardiac ion channel disease. In the last decade additional genes have been linked to LQTS[1-3] so that at present time it is possible to identify the genetic substrate in approximately 60% of clinically affected patients. Interestingly, only one form of LQTS is not caused by mutations in genes encoding for proteins that are not component of cardiac ion channels: this variant, LQT4, is caused by a protein, ankyrin B that regulates the proper localization of ion channels in the membrane of the cardiac myocytes[3]. Therefore, even LQT4 is caused by abnormalities of ion channels thus confirming a unifying pathogenetic mechanism for the disease.

Based on its genetic substrate, the Romano-Ward syndrome includes at least six different subtypes: LQT1, due to mutations on *KCNQ1*, that encodes for the ion channel for the IKs component of the IK delayed rectifier current, one of the main determinants of the phase 3 of the cardiac action potential; LQT2, due to mutations on *KCNH2* gene, that encodes for the second

component of the IK current, IKr; LQT3 related to mutations on the *SCN5A* gene that encodes for the α-subunit of the cardiac sodium channel; LQT4 caused by mutations in the ankyrin B gene; LQT5 associated with mutations of the *KCNE1* gene, that encodes for the β-subunit of the IKs ion channel; LQT6 due to mutations on the *KCNE2* gene, that encodes for the β-subunit of the ion channel that conducts IKr[1-3]. The Jervell-Lange-Nielsen syndrome is caused by homozygous or compound heterozygous mutations on the *KCNQ1* gene or on the *KCNE1* gene[1].

Recently, the genetic substrate of two autosomal dominant forms of LQTS with extracardiac involvement has been described. The first of these conditions is also called Andersen syndrome, and it is often referred to as LQT7[4,5]. Andersen syndrome is characterized by potassium-sensitive periodic paralysis of skeletal muscles and cardiac involvement is characterized by long QT interval with prominent U waves at surface ECG and ventricular arrhythmias. Furthermore, patients present with peculiar dysmorphic features such as hypertelorism, short stature, micrognatia, clinodactyly, broad forehead[4]. This form of LQTS is caused by loss of function mutations on the *KCNJ2* gene, that encodes for the cardiac ion channel Kir2.1 that conducts the inwardly rectifier IK1 current[5].

At the end of 2004, in a collaborative research between our team and the group of Keating, a new form of LQTS was genetically characterized[6]. The name Timothy syndrome was given to this distinguishing form of LQTS associated with syndactyly of hands and/or feet, congenital heart disease, immune deficiency, intermittent hypoglycemia, paroxysmal hypothermia and cognitive abnormalities that may resemble a disease in the spectrum of autism.

The gene implicated in this form of LQTS called LQT8 is the *CACNA1C* gene that encodes for the L-type calcium channel. Interestingly, all the patients with LQT8 identified so far in the world present with the same mutation that causes a gain of function resulting in augmented calcium influx in cardiac cells. The fact that Andersen syndrome and Timothy syndrome present multiorgan abnormalities suggests that the two genes *KCNJ2* and *CACNA1C* encode proteins that may not only be important for the regulation of electrical activity in the heart, but that may also play a role in the control of embryonic development at a very early stage of differentiation.

Functional characterization of several mutants identified in LQTS patients has helped defining a tight link between QT prolongation and DNA abnormalities. It is now established that mutations on the α- or β-subunits of the IKs or the IKr potassium channels found in LQT1, LQT2, LQT5 and LQT6 patients determine a loss of function that reduces repolarizing potassium currents thus determining prolongation of the QT interval. Similarly, mutations on the *SCN5A* gene associated with the LQT3 phenotype cause a gain of function in the channel, provoking an increased inward INa current that prolongs action potential duration.

Clinical presentation. The clinical manifestation of LQTS is the occurrence of syncope or cardiac arrest precipitated by physical or emotional stress. The distinguishing arrhythmias precipitating syncope in LQTS is a polymorphic ventricular tachycardia (VT) called torsade de pointe[1]. Not all LQTS patients experience cardiac arrhythmias during their life and several affected individuals may have a benign course even without therapy. Even more puzzling is the fact that a minority of patients carriers of LQTS-related mutations have a normal QT interval: such heterogeneity of clinical manifestations is called incomplete penetrance. The factors that attenuate the phenotype in some individuals are referred to as "modifiers" but none of them has been identified until now. Identification of factors others than the primary mutation that influence the clinical course of the disease represents the next challenge in the understanding of genetic arrhythmogenic diseases.

Genotype-phenotype correlations and risk stratification. Thanks to the large registries, that have been created to collect patients affected by LQTS both in the United States and in Europe, it has been possible to obtain in a relatively short period of time a large number of genotyped individuals, so that clinically relevant genotype-phenotype correlations have been established. At present, molecular information can be used for risk stratification and management[7,8] at least in the three most prevalent LQTS variants (LQT1, LQT2 and LQT3).

LQT1 patients often have symptoms during physical activity, especially while swimming, and in these patients the QT interval does not shorten adequately with the increase of heart rate during exercise. On the contrary LQT2 patients are at higher risk of arrhythmic events when exposed to emotional stress and acoustic stimuli and finally LQT3 patients experience most events during sleep or at rest[7,9] (Fig. 1). We have recently demonstrated[8] that genotype may contribute to risk stratification in LQTS. Based on the study of 647 genotyped patients we showed that the incidence of a cardiac event before age 40 is lower in LQT1 patients than in LQT2 or LQT3. Moreover, female sex resulted a risk indicator in LQT2, while male sex is associated with adverse outcome in LQT3 individuals. In the LQT1 and LQT2 genotypes the presence of a QTc interval > 500 ms represented a further indicator of risk of events.

The Jervell-Lange-Nielsen syndrome represents a form of LQTS with a high malignancy: these patients have the earliest occurrence of symptoms, and by age 8, about 90% of subjects have had their first cardiac event[10].

Therapy. Antiadrenergic therapy with beta-blockers is the main treatment for the LQTS[1,11].

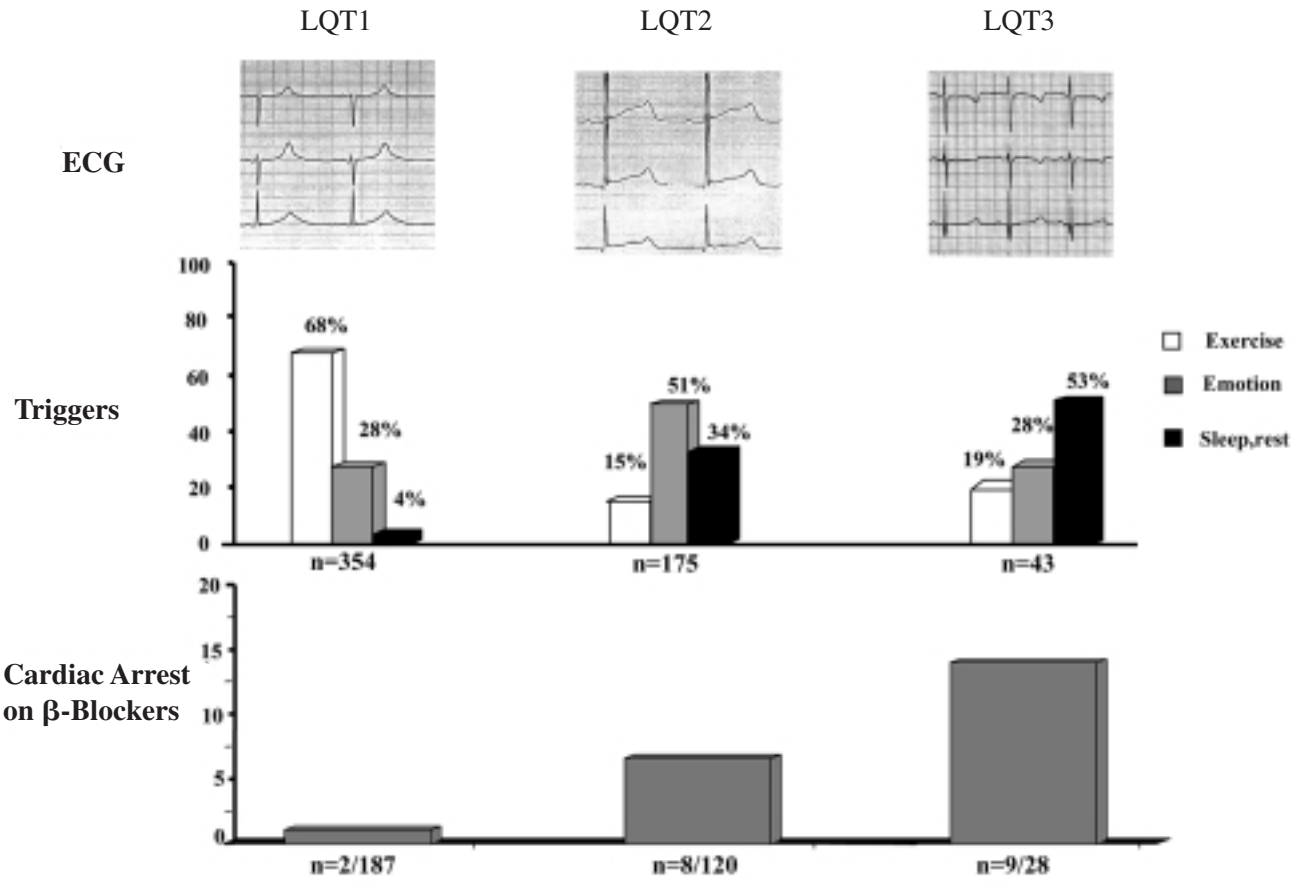

Figure 1. *Genotype-phenotype correlations in long QT syndrome. The* upper panel *presents the different T-wave morphologies related to the three most represented genotypes. In the* middle panel *are shown different triggers for cardiac events and in the* lower panel *the incidence of cardiac arrest despite beta-blocker therapy in LQT1, LQT2 and LQT3 groups, respectively.*

We have recently compared[12] the response to beta-blockers among LQT1, LQT2 and LQT3 patients and demonstrated that both LQT2 and LQT3 genotypes have an increased risk of recurrences on therapy as compared to LQT1 patients (Fig. 1).

At present the implant of a cardioverter-defibrillator (ICD) is recommended in LQTS patients who suffered an aborted cardiac arrest and has to be carefully considered in LQT2 and in the LQT3 individuals who present a QTc interval > 500 ms especially if they have had recurrences while taking beta-blockers[12].

So far only few retrospective studies have investigated the role of the ICD in LQTS[13,14]. The largest of these studies is the one reported by Zareba et al.[13], that compared mortality in two groups of patients treated with beta-blockers or with beta-blockers plus ICD and showed a significant reduction of lethal events in the ICD group, reporting that the 3-year mortality rate was 2% in the ICD group and 9% in the non-ICD patients.

Another intervention proposed for the treatment of LQTS patients unresponsive to beta-blockers is the left cardiac sympathetic denervation. This intervention[1,15] is based on the surgical removal of the lower part of the stellate ganglion and of the first three to five thoracic ganglia. The rationale of this intervention resides in the arrhythmogenic potential of the left-stellate ganglion stimulation and in the antifibrillatory effect of stellectomy seen in animal models[16].

Recently a large report has confirmed[17] the effectiveness of left cardiac sympathetic denervation in reducing the occurrence of cardiac events with a 10-year survival of 90%.

Brugada syndrome

Clinical, genetic, and electrophysiological features. Brugada syndrome (BS) is a primary electrical disease associated with high risk of ventricular arrhythmias and SCD in young individuals. This syndrome, described in 1992 by Brugada and Brugada[18], is characterized by a typical ECG pattern: ST-segment elevation in the right precordial leads V_1-V_3 with or without complete or incomplete right bundle branch block.

The ST-segment abnormality is the hallmark of BS. Three main different patterns (Fig. 2) have been identified and they may bear different diagnostic implications[19].

Type 1 is characterized by a prominent ST-segment elevation ≥ 2 mm followed by a negative T wave and is

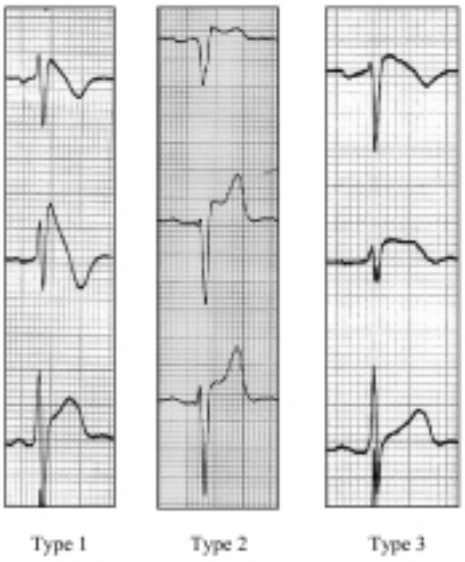

Figure 2. *Three main different ECG patterns associated with the Brugada syndrome.*

named "coved type". Type 2 is also characterized by ST-segment elevation ≥ 2 mm, but the J-wave amplitude gives rise to a descending ST segment followed by a positive or biphasic T wave that gives origin to a "saddle-back" configuration. Finally type 3 ECG pattern may appear as a "coved-type" or "saddle-back" type but the amount of ST segment upward displacement is less pronounced (< 1 mm) (Fig. 2). Accordingly to current guidelines, type 1 is the only that confirms the diagnosis of BS[19]. Since the diagnostic coved pattern is not constantly present in most patients affected by BS, pharmacological provocative test with flecainide, ajmaline and procainamide may be used to document a coved type ECG pattern[20].

Syncope and cardiac arrest are the symptoms of BS: SCD frequently occurs during sleep, in the early morning hours[21]. Polymorphic VTs initiated by a short coupled extrasystolic beat and rapidly degenerating into ventricular fibrillation (VF) are the most commonly documented ventricular arrhythmias in the syndrome.

Supraventricular tachyarrhythmias are a common finding in these patients[22] and up to 10% of patients may experience atrial fibrillation. The mean age of symptom onset is in the third to fourth decade, but early onset during childhood has been reported[23,24]; males are at higher risk of arrhythmic events than females[25].

Only one BS gene has been identified so far: Chen et al.[26] linked BS to the presence of mutations in the *SCN5A* gene encoding the α-subunit of the cardiac sodium channel.

This gene is the same involved in the pathogenesis of the LQT3 form of LQTS. At variance of LQT3 mutations, that cause a gain of function, *SCN5A* defects in BS lead to a loss of function that reduces the amount of inward depolarizing current flowing into cardiac myocytes. *SCN5A* is the only gene thus far associated with BS, but mutations on this gene account only for 20% of clinically affected patients. Given the presence of only one gene associated with the disease, at present time it is not possible to draw genotype-phenotype correlations in BS.

From the genetic substrate to the electrocardiographic morphology. One of the most intriguing and largely unsolved issues regarding BS is how to account for the distinguishing ECG pattern. It has been speculated that the accelerated inactivation of INa or its reduction present in the BS may leave the repolarizing current Ito unopposed during phase 1 of the action potential. The presence of an Ito-mediated spike-and-dome morphology in the right ventricular epicardium, but not in the endocardium would thus generate a prominent J wave, that originates the typical ECG pattern[27].

Therapy with drugs and devices. Based on only few studies[28-30] ICD is now recommended in all survivors of cardiac arrest (secondary prevention) and in all patients with a spontaneous type 1 pattern with a history of syncope. Some disagreement exists[28-33] on whether asymptomatic patients in whom a VF is induced during programmed electrical stimulation (PES) should also become candidates for a prophylactic ICD. Management of asymptomatic patients is still debated, as no conclusive evidence exists in the risk stratification of these subjects[34], even if an 8% event rate in young asymptomatic individuals with the ECG pattern is reported.

Neither beta-blockers nor amiodarone are considered useful for arrhythmia prevention in the syndrome[35,36]. In one of these studies[36] 86 patients were randomized to receive either ICD or propranolol. After a follow-up of 3 years there was an 18% of SCD in the beta-blockers group and no SCD in the ICD group, thus suggesting that beta-blockade may be detrimental.

Sporadic observations[24,37] suggested that quinidine may be protective in patients with BS and *in vitro* studies indicated that the efficacy might be exerted through the blockade of the Ito current[38]. In 1999 Belhassen et al.[39] observed that quinidine may prevent inducibility at PES in 4 out of 5 survivors of cardiac arrest with a structurally intact heart. Hermida et al.[40] studied 35 patients treated with quinidine and confirmed that the drug suppressed inducibility in 76% of them. Despite the data on quinidine should still be regarded as preliminary and not sufficient to indicate extended clinical use of this drug, they at least encourage the planning of larger investigations to adequately test the hypothesis.
Isoproterenol may facilitate arrhythmia suppression for acute treatment of arrhythmic storms in BS[24,27,41]: its mechanism of action is unknown but it has been suggested that β-adrenergic agonists could be protective because they could restore the "dome" of the action potential by increasing ICa[42].

Short QT syndrome

Clinical and genetic aspects. Just like it has been recognized that prolongation of the QT interval predisposes to ventricular arrhythmias and SCD, it is a recent concept that even an excessive shortening of repolarization may expose to the same risk[43] and that a QT shortening may be genetically mediated[44,45].

The short QT syndrome (SQTS) is characterized by an excessively fast ventricular repolarization: the cut-off value for the diagnosis of short QT interval is still under definition. Based on the initial cases reported it was suggested that a QTc < 300 ms may be an appropriate definition even if more recent and unpublished observations may call for a reappraisal of this value. In analogy with the other inherited arrhythmogenic syndromes, SQTS is characterized by a high incidence of syncope, SCD and supraventricular arrhythmias, a short refractory period and inducibility of VF with PES, and patients appear to have a structurally intact heart[45]. Few families and sporadic cases with this syndrome have been described thus far[44-47].

In most affected patients QT interval duration was < 300-310 ms without significant dynamic changes during heart rate variation and clinical symptoms range from palpitations to syncope and cardiac arrest. In those patients in whom an electrophysiological study was performed both atrial and ventricular effective refractory periods were significantly shorter than normal and sustained VT or VF were induced with PES in most affected patients.

Even within a small cohort of patients arrhythmic events and SCD has occurred at different ages ranging from early infancy to old age. Two genes have been so far identified in the syndrome: *KCNH2* and *KCNQ1*[46,47]. As described in the section dedicated to the LQTS, these genes encode for the cardiac ion channels that conduct the IKr and IKs component of the delayed rectifier repolarizing current. As expected, in order to account for the abbreviated repolarization, mutations identified in patients with SQTS increase the amount of potassium current flowing into the heart and therefore have the opposite effect than that observed in mutations of the same genes that cause LQTS. Thus, we have now evidence that, based on their functional consequence, mutations in the same gene may cause opposite phenotypes depending on whether they increase or decrease the amount of current conducted by the protein. To summarize, a mutation causing a gain of function in the *SCN5A* gene is associated with the LQT3, whereas a mutation leading to a loss of function in the same gene causes BS; a gain of function mutation in the *KCNH2* gene or in the *KCNQ1* gene causes SQTS, whereas a loss of function of these proteins is linked, respectively, to LQT2 and LQT1.

Therapy. As it is always the case, when a disease is initially described the cases that come to observation are rather severe. As the diagnostic skills improve and more incompletely penetrant forms are identified, the overall profile of survival improves. Accordingly, among the very few cases of SQTS identified so far, there is a high incidence of SCD. Given the limited experience in managing these patients, the role of pharmacological therapy is still under evaluation.

The ICD seems a plausible treatment for high-risk patients and for those who survived a cardiac arrest.

In the attempt to normalize the augmented IKr current present in SQTS, sotalol and ibutilide were tested but surprisingly they failed to shorten repolarization in SQTS patients[48]. *In vitro* studies[47] suggested that this unexpected observation may be due to the fact that IKr blockers preferentially bind to the open state of the channel, but that inactivation is critical for stabilizing the drug binding and its affinity. Since in the mutant channels the rectification process is abolished, this may reduce the effect of class III antiarrhythmic drugs.

More promising results, at least in terms of prolongation of the effective refractory period and in the suppression of arrhythmia inducibility during PES, were obtained with flecainide and even more with quinidine that exerts a composite electrophysiological effect on multiple ion currents[48]. It will be interesting to investigate if the drug will also prove effective in the prevention of spontaneously occurring life-threatening arrhythmias.

Catecholaminergic polymorphic ventricular tachycardia

Clinical features and molecular bases. Coumel et al.[49] in 1978 first described isolated cases of stress-related bidirectional or polymorphic VT occurring in children or young people with structurally normal heart. In 1995, Leenhardt et al.[50] identified the catecholaminergic polymorphic VT (CPVT) as a peculiar clinical entity that could lead to syncope or SCD in young people.

A familial transmission was noted since the initial reports. Patients affected by CPVT experience syncope or cardiac arrest triggered by physical or emotional stress: first clinical manifestations usually occur during childhood and adolescence[50,51].

Baseline ECG in these subjects is unremarkable: therefore diagnosis is based on the induction of ventricular tachyarrhythmias during exercise stress test. The distinguishing arrhythmia in CPVT is bidirectional VT (Fig. 3), however polymorphic VT and VF are also documented in affected patients[51,52].

For the diagnosis in CPVT, long-term ECG monitoring by Holter or prolonged ECG recording by 7-day recorder or with the implantable loop recorder are very valuable for establishing the diagnosis of the disease in patients with history of syncope occurring during exer-

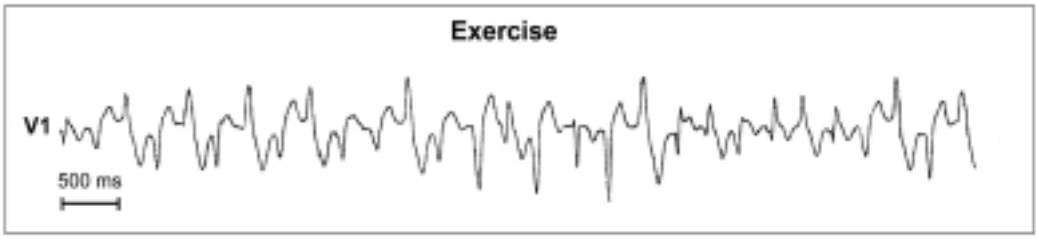

Figure 3. *Example of bidirectional ventricular tachycardia, recorded during exercise stress test in one patient affected by catecholaminergic polymorphic ventricular tachycardia.*

cise, stress or emotion. On the contrary the electrophysiological study as induction of arrhythmias during PES is often unsuccessful.

Bidirectional VT is a typical arrhythmia observed during calcium overload particularly during digitalis intoxication and it has been suggested that it is the consequence of triggered activity initiated by adrenergically-mediated delayed afterdepolarizations[53].

Genetic basis of catecholaminergic polymorphic ventricular tachycardia. Swan et al.[54] demonstrated the linkage of CPVT to chromosome 1q42-q43 and in 2001 Priori et al.[52] identified the *hRYR2* gene, that encodes for the cardiac ryanodine receptor, as the gene involved in the pathogenesis of CPVT.

The ryanodine receptor is localized across the membrane of the sarcoplasmic reticulum and it releases Ca^{2+} from the sarcoplasmic reticulum in response to the calcium influx through the L-type channels, during the phase 2 of the action potential. Mutations found in *hRYR2* gene linked to a CPVT phenotype are all missense mutations located in functionally important regions of the protein: functional characterization of the mutants[55] has shown that they all produce abnormal calcium release in response to adrenergic stimulation. This mechanism supports the hypothesis that arrhythmias are induced by triggered activity.

In 2001, Lahat et al.[56] described also an autosomal recessive variant of CPVT, linked to a mutation on the *CASQ2* gene on chromosome 1p11-p13 that encodes for calsequestrin, that is another protein involved in the control of intracellular calcium.

Only few mutations in the *CASQ2* gene have been reported thus far and functional studies have characterized only one mutant[57], leading to the hypothesis that *CASQ2* defects may alter calcium homeostasis by decreasing the Ca^{2+} buffering in the sarcoplasmic reticulum, leading to spontaneous discharges of Ca^{2+} stores from the sarcoplasmic reticulum, that may induce delayed afterdepolarizations.

Based on genetic characterization of 68 families referred to our clinic, we estimate that 75% of CPVT patients have mutations on the *hRYR2* or *CASQ2* gene: the genetic bases of the remaining 25% of cases are still unknown.

Therapy. Since the first descriptions of the disease it was suggested that beta-blockers are an effective treatment for patients with CPVT. These data are now confirmed in larger series of patients[51,52].

Beta-blockers are effective in controlling arrhythmias in most of CPVT patients, whereas other antiarrhythmics did not result useful[50,52]. Beta-blockers are also fundamental in the acute setting when termination of sustained polymorphic VTs is needed: amiodarone, magnesium or lidocaine infusion on the contrary has been reported to lack efficacy[58].

It is important to recognize that beta-blocker therapy does not abolish ventricular arrhythmias in most patients: the objective of therapy should be the prevention of poorly tolerated sustained VT and VF. In most patients this objective can be achieved even if short runs of VT can still be observed during exercise or emotion. Failure of beta-blockers has been reported and Leenhardt et al.[50] described one SCD and one recurrence of syncope in 2 out of 21 cases. We observed[51] that up to 30% of patients required an ICD because sustained VT could still be observed during exercise stress test or Holter monitoring. Up to 50% of the patients treated with ICD and beta-blockers received an appropriate shock during a mean follow-up period of 2 years.

Other antiarrhythmic drugs have been used only in few reports but always with unsatisfactory results. Thus, considering the high malignancy of CPVT, the prophylactic use of an ICD should be considered when beta-blockers fail to control the occurrence of arrhythmias.

References

1. Schwartz PJ, Priori SG, Napolitano C. The long QT syndrome. In: Zipes DP, Jalife J, eds. Cardiac electrophysiology: from cell to bedside. 3rd edition. Philadelphia, PA: WB Saunders, 2000: 597-615.
2. Abbott GW, Sesti F, Splawski I, et al. MiRP1 forms IKr potassium channels with HERG and is associated with cardiac arrhythmia. Cell 1999; 97: 175-87.
3. Mohler PJ, Schott JJ, Gramolini AO, et al. Ankyrin-B mutation causes type 4 long-QT cardiac arrhythmia and sudden cardiac death. Nature 2003; 421: 634-9.
4. Tawil R, Ptacek LJ, Pavlakis SG, et al. Andersen's syndrome: potassium-sensitive periodic paralysis, ventricular

ectopy, and dysmorphic features. Ann Neurol 1994; 35: 326-30.
5. Tristani-Firouzi M, Jensen JL, Donaldson MR, et al. Functional and clinical characterization of KCNJ2 mutations associated with LQT7 (Andersen syndrome). J Clin Invest 2002; 110: 381-8.
6. Splawski I, Timothy KW, Sharpe LM, et al. Cav1.2 calcium channel dysfunction causes a multisystem disorder including arrhythmia and autism. Cell 2004; 119: 19-31.
7. Schwartz PJ, Priori SG, Spazzolini C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. Circulation 2001; 103: 89-95.
8. Priori SG, Schwartz PJ, Napolitano C, et al. Risk stratification in the long-QT syndrome. N Engl J Med 2003; 348: 1866-74.
9. Zareba W, Moss AJ, Schwartz PJ, et al. Influence of genotype on the clinical course of the long-QT syndrome. International Long-QT Syndrome Registry Research Group. N Engl J Med 1998; 339: 960-5.
10. Cerrone M, Schwartz PJ, Priori SG, et al. Natural history and genetic aspects of the Jervell-Lange-Nielsen syndrome. (abstr) Circulation 2001; 104: 2193.
11. Moss AJ, Zareba W, Hall WJ, et al. Effectiveness and limitations of beta-blocker therapy in congenital long-QT syndrome. Circulation 2000; 101: 616-23.
12. Priori SG, Napolitano C, Schwartz PJ, et al. Association of long QT syndrome loci and cardiac events among patients treated with beta-blockers. JAMA 2004; 292: 1341-4.
13. Zareba W, Moss AJ, Daubert JP, Hall WJ, Robinson JL, Andrews M. Implantable cardioverter defibrillator in high-risk long QT syndrome patients. J Cardiovasc Electrophysiol 2003; 14: 337-41.
14. Groh WJ, Silka MJ, Oliver RP, Halperin BD, McAnulty JH, Kron J. Use of implantable cardioverter-defibrillators in the congenital long QT syndrome. Am J Cardiol 1996; 78: 703-6.
15. Schwartz PJ, Locati EH, Moss AJ, Crampton RS, Trazzi R, Ruberti U. Left cardiac sympathetic denervation in the therapy of congenital long QT syndrome: a worldwide report. Circulation 1991; 84: 503-11.
16. Schwartz PJ. The rationale and the role of left stellectomy for the prevention of malignant arrhythmias. Ann NY Acad Sci 1984; 427: 199-221.
17. Schwartz PJ, Priori SG, Cerrone M, et al. Left cardiac sympathetic denervation in the management of high-risk patients affected by the long QT syndrome. Circulation 2004; 109: 1826-33.
18. Brugada P, Brugada J. 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 1992; 20: 1391-6.
19. Wilde AA, Antzelevitch C, Borggrefe M, et al, for the Study Group on the Molecular Basis of Arrhythmias of the European Society of Cardiology. Proposed diagnostic criteria for the Brugada syndrome: consensus report. Circulation 2002; 106: 2514-9, and Eur Heart J 2002; 23: 1648-54.
20. Brugada R, Brugada J, Antzelevitch C, et al. Sodium channel blockers identify risk for sudden death in patients with ST-segment elevation and right bundle branch block but structurally normal hearts. Circulation 2000; 101: 510-5.
21. Matsuo K, Kurita T, Inagaki M, et al. The circadian pattern of the development of ventricular fibrillation in patients with Brugada syndrome. Eur Heart J 1999; 20: 465-70.
22. Eckardt L, Kirchhof P, Loh P, et al. Brugada syndrome and supraventricular arrhythmias: a novel association? J Cardiovasc Electrophysiol 2001; 12: 680-5.
23. Priori SG, Napolitano C, Giordano U, Collisani G, Memmi M. Brugada syndrome and sudden cardiac death in children. Lancet 2000; 355: 808-9.
24. Suzuki H, Torigoe K, Numata O, Yazaki S. Infant case with a malignant form of Brugada syndrome. J Cardiovasc Electrophysiol 2000; 11: 1277-80.
25. Di Diego JM, Cordeiro JM, Goodrow RJ, et al. Ionic and cellular basis for the predominance of the Brugada syndrome phenotype in males. Circulation 2002; 106: 2004-11.
26. Chen Q, Kirsch GE, Zhang D, et al. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. Nature 1998; 392: 293-6.
27. Antzelevitch C. The Brugada syndrome: ionic basis and arrhythmia mechanisms. J Cardiovasc Electrophysiol 2001; 12: 268-72.
28. Brugada P, Brugada R, Mont L, Rivero M, Geelen P, Brugada J. Natural history of Brugada syndrome: the prognostic value of programmed electrical stimulation of the heart. J Cardiovasc Electrophysiol 2003; 14: 455-7.
29. Brugada J, Brugada R, Brugada P. Determinants of sudden cardiac death in individuals with the electrocardiographic pattern of Brugada syndrome and no previous cardiac arrest. Circulation 2003; 108: 3092-6.
30. Priori SG, Napolitano C, Gasparini M, et al. Clinical and genetic heterogeneity of right bundle branch block and ST segment elevation syndrome. A prospective evaluation of 52 families. Circulation 2000; 102: 945-7.
31. Priori SG, Napolitano C, Gasparini M, et al. Natural history of Brugada syndrome: insights for risk stratification and management. Circulation 2002; 105: 1342-7.
32. Gasparini M, Priori SG, Mantica M, et al. Programmed electrical stimulation in Brugada syndrome: how reproducible are the results? J Cardiovasc Electrophysiol 2002; 13: 880-7.
33. Eckardt L, Kirchhof P, Schulze-Bahr E, et al. Electrophysiologic investigation in Brugada syndrome. Yield of programmed ventricular stimulation at two ventricular sites up to three premature beats. Eur Heart J 2002; 23: 1394-401.
34. Priori SG, Aliot E, Bromstrom-Lundqvist C, et al. Task Force on Sudden Cardiac Death of the European Society of Cardiology. Eur Heart J 2001; 22: 1374-450.
35. Brugada J, Brugada R, Brugada P. Right bundle branch block and ST-segment elevation in leads V_1 through V_3: a marker for sudden death in patients without demonstrable structural heart disease. Circulation 1998; 97: 457-60.
36. Nademanee K, Veerakul G, Mower M, et al. Defibrillator versus beta-blockers for unexplained death in Thailand (DEBUT): a randomized clinical trial. Circulation 2003; 107: 2221-6.
37. Alings M, Dekker L, Sadee A, Wilde A. Quinidine induced electrocardiographic normalization in two patients with Brugada syndrome. Pacing Clin Electrophysiol 2001; 24 (Part 1): 1420-2.
38. Yan GX, Antzelevitch C. Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST-segment elevation. Circulation 1999; 100: 1660-6.
39. Belhassen B, Viskin S, Fish R, Glick A, Setbon I, Eldar M. Effects of electrophysiologic-guided therapy with class-IA antiarrhythmic drugs on the long-term outcome of patients with idiopathic ventricular fibrillation with or without the Brugada syndrome. J Cardiovasc Electrophysiol 1999; 10: 1301-12.
40. Hermida JS, Denjoy I, Clerc J, et al. Hydroquinidine therapy in Brugada syndrome. J Am Coll Cardiol 2004; 43: 1853-60.
41. Tanaka H, Kinoshita O, Uchikawa S, et al. Successful prevention of recurrent ventricular fibrillation by intravenous

isoproterenol in a patient with Brugada syndrome. Pacing Clin Electrophysiol 2001; 24 (Part 1): 1293-4.
42. Miyazaki T, Mitamura H, Miyoshi S, Soejima K, Aizawa Y, Ogawa S. Autonomic and antiarrhythmic drug modulation of ST segment elevation in patients with Brugada syndrome. J Am Coll Cardiol 1996; 27: 1061-70.
43. Algra A, Tijssen JG, Roelandt JR, Pool J, Lubsen J. QT interval variables from 24 hour electrocardiography and the two year risk of sudden death. Br Heart J 1993; 70: 43-8.
44. Gussak I, Brugada P, Brugada J, et al. Idiopathic short QT interval: a new clinical syndrome? Cardiology 2000; 94: 99-102.
45. Gaita F, Giustetto C, Bianchi F, et al. Short QT syndrome: a familial cause of sudden death. Circulation 2003; 108: 965-70.
46. Bellocq C, van Ginneken AC, Bezzina CR, et al. Mutation in the KCNQ1 gene leading to the short QT-interval syndrome. Circulation 2004; 109: 2394-7.
47. Brugada R, Hong K, Dumaine R, et al. Sudden death associated with short-QT syndrome linked to mutations in HERG. Circulation 2004; 109: 30-5.
48. Gaita F, Giustetto C, Bianchi F, et al. Short QT syndrome: pharmacological treatment. J Am Coll Cardiol 2004; 43: 1494-9.
49. Coumel P, Fidelle J, Lucet V, et al. Catecholaminergic-induced severe ventricular arrhythmias with Adam-Stokes syndrome in children: report of four cases. Br Heart J 1978; 40: 28-37.
50. Leenhardt A, Lucet V, Denjoy I, Grau F, Ngoc DD, Coumel P. Catecholaminergic polymorphic ventricular tachycardia in children. A 7-year follow-up of 21 patients. Circulation 1995; 91: 1512-9.
51. Priori SG, Napolitano C, Memmi M, et al. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. Circulation 2002; 106: 69-74.
52. Priori SG, Napolitano C, Tiso N, et al. Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia. Circulation 2001; 103: 196-200.
53. Priori SG, Corr PB. Mechanisms underlying early and delayed afterdepolarizations induced by catecholamines. Am J Physiol 1990; 258 (Part 2): H1796-H1805.
54. Swan H, Piippo K, Viitasalo M, et al. Arrhythmic disorder mapped to chromosome 1q42-q43 causes malignant polymorphic ventricular tachycardia in structurally normal hearts. J Am Coll Cardiol 1999; 34: 2035-42.
55. Jiang D, Xiao B, Zhang L, Chen SR. Enhanced basal activity of a cardiac Ca^{2+} release channel (ryanodine receptor) mutant associated with ventricular tachycardia and sudden death. Circ Res 2002; 91: 218-25.
56. Lahat H, Pras E, Olender T, et al. A missense mutation in a highly conserved region of CASQ2 is associated with autosomal recessive catecholamine-induced polymorphic ventricular tachycardia in Bedouin families from Israel. Am J Hum Genet 2001; 69: 1378-84.
57. Viatchenko-Karpinski S, Terentyev D, Gyorke I, et al. Abnormal calcium signaling and sudden cardiac death associated with mutation of calsequestrin. Circ Res 2004; 94: 471-7.
58. De Rosa G, Delogu AB, Piastra M, Chiaretti A, Bloise R, Priori SG. Catecholaminergic polymorphic ventricular tachycardia: successful emergency treatment with intravenous propranolol. Pediatr Emerg Care 2004; 20: 175-7.