The Cardiac Channelopathies

Can the molecular tale wag the clinical dog?

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Interest:
Genetics of arrhythmia susceptibility
Catheter ablation of arrhythmia
Cardiac Resynchronization Therapy

Over the last decade, the advent of molecular medicine has led to the definition of a new subclass of cardiovascular diseases referred to as the channelopathies. The hallmark of the channelopathies is inherited risk of life-threatening arrhythmias due to the physiologic impact of mutations in genes that encode ion channels, the proteins that control the electrical activation of the heart. Thus far, the channelopathies include Hereditary Long-QT Syndrome (LQTS), Brugada Syndrome, Progressive Conduction System Disease, Catecholaminergic and Idiopathic Ventricular Fibrillation, Atrial Fibrillation and Congenital Absence of the Sinus Node. This Grand Rounds will focus on how understanding the molecular mechanisms underlying LQTS and BS has altered our comprehension and therapeutic approach to these diseases and the potential impact on the prevention of sudden cardiac death in general.

Hereditary LQTS

LQTS is characterized by congenital prolongation of the QT interval, sometimes with bradycardia, and an elevated risk of sudden cardiac death from the torsades de pointes for of polymorphic ventricular tachycardia (Figure 1).[2,3] Occurring in approximately 1 in 5000 individuals, more commonly in women, a hallmark of the disease is heterogeneity in QT prolongation and clinical symptoms both within and among different families.

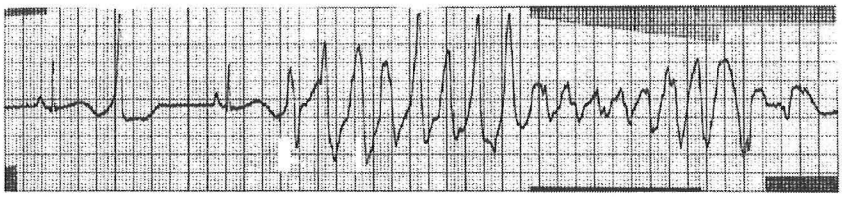


Figure 1: Spontaneous torsades de pointes in a patient with LQTS. [1]

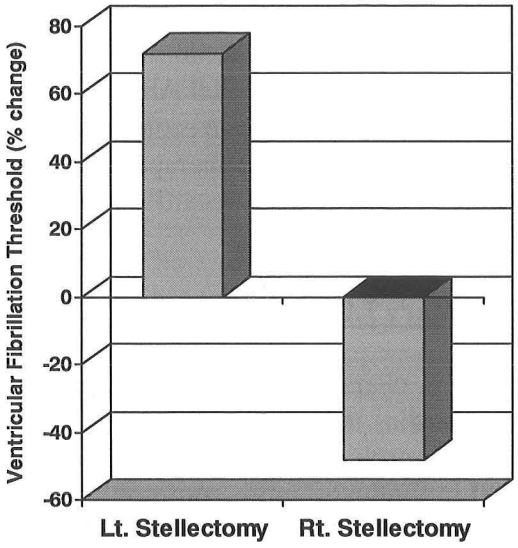
Background

In 1956, Jervell and Lange-Neilsen described four siblings with congenital deafness and syncope.[4] Extensive evaluation revealed normal metabolic and cardiac function except for the presence of mild bradycardia and marked QT interval prolongation. The parents were clinically normal suggesting autosomal recessive inheritance. Three of the four children had recurrent syncope and seizures while playing or swimming. Anti-epileptics were ineffective. In contrast to normal individuals, the QT prolongation was noted to worsen in the setting of exercise. These three children died suddenly at the ages of 4, 5 and 9 years.

Subsequently, Romano and Ward separately described similar syndromes without deafness that appeared to follow autosomal dominant patterns of inheritance.[5,6] Analysis of a growing number of affected patients revealed that syncope and death occurred principally in the setting of exercise, emotion, or surprise (i.e. rapid elevations in adrenergic tone), due to torsades de pointes. In early reports, mortality rates in symptomatic patients were as high as 73%.[7]

Both patient-based and animal studies suggested that disruption of adrenergic innervation to the right heart mirrored the increased susceptibility to ventricular arrhythmias in LQTS whereas left stellectomy decreased the risk of arrhythmia (Figure 2). Stimulation of the left stellate ganglia reproduced the QT interval prolongation, T wave alternans, and prolonged action potential duration observed of LQTS. Concordantly, rapid infusion of epinephrine in LQTS patients further prolonged the QT interval and could trigger arrhythmia. These data supported a viewpoint that a congenital sympathetic imbalance with a diminution of right-sided inputs to the heart produced LQTS.[8] Left stellectomy (to produce left-sided sympathetic dennervation) was thus used to treat symptomatic patients. This was subsequently overshadowed by beta-blocker therapy. Several factors pointed to limitations of this "sympathetic imbalance" hypothesis; normal autonomic innervation to the heart is left predominant, left stellectomy often did not normalize the QT interval and antiarrhythmic drugs could prolong the QT in the absence of increased adrenergic tone. These findings pointed to an intrinsic abnormality of the myocardium as causative of LQTS.[9]

Figure 2: Effect of stellectomy on arrhythmia threshold.



To better characterize LQTS, an international registry was established in 1979. Using a diagnostic criteria of a QTc interval of 0.44 $sec^{-1/2}$ for affected individuals, 328 probands, 688 affected family members and 1004 unaffected family members were identified. While the study was limited by variable use of therapy and by the unproven diagnostic criteria, it provided the best compilation of patients to date.[10] Probands and affected individuals were more likely to be female and younger. Only 10% of probands failed to have affected family members and 58% reported a family history of sudden cardiac death, confirming the familial nature of LQTS. Syncope occurred in various settings, with intense emotion accounting for 47% of events, vigorous exercise triggering 41%, swimming in 15%, awakening in 19% and 8% following abrupt auditory stimuli (Table I). Among patients who had sudden cardiac death, 57% died before the age of 20 years. Probands were more likely to have initial events with a cumulative rate of over 90% by 50 years of age. While this was significantly lower in affected family members, at least 36% of <u>all</u> patients with a QTc≥0.44 $sec^{-1/2}$ had events by the age of 20. In addition, the data highlighted the fact that there was significant heterogeneity in the extent QT

Table I: Triggers for Syncope in LQTS

Trigger	% with Trigger
Intense emotion	47%
Vigorous exercise	41%
Swimming	15%
Awakening	19%
Abrupt Auditory Stimuli	6%

1993 LQTS Diagnostic Criteria	Points
ECG Findings	
A. QTc	
≥480	3
460-470	2
450	1
B. Torsades de pointes	2
C. T-Wave alternans	1
D. Notched T waves in three leads	1
E. Low heart rate for age	0.5
Clinical History	
A. Synope	
With stress	2
Without stress	1
B. Congential Deafness	0.5
Family History	
A. Family members with definite LQTS	1
B. Unexplained SCD below age 30 among immediate family	0.5

ECG Findings: In absence of medications known to affect QT interval
Family history: Same member may not count for both A and B
Definite LQTS defined as score >4
Scoring: ≤1 point, low probability; 2-3 points, intermediate probability of LQTS; ≥4 pints, high probability of LQTS

prolongation as well as the frequency of cardiac events and mortality among those affected with LQTS, even within the same family. Empiric use of beta-blocking agents led to a significant reduction in syncope, but sudden cardiac death remained as high as 6% cumulatively.

To account for the heterogeneity in clinical severity, a diagnostic algorithm was proposed in 1993 accounting for ECG findings, symptoms and family history. These criteria were limited by the absence of a "gold standard" to validate the algorithm.[11]

Molecular Physiology of the Cardiac Action Potential

A better understanding of the molecular and cellular physiology underlying LQTS warrants review of normal cardiac electrical activity. Cardiac depolarization mediates coordinated activation of the myocyte contractile apparatus and ejection of blood from the heart. The process of repolarization resets contractile apparatus and allows the myocyte to respond to subsequent depolarizing signals. The cardiac action potential reflects this change in voltage across the myocyte cell membrane. The surface ECG is a summation of all myocyte action potentials.

At baseline, the differential concentrations of Na^+, K^+, Cl^- and Ca^{2+} maintain a "resting potential" of –80 mV potential across the cell membrane. Depolarization and repolarization are achieved through movement of specific ions across the cell membrane via protein channels, leading to voltage changes across the cell membrane that activate contraction. These channels can be activated, or "gated," by the very voltage changes they produce or by time, cellular metabolites, neurohormones or autonomic tone. *Inward* ionic currents produce *depolarizing* voltage changes and outward currents restore the baseline, resting potential. In cardiac myocytes, the depolarized state is prolonged to allow for full contraction. Until completion of repolarization, the myocytes are refractory to further depolarization.

The action potential has four distinct phases dictated by the activation of specific ion currents (Figure 3).[12] Initial rapid *depolarization* (phase 0) is caused by an *inward* movement of sodium ions referred to as I_{Na}, and produces the surface QRS complex. The change in voltage triggers an early, transient <u>outward</u> current, I_{to}, which competes with remaining I_{Na} to begin <u>repolarization</u> (phase 1). *Inward* calcium channels subsequently open to maintain plateau phase of *depolarization* (phase 2) during which cardiac contraction is completed. Since no change occurs in the membrane voltage, this appears on the surface ECG as the isoelectric ST segment. <u>Outward</u> potassium currents are then activated to complete <u>repolarization</u> of the myocyte (phase 3) and yield the T wave on the ECG. This K^+current can further be divided into rapidly and slowly activating components, (I_{ks} and I_{kr}).[13] These components behave distinctly; for example, it is the regulation of I_{ks} activity by sympathetic tone that yields the shortening of the QT interval that is physiologically observed with exercise.

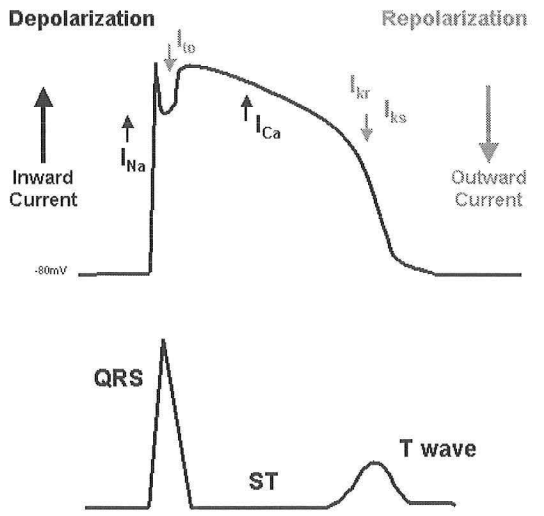


Figure 3: Cardiac action potential (above) and its relationship to the ECG

The width of the QRS complex and T waves represent the temporal non-simultaneous nature of activation across the surface of the heart (Figure 4). The width of the latter half of the T wave is representative of the temporal variation in cellular repolarization and refractoriness at the end of the cardiac cycle. Increases in this "dispersion of refractoriness" facilitate arrhythmias.

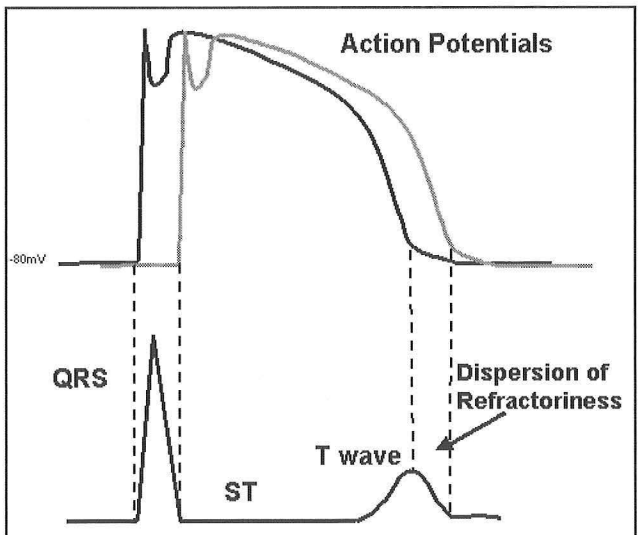


Figure 4: The ECG is a summation of action potentials from temporally and spatially distinct portions of the heart.

<u>Molecular Biology of LQTS</u>

This emerging understanding of cellular electrophysiology fueled the drive to define the molecular defect underlying LQTS. The LQTS registry identified large kindreds to facilitate mapping of the disease gene. Consistent with the heterogeneous presentation of the syndrome, multiple mutations have been mapped six loci, LQT1-LQT6,. Employing both positional cloning and candidate gene approaches, the loci were identified as the

channel components of the I_{ks} potassium current (KvLQT1 [LQT1] and its cofactor min K [LQT5]), the I_{kr} potassium current (HERG [LQT2] and its putative cofactor MiRP1 [LQT6]) and the sodium current I_{Na} (SCN5a [LQT3]).[14-18] A heterozygous mutation in one of these loci can be identified in 70% of patients with LQTS. Rarely, homozygous mutations are observed; when occurring in the KvLQT1 gene, deafness is observed due to the role of this channel in the membrane of Corti. LQT4, observed in one family, was recently identified as Ankyrin-B.[19] While not an ion channel, the gene product is believed to regulate Na^+ and Ca^{2+} channels.

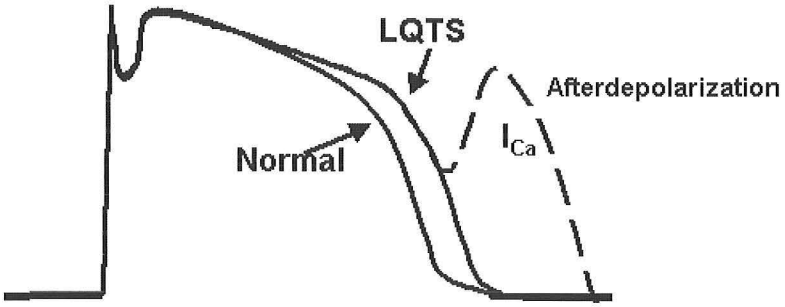


Figure 5: Prolongation of the action potential due to a LQTS mutation can lead to afterdepolarizations and arrhythmia.

Mechanistically, *in vitro* studies have revealed that the mutations in the KvLQT1 and HERG, as well as their cofactors, appear to diminish outward repolarizing current. In contrast, the SCN5a mutations increase late *inward* current. In each case, the defects delay repolarization (Figure 5). This delay allows for Ca^{2+} channel recovery and voltage-gated reopening triggered by the persistent depolarized membrane potential. This recurrent inward current produces early afterdepolarizations, premature ventricular contractions, and torsades de pointes. If sustained, the rhythm can degenerate to ventricular fibrillation, causing sudden cardiac death, or spontaneously terminate if the wave front of arrhythmia collides with refractory myocardium. In this latter case, a patient would sense either palpitations or suffer syncope.

Penetrance of the LQT Genotype

The discovery that heterogeneous mutations cause LQTS helped explain the heterogeneous clinical presentation and response to therapy by providing a diagnostic "gold standard." An analysis of 3 LQT1 families revealed a wide variation in QTc intervals in affected family members, ranging from 0.44-0.590 $sec^{-½}$.[20] Sixty-three percent had at least one syncopal episode; 4 of 83 suffered cardiac arrest. Nine family members had sudden cardiac death, four without prior symptoms. Genotypic diagnosis revealed misclassification of 6% of mutation carriers and 17% of noncarriers using the classic diagnostic criterion of QTc>0.44 $sec^{-½}$. Among women, 19% of noncarriers would be misclassified. This heterogeneity of symptom severity and penetrance was further demonstrated in an analysis of the families of 9 Italian probands that appeared to represent sporadic cases of LQTS.[21] Following genotypic analysis, 15 of 43 family members were found to be LQT gene carriers yielding a penetrance of 35%.

Genotype-Phenotype Correlation in LQTS

Genotype plays a significant role in the mortality and clinical presentation of LQTS. In a study of 38 families, Zareba, and colleagues[22] (Table II), found that patients with LQT1 were more likely to have syncope or cardiac arrest at a younger age than those with LQT2 or LQT3. By age 40, in the absence of therapy, 62% of LQT1 carriers and 46% of LQT2 carriers had suffered at least 1 cardiac event while only 18% of LQT3 patients became symptomatic. Despite this gene-specific difference in symptom frequency, the incidence in mortality in untreated patients across the LQT genotypes was similar with a cumulative probability of mortality by age 40 of 6-8%, suggesting that the lethality of events is higher in LQT3.

In a larger study of 193 families, Priori and colleagues[23] (Table II) recently reported differing data revealing that cardiac arrest and sudden cardiac death rates were lower in LQT1 (0.3%/year) with the greatest severity in LQT2 (0.6%/year). The overall rate of sudden cardiac death or any cardiac event in untreated patients <40 years of age was 13% and 36% respectively. In both studies, the degree of QT prolongation predicted events; however, significant numbers of affected individuals had QTc<0.440 $sec^{-½}$ (36% LQT1, 19% LQT2, 10% LQT3). Smaller studies have found significant cardiac event rates in these patients as well.[24]

Table II

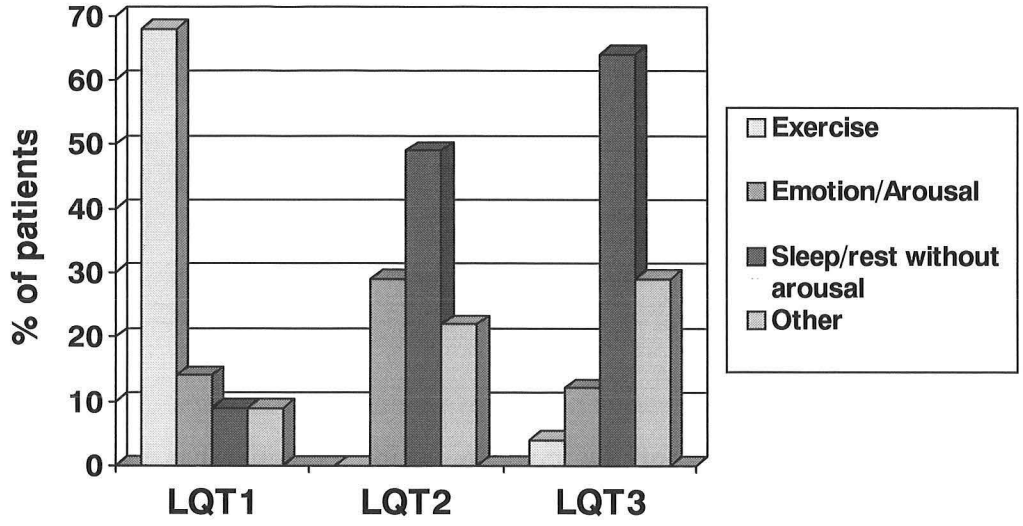
	Any Cardiac Event (%)			Cardiac Arrest or Sudden Death (%/yr)			
	LQT1	**LQT2**	**LQT3**	**LQT1**	**LQT2**	**LQT3**	**No. Families**
Zareba	**62%**	**46%**	**18%**	**0.22**	**0.15**	**0.15**	**38**
Priori	**30%**	**46%**	**42%**	**0.30**	**0.60**	**0.56**	**193**

These data underscore that notion that phenotypic differences in LQTS correspond not only to the affect gene locus, but may vary due to the severity of a mutation within the same gene.[25,26] For example, mutations in the pore-forming region of the HERG gene lead to highly penetrant and lethal phenotypes relative to LQT2 mutations. An in-depth discussion of this phenomenon is beyond the scope of this Grand Rounds.

Gene-specific propensities in the types of stimuli that trigger cardiac events have also been noted (Figure 6).[27] Exercise triggers 62% of events in LQT1 patients but only 13% of events in LQT2 or LQT3. Within LQT1, swimming caused up to 33% of all events and 45% of lethal events in one cohort.[20,28] In contrast, LQT2 patients appear to have a preponderance of events triggered by emotion and psychologically stressful events. In particular, up to 67% of events are triggered by acoustic stimuli, such as the ringing of a doorbell or alarm clock (Figure 7).[29] Finally, most LQT3 patients have events during sleep with very few events during exercise. In patients who had multiple triggers for

events (10-25%), the triggers were typically similar. Only 2% of patients have events in the setting of both exercise and sleep/rest. Triggers in family members have also highly concordant with those observed in probands.[30]

Figure 6: Gene-specific triggers of cardiac arrest.



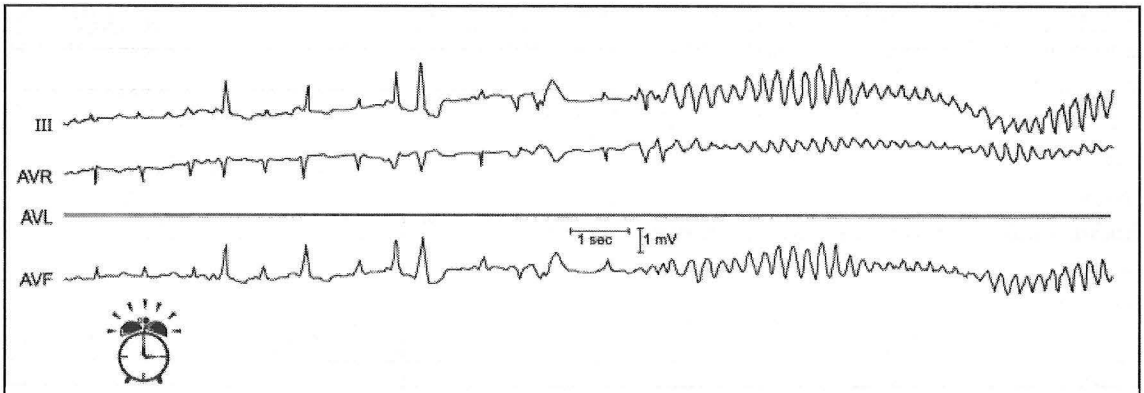
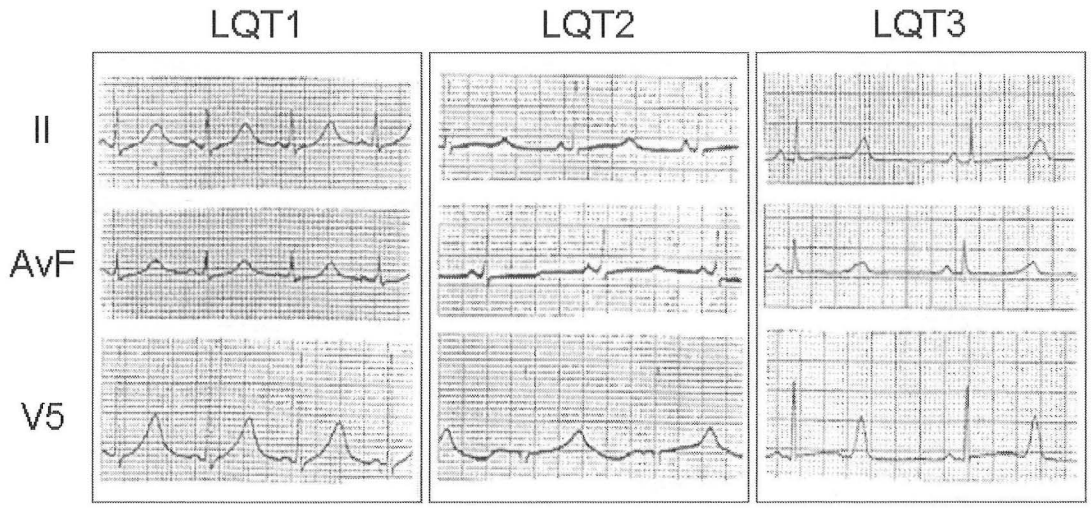


Figure 7: Spontaneous torsdes de pointes triggered by an alarm clock in a patient with a LQT2 mutation.

ECG morphology of the QT interval and T waves has also been found to differ in a genotype-specific manner (Figure 8).[31,32] In a study of 29 LQTS families, LQT1 was associated with four ECG patterns characterized by the presence of QT interval prolongation and normal or broad-based T waves. The T waves in LQT2 patients tended to be broad, but reduced in amplitude, often with a bifid morphology. LQT3 was associated with late onset T waves with a peaked, biphasic or asymmetrically peaked morphology. Typical patterns were noted in 88% of patients.

Figure 8: Genotype-specific ECG patterns in LQTS.



Gene-Specific Cellular Physiology

A more complex understanding of the myocyte action potential has facilitated our understanding of the gene-specific cellular physiology that underlies the heterogeneity observed in LQTS. Electrically, three types of myocytes have been recorded across the layers of the ventricular myocardium: epicardial, M and endocardial cells (Figure 9).[33] In epicardial cells (EPI), the action potential has an increase in outward current at phase 1, leading to a characteristic "spike and dome" morphology which is not present in the endocardial cell (ENDO) layer. Greater I_{to} current in epicardial cells relative to other layers accounts for this appearance. A third layer of myocytes, termed the M cells, has an intermediate degree of I_{to} function; it is characterized by significantly less I_{ks} outward current relative to the other layers.

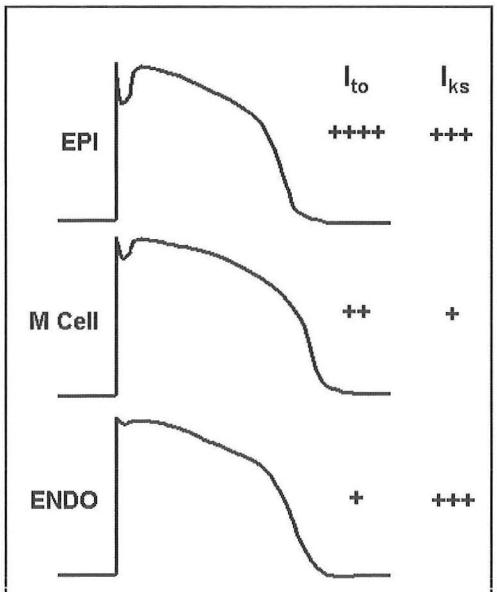


Figure 9: Depiction of the action potentials and currents from different layers of the ventricle.

Recapitulation of a LQT1 mutation by the administration of chromanol 293B (Figure 10), a specific I_{ks} antagonist, results in prolongation of the action potential plateau in all three myocardial layers and is accompanied by QT prolongation on the ECG.[34,35] As such, the dispersion (or time delay) of refractoriness between layers does not significantly increase. However, in the setting of adrenergic stimulation with isoproterenol, the action potential disproportionately prolongs in the M cell layer, lengthening the QT interval and increasing dispersion of refractoriness. B-adrenergic stimulation normally leads to induction of both *depolarizing* (*inward*) and

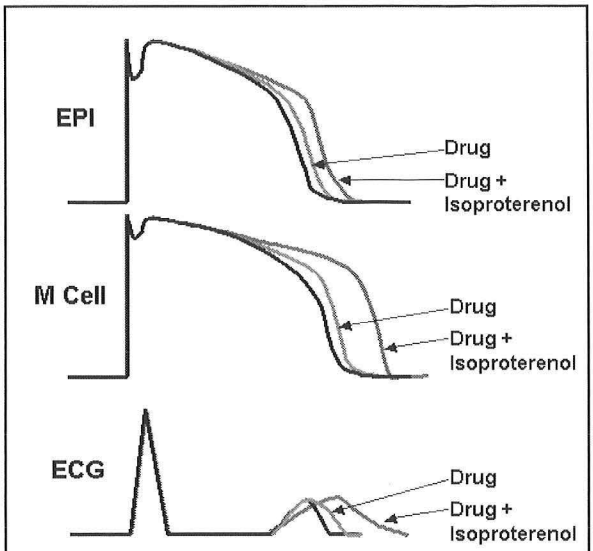


Figure 10: Cellular model of LQT1.

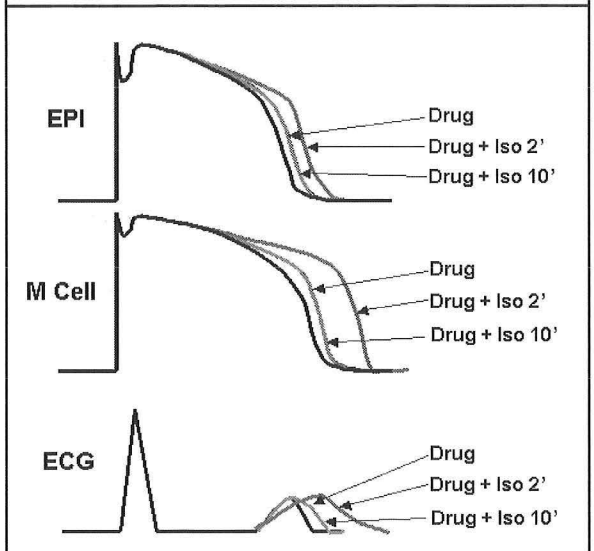


Figure 11: Cellular model of LQT2

repolarizing (outward) currents. In the setting of an LQT1 (I_{ks}) defect, the *inward* currents overmatch the defective outward I_{ks}, particularly in the M cells where I_{ks} is expressed at a lower level at baseline. As a result, both the QT interval and the dispersion of refractoriness between layers increases providing the substrate for triggered ventricular arrhythmias in the setting of adrenergic stimulation. These findings correlate well with the predominance of exercise as a trigger for arrhythmia. Predictably, co-administration of beta-blocking agents prevents this response in these models.

When LQT2 is modeled by administration of an I_{kr} blocker such as dofetilide or sotalol, QT prolongation occurs with a larger resting dispersion of refractoriness and arrhythmias are observed in the absence of further manipulation (Figure 11). This is consistent with the broader, bifid T waves on the surface ECG and higher frequency of rest-related arrhythmias in these subjects *in vivo*. B-adrenergic stimulation produces further increase in the QT interval and the dispersion of refractoriness which is only transient, likely due to a more abrupt activation of *inward* currents relative to outward I_{ks} current with isoproterenol; QT intervals gradually return to baseline with continued stimulation. The frequency of arrhythmia is dramatically increased upon initial adrenergic stimulation, but rapidly normalizes. Furthermore, the administration of propranolol does not significantly alter the electrical patterns or frequency of arrhythmia in these preparations. These findings are consistent with the association of emotional stresses and in particular, auditory stimuli, in triggering arrhythmias in LQT2. These triggers are likely to produce abrupt prolongations in the QT interval, dispersion of refractoriness and arrhythmia. In the setting of exercise with gradual onset, these changes would progressively normalize over time. Even normal individuals have been shown to undergo QT interval abnormalities and T wave inversion in the setting of abrupt awakening.

In the model of LQT3 produced by treatment with the Na^+ channel opener, ATX-II, significant QT prolongation is also observed (Figure 12). However, in the setting isoproterenol, the QT interval shortens and fewer spontaneous and induced arrhythmias are observed. With preserved I_{ks}, outward currents predominate in the setting of adrenergic stimulation. Interestingly, propranolol increases the rate of arrhythmia, a finding concordant with the role of sleep/rest as an arrhythmia trigger and the observed poor response to ß-blockers.

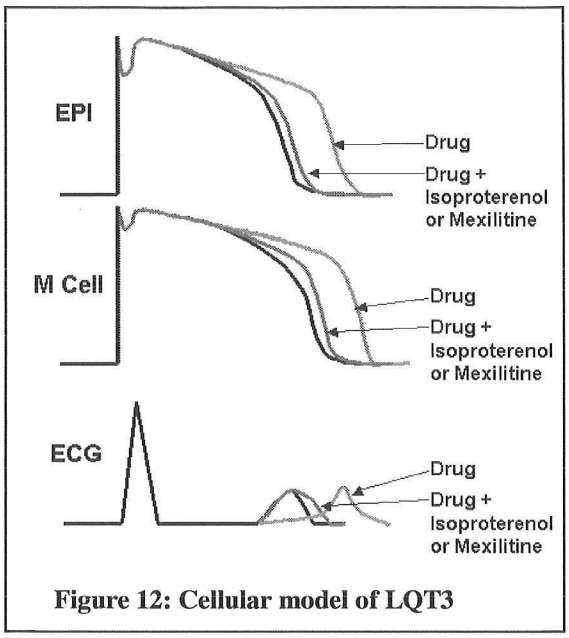


Figure 12: Cellular model of LQT3

Gene-Specific Therapy

These gene-specific differences in the cellular physiology of LQTS suggest a role for gene-specific therapy. ß-blockers have been the mainstay of treatment and prophylaxis against events in LQTS due to the early finding associating exercise with cardiac events. When beta-blocker therapy leads to significant bradycardia, adjunctive pacemaker therapy has been employed successfully. Retrospective analyses have demonstrated significant reductions in new and recurrent cardiac events in probands and asymptomatic family members.[36] Patients with the greatest pre-β-blocker event rates derived the greatest benefit. Despite these favorable results, the rate of recurrent events is not trivial and can exceed 30% at 5 years. Cardiac arrest and sudden cardiac death on therapy remains at 4-9% and is as high as 14% in patients who were symptomatic prior to initiation of β-blockers. Consistent with molecular and physiologic data, in a genotype-specific context, LQT1 patients appear to have the greatest response to β-blockade. No apparent benefit in LQT3 patients was observed. Since the data on left sympathetic stellectomy remains controversial, adrenergic antagonism with such invasive therapy is rarely employed.

Beyond the use of β-blockade, molecular and physiologic studies suggest that therapy tailored toward the mutant gene may improve clinical outcomes. The HERG channel, which underlies LQT2, has the peculiar property of increased activity in the presence of greater extra-cellular $[K^+]$, in spite of this lowering the $[K^+]$ gradient across the membrane.[37] In an acute study, 7 LQT2 patients demonstrated shortening of the QT interval, decrease QTc dispersion and an improvement in T wave morphology following administration of K^+ and spironolactone.[38] The utility of chronic hyperkalemic therapy has not been examined. Some preliminary experiments are also underway to test nicorandil, an agent that activates potassium channel outward currents and could counteract the molecular defects underlying LQT1 and particularly LQT2.

In the setting of LQT3, clinical triggers and *in vitro* predict not only the poor efficacy of β-blockers but suggest the potential benefit of sodium channel blockade with mexiletine

to counteract the persistent inward current observed in mutant sodium channels. In a study including 8 LQT3 patients some of whom remained symptomatic despite medical therapy, mexiletine led to a significant decrease in QTc (from 535±32 ms to 445±31 ms) and additional QTc reduction during exercise.[39] These findings were not observed in LQT2 patients. Prospective trials of mexiletine therapy are underway. Given the inverse relationship between heart rate and the QT interval as well as the propensity of events during sleep or rest, pacing may be advantageous in these patients as well.

In high-risk subgroups presenting with aborted cardiac arrest or recurrent symptoms with pharmacologic therapy, implantable defibrillators (ICD) have been successful.[40] Among 35 high-risk patients treated with ICD therapy, 60% had at least 1 appropriate ICD discharge over a mean of 31 months of follow-up. No mortality was observed in ICD patients despite the 0.9%-2.6%/year mortality expected for such patients. In this group, ß-blockers did not appear to reduce the need for ICD therapy.

The presence of gene-specific triggers also point to a role therapeutic behavioral modification. LQT1 patients should avoid competitive activity and all forms of swimming. Likewise, LQT2 patients should remove loud telephones and alarm clocks.

Diagnosis

Both the prospects for gene-specific therapy as well as heterogeneity and incomplete penetrance make diagnosis of LQTS critical but difficult. Genetic diagnosis of affected families has demonstrated flaws with current the diagnostic algorithm; in one cohort, the sensitivity of intermediate probability of LQTS was only 54%.[21] Furthermore, the large variety of mutations in the multiple LQT loci makes genetic diagnosis prohibitive until inexpensive resequencing arrays become available.

Using the gene-specific ECG criteria, Zhang, *et al* demonstrated that genotype could be predicted with 100% sensitivity and specificity in 2/3 of families.[32] Furthermore, event triggers such as swimming and auditory stimuli have been 99% and 80% specific for LQT1 and LQT2, respectively.[27] By complementing ECG data, symptom-related triggers and demographic data the candidate gene could be determined in 63% of families and correct phenotype could be determined in 80% of genotyped cases.[41] Recently, a novel risk stratification strategy devised from data obtained from 193 families has stratified risk according to clinical and genotypic variables (Figure 13).[23] Future studies will be needed to confirm whether these criteria can guide therapy. Optimal strategies for

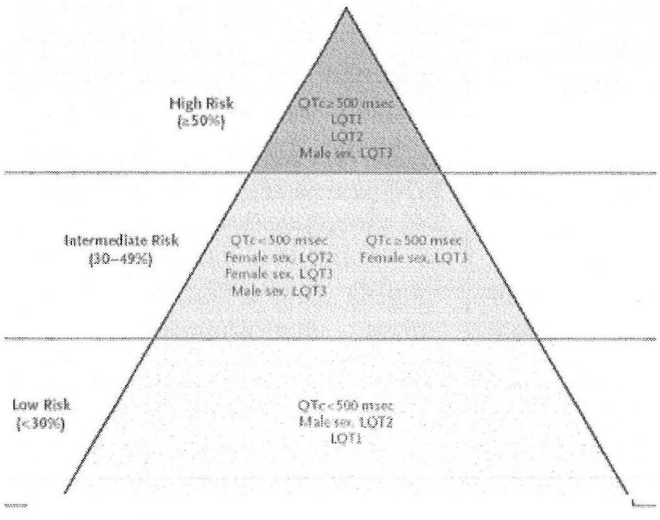


Figure 13: Risk stratification in LQTS.

identifying "silent" gene carriers also remain to be established.

Brugada Syndrome

Brugada Syndrome is characterized by the high prevalence of life-threatening VF during rest or sleep, most often in young to middle-aged men, in the setting of a structurally normal heart but early precordial ST-segment elevation on the surface ECG with closely coupled PVCs (Figure 14).[42] As with LQTS, ventricular arrhythmias can be self-terminating leading to recurrent syncope. The association with this ECG pattern was first recognized in the 1953 but better characterized by Josep and Pedro Brugada in 1992. The disease is phenotypically and genetically identical to Sudden Unexplained Death Syndrome (SUDS). Dubbed "bangungut" (to rise and moan in sleep) in the Philippines and "lai tai" (death during sleep) in Thailand, it is the leading cause of non-traumatic death in young men in southeast Asia.[43]

The characteristic ECG pattern of Brugada Syndrome can be transient and be present in the absence of syncope, cardiac arrest or sudden cardiac death. Sodium channel blockers appear to unmask, or exaggerate the pattern. Fever, vagotonic states, ß-blockers and cocaine appear to have similar effects.

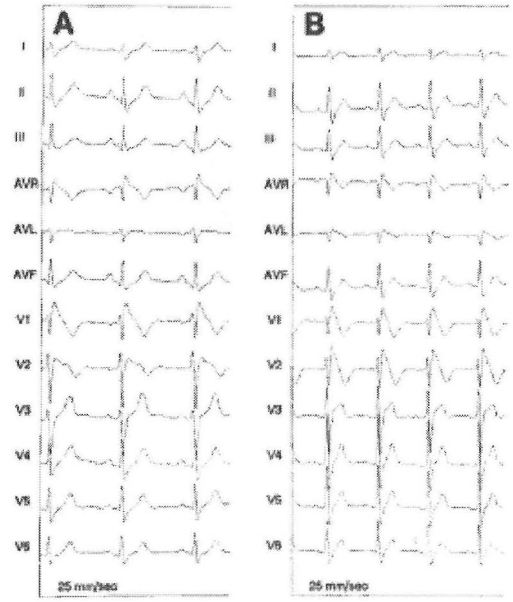


Figure 14: Characteristic Brugada ECG pattern in a symptomatic (A) and asymptomatic (B) man.

Clinical Presentation

Studies defining the clinical risk associated with Brugada Syndrome have yielded varied results (Table IV). In a longitudinal study of patients with the syndrome, Brugada, *et al* observed significant rates of new and recurrent life-threatening events among all categories of patients.[42] In this population, the clinical electrophysiology study appeared to have adequate negative predictive value for future events, particularly in asymptomatic patients.

Differing results were found however in a study of 60 patients from 52 families by Priori and colleagues.[44] Among these subjects, recurrent cardiac arrest or sudden cardiac death was infrequent and new events were not observed in patients who were asymptomatic at baseline. In this cohort, the electrophysiology study was not predictive of future.

Molecular Genetics

With a candidate gene approach, mutations in the cardiac sodium channel, SCN5a, have been linked to Brugada Syndrome and are identifiable in 15-30% of families.[45] In contrast to the findings in LQT3, the sodium channel defects in Brugada Syndrome *decrease* inward, depolarizing currents, especially during phase 1 of the action potential by reducing the number of active channels or altering their activation-inactivation properties. As in LQTS, the ability to perform molecular diagnosis in a subset of families has allowed for the identification of unaffected carriers. In eight genotyped families, penetrance ranged from 12.5% to 50% owing likely to variability in the phenotypic severity of different mutations as well as the importance of possible modifying genes or triggers such as vagal tone, fever and pharmacologic agents.[44] Interestingly, several mutations appear to produce more profound dysfunction at higher temperatures, suggesting a mechanism for the unmasking of Brugada Syndrome in febrile patients.

Table IV

	Brugada		Priori	
Event	Baseline (n)	Event during F/U	Baseline (n)	Event during F/U
Cardiac Arrest	71	62%	17	29%
Syncope	73	19%	13	0%
Asymptomatic	190	8%	30	0%
Total	334	22%	60	8%
F/U period		26-54 mos.		33 mos

Cellular physiology

Both the finding of phenotypic unmasking with sodium channel blockers and the identification of "loss of function" sodium channel mutations in patients point to a decrease in inward depolarization in the pathophysiology of Brugada Syndrome. Sodium channel blockers can simulate a relative decrease in inward current leading to shortening of the action potential duration *in vivo*.[46] In this setting (Figure 15), disproportionate action potential shortening is observed in the epicardial (EPI) cell layer compared with endocardial (ENDO) cells, again due to the greater component of the I_{to} in epicardial cells. In the epicardial cells, exaggerated early repolarization can prevent activation of the Ca2+ current that is responsible for the action potential "dome," leading to an all-or-nothing phenomenon of early repolarization.

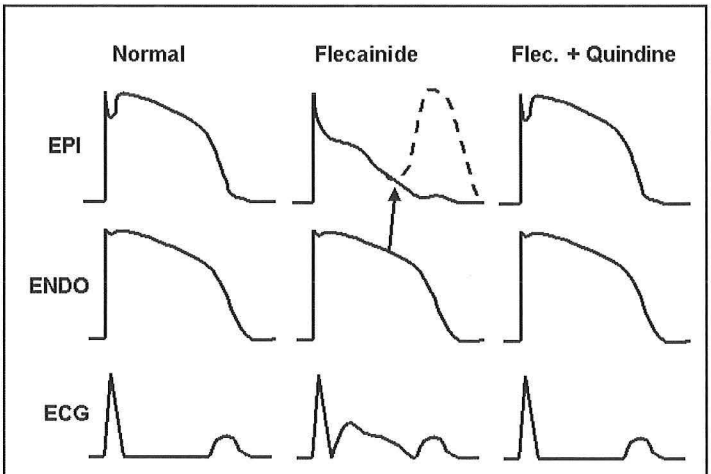


Figure 15: Cellular model of Brugada Syndrome. High transmural voltage gradients can trigger phase 2 reentry.

This phenomenon is not observed in endocardial cells and can be prevented by 4-AP and quinidine, blockers of I_{to}. The addition of acetylcholine (ACh) in these experiments further shortens the action potential and augments the differences between cell layers, likely by stimulating ACh-sensitive K^+ channels. As expected, the adrenergic agonist, isoproterenol reverses this effect.

The dispersion of action potential duration (i.e. refractoriness) across the EPI and ENDO layers produces a transmural voltage gradient leading to ST elevation on the surface ECG similar to that seen in Brugada Syndrome patients. These intramyocardial voltage gradients can facilitate reactivation of repolarized EPI cells leading to short coupled PVCs, termed "phase 2 reentry." When severe, these differences can facilitate sustained VF. Thus, the cellular model of Brugada Syndrome can recapitulate the ECG findings, the proarrhythmia and susceptibility to vagal tone. Finally, the importance of unopposed I_{to} in the physiology of Brugada Syndrome explains the right-sided predominance of the ECG manifestations; I_{to} is more densely expressed in the right ventricular epicardium than in the left ventricle.

Diagnosis

Because of the variable presentation, low incidence of genotypic data and the varied results with provocative testing, the diagnosis of Brugada Syndrome remains problematic. Challenge with a class Ic sodium channel blocker has been shown to reproduce the classic ECG patterns of early precordial ST-elevation in mutation carriers and in symptomatic patients with borderline ECGs.[47] However, others have reported mixed results and poor reproducibility.[48] Diagnostic criteria[49] have now been formulated which suggest a diagnosis of Brugada Syndrome in patients with: 1) a classic ECG pattern (coved 2mm ST-elevation in V1-3) with either ventricular fibrillation, nonsustained polymorphic ventricular tachycardia, family history of sudden cardiac death under the age of 45, abnormal ST segments in family members, a positive electrophysiologic study, syncope or nocturnal agonal respiration and no other cause for the ECG findings; or, 2) the presence of 2mm "saddleback" ST elevation with conversion to a "coved" pattern with sodium blocker challenge with clinical criteria as above. A non-diagnostic ECG or negative drug challenge in the presence of presence of clinical symptoms warrants repeated evaluations over time.

Treatment

In patients with severe symptoms, ICD therapy is of proven benefit, lowering mortality at three years from 18% to 0% in an Asian SUDS population.[50] Fifteen percent of ICD patients received appropriate therapy, accentuating the fact that ICDs terminate arrhythmias but do not prevent the substrate for their initiation. The molecular genetic and cellular physiology predict that quinidine with both its I_{to} blockade and vagalytic properties represents a potential therapeutic approach; several case reports have demonstrated its efficacy. Adrenergic agonists may also control episodes of incessant VF. Risk stratification algorithms have not been prospectively tested, but appear to suggest that those with symptoms and "coved" ST-elevations represent a minority of patients who

are at highest risk. Patients without these classic findings at baseline are likely at low risk for cardiac events. It is not yet clear how to best manage patients whose ECG reveals an asymptomatic "Brugada Pattern."

Summary and Future Directions

LQTS and Brugada Syndrome are caused by molecular defects in genes that encode the ion channels controlling cardiac repolarization. Our growing understanding of the molecular heterogeneity within these syndromes has provided insight into both the clinical heterogeneity and mechanism of arrhythmogenesis creating opportunity for gene-specific therapy for these illnesses. Significant gaps in our knowledge remain; while the sodium channel defects which cause Brugada Syndrome and LQTS appear to have opposing effects, a sodium channel mutation has been observed which cause a Brugada Syndrome phenotype in some family members and a LQT3 phenotype in others.[51] Additional mutations in the sodium channel have been described that alter depolarization leading to AV block and sinus bradycardia. Such findings suggest that genetic or environmental modifiers may play a substantial role in the clinical phenotype in these entities.

These studies of rare genetic arrhythmias could potentially alter our approach to risk stratification for sudden cardiac death in general. The variation in mutant phenotypes further suggests that some individuals may have quite subtle genetic variations in either channel proteins, or proteins that affect their function. At baseline, these may be sub-clinical but could substantially increase risk for sudden cardiac death in the setting of risk factors such as left-ventricular dysfunction or myocardial infarction. Roden and colleagues have found that up to 10% of patients with acquired LQTS (in which patients are at increased risk for torsades de pointes in the setting of various stressors (including QT-prolonging drugs, LVH and hypokalemia) have polymorphisms or sub-clinical mutations in channel genes.[52] Currently, none have been of sufficient frequency to warrant study in large populations. Further, the ST elevation of Brugada Syndrome is reminiscent of ischemic syndromes suggesting that "Brugada-like" polymorphism could lead to susceptibility to VF in the setting of acute coronary syndromes. In the future, analysis of "high-risk" polymorphisms could be part of a broader noninvasive strategy to prevent sudden cardiac death.

References

1. Khan IA. Clinical and therapeutic aspects of congenital and acquired Long QT Syndrome. *American Journal of Medicine.* 2002;112:58-66.
2. Chiang CC, Roden DM. The Long QT Syndrome: Genetic basis and clinical implications. *Journal of the American College of Cardiology.* 2000;36:1-12.
3. Vincent GM. Long QT syndrome. *Cardiology Clinics.* 2000;18:309-25.

4. Jervell A, Lanfge-Nielsen F. Congenital deaf-mutism, functional heart disease with prolongation of the Q-T interval and sudden death. *American Heart Journal.* 1957;54:59-68.
5. Romano C, Gemme G, Pongiglione R. Aritmie cardiache rare dell'eta' pediatrica. *Clin Pediatr.* 1963;45:656-83.
6. Ward OC. A new familial cardiac syndrome in children. *J Iri Med Assoc.* 1964;54:103-6.
7. Schwartz PJ, Periti M, Malliani A. The long Q-T syndrome. *American Heart Journal.* 1975;89:378-90.
8. Schwartz PJ, Locati E. The idiopathic long QT syndrome: pathogenetic mechanisms and therapy. *European Heart Journal.* 1985;6:103-14.
9. Zipes DP. The Long QT Syndrome: A rosetta stone for sympathetic related ventricular tachyarrhythmias. *Circulation.* 1991;84:1414-19.
10. Moss AJ, Schwartz PJ, Crampton RS, Tzivoni D, Locati EH, MacCluer J, Hall WJ, Weitkamp L, Vincent GM, Garson A, Jr., et al. The long QT syndrome. Prospective longitudinal study of 328 families. *Circulation.* 1991;84:1136-44.
11. Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long QT syndrome. An update. *Circulation.* 1993;88:782-4.
12. Marban E. Cardiac channelopathies. *Nature.* 2002;415:213-8.
13. Liu D-W, Antzelevitch C. Characteristics of the delayed rectifier current (I_{ks} and I_{kr}) in canin ventricular epicardial, midmyocardial and endocardial myocytes. *Circulation Research.* 1995;76:351-365.
14. Abbott GW, Sesti F, Splawski I, Buck ME, Lehmann MH, Timothy KW, Keating MT, Goldstein SA. MiRP1 forms IKr potassium channels with HERG and is associated with cardiac arrhythmia. *Cell.* 1999;97:175-87.
15. Curran ME, Splawski I, Timothy KW, Vincent GM, Green ED, Keating MT. A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. *Cell.* 1995;80:795-803.
16. Splawski I, Tristani-Firouzi M, Lehmann MH, Sanguinetti MC, Keating MT. Mutations in the hminK gene cause long QT syndrome and suppress IKs function. *Nature Genetics.* 1997;17:338-40.
17. Wang Q, Shen J, Splawski I, Atkinson D, Li Z, Robinson JL, Moss AJ, Towbin JA, Keating MT. SCN5A mutations associated with an inherited cardiac arrhythmia, long QT syndrome. *Cell.* 1995;80:805-11.
18. Wang Q, Curran ME, Splawski I, Burn TC, Millholland JM, VanRaay TJ, Shen J, Timothy KW, Vincent GM, de Jager T, Schwartz PJ, Toubin JA, Moss AJ, Atkinson DL, Landes GM, Connors TD, Keating MT. Positional cloning of a novel potassium channel gene: KVLQT1 mutations cause cardiac arrhythmias. *Nature Genetics.* 1996;12:17-23.
19. Mohler PJ, Schott JJ, Gramolini AO, Dilly KW, Guatimosim S, duBell WH, Song LS, Haurogne K, Kyndt F, Ali ME, Rogers TB, Lederer WJ, Escande D, Le Marec H, Bennett V. Ankyrin-B mutation causes type 4 long-QT cardiac arrhythmia and sudden cardiac death.[comment]. *Nature.* 2003;421:634-9.
20. Vincent GM, Timothy KW, Leppert M, Keating M. The spectrum of symptoms and QT intervals in carriers of the gene for the long-QT syndrome.[comment]. *New England Journal of Medicine.* 1992;327:846-52.

21. Priori SG, Napolitano C, Schwartz PJ. Low penetrance in the long-QT syndrome: clinical impact. *Circulation.* 1999;99:529-33.
22. Zareba W, Moss AJ, Schwartz PJ, Vincent GM, Robinson JL, Priori SG, Benhorin J, Locati EH, Towbin JA, Keating MT, Lehmann MH, Hall WJ. Influence of genotype on the clinical course of the long-QT syndrome. International Long-QT Syndrome Registry Research Group. *New England Journal of Medicine.* 1998;339:960-5.
23. Priori S, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Gillo M, Vicentini A, Spazzolini C, Nastoli J, Bottelli G, Folli R, Cappelletti D. Risk stratification in the Long-QT Syndrome. *New England Journal of Medicine.* 2003;348:1866-74.
24. Vincent GM, Zhang L, Timothy K. Long QT Syndrome patients with normal to borderline prolonged QTc intervals are at risk for syncope, cardiac arrest and sudden cardiac death [abstract]. *Circulation.* 1999;100:1272.
25. Splawski I, Shen J, Timothy KW, Lehmann MH, Priori S, Robinson JL, Moss AJ, Schwartz PJ, Towbin JA, Vincent GM, Keating MT. Spectrum of mutations in long-QT syndrome genes. KVLQT1, HERG, SCN5A, KCNE1, and KCNE2. *Circulation.* 2000;102:1178-85.
26. Moss AJ, Zareba W, Kaufman ES, Gartman E, Peterson DR, Benhorin J, Towbin JA, Keating MT, Priori SG, Schwartz PJ, Vincent GM, Robinson JL, Andrews ML, Feng C, Hall WJ, Medina A, Zhang L, Wang Z. Increased risk of arrhythmic events in long-QT syndrome with mutations in the pore region of the human ether-a-go-go-related gene potassium channel. *Circulation.* 2002;105:794-9.
27. Schwartz PJ, Priori SG, Spazzolini C, Moss AJ, Vincent GM, Napolitano C, Denjoy I, Guicheney P, Breithardt G, Keating MT, Towbin JA, Beggs AH, Brink P, Wilde AA, Toivonen L, Zareba W, Robinson JL, Timothy KW, Corfield V, Wattanasirichaigoon D, Corbett C, Haverkamp W, Schulze-Bahr E, Lehmann MH, Schwartz K, Coumel P, Bloise R. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation.* 2001;103:89-95.
28. Ackerman MJ, Tester DJ, Porter CJ. Swimming, a gene-specific arrhythmogenic trigger for inherited long QT syndrome. *Mayo Clinic Proceedings.* 1999;74:1088-94.
29. Wilde AA, Jongbloed RJ, Doevendans PA, Duren DR, Hauer RN, van Langen IM, van Tintelen JP, Smeets HJ, Meyer H, Geelen JL. Auditory stimuli as a trigger for arrhythmic events differentiate HERG-related (LQTS2) patients from KVLQT1-related patients (LQTS1). *Journal of the American College of Cardiology.* 1999;33:327-32.
30. Moss AJ, Robinson JL, Gessman L, Gillespie R, Zareba W, Schwartz PJ, Vincent GM, Benhorin J, Heilbron EL, Towbin JA, Priori SG, Napolitano C, Zhang L, Medina A, Andrews ML, Timothy K. Comparison of clinical and genetic variables of cardiac events associated with loud noise versus swimming among subjects with the long QT syndrome. *American Journal of Cardiology.* 1999;84:876-9.
31. Moss AJ, Zareba W, Benhorin J, Locati EH, Hall WJ, Robinson JL, Schwartz PJ, Towbin JA, Vincent GM, Lehmann MH. ECG T-wave patterns in genetically distinct forms of the hereditary long QT syndrome.[comment]. *Circulation.* 1995;92:2929-34.
32. Zhang L, Timothy KW, Vincent GM, Lehmann MH, Fox J, Giuli LC, Shen J, Splawski I, Priori SG, Compton SJ, Yanowitz F, Benhorin J, Moss AJ, Schwartz PJ, Robinson JL, Wang Q, Zareba W, Keating MT, Towbin JA, Napolitano C, Medina A.

Spectrum of ST-T-wave patterns and repolarization parameters in congenital long-QT syndrome: ECG findings identify genotypes.[comment]. *Circulation.* 2000;102:2849-55.
33. Antzelevitch C. Electrical heterogeneity within the ventricular wall. *Basic Research in Cardiology*. 2001;96:517-27.
34. Shimizu W, Antzelevitch C. Differential effects of beta-adrenergic agonists and antagonists in LQT1, LQT2 and LQT3 models of the long QT syndrome. *Journal of the American College of Cardiology.* 2000;35:778-86.
35. Shimizu W, Antzelevitch C. Cellular basis for the ECG features of the LQT1 form of the long-QT syndrome: effects of beta-adrenergic agonists and antagonists and sodium channel blockers on transmural dispersion of repolarization and torsade de pointes.[comment]. *Circulation.* 1998;98:2314-22.
36. Moss AJ, Zareba W, Hall WJ, Schwartz PJ, Crampton RS, Benhorin J, Vincent GM, Locati EH, Priori SG, Napolitano C, Medina A, Zhang L, Robinson JL, Timothy K, Towbin JA, Andrews ML. Effectiveness and limitations of beta-blocker therapy in congenital long-QT syndrome.[comment]. *Circulation.* 2000;101:616-23.
37. January CT, Gong Q, Zhou Z. Long QT syndrome: cellular basis and arrhythmia mechanism in LQT2. *Journal of Cardiovascular Electrophysiology.* 2000;11:1413-8.
38. Compton SJ, Lux RL, Ramsey MR, Strelich KR, Sanguinetti MC, Green LS, Keating MT, Mason JW. Genetically defined therapy of inherited long-QT syndrome. Correction of abnormal repolarization by potassium.[comment]. *Circulation.* 1996;94:1018-22.
39. Schwartz PJ, Priori SG, Locati EH, Napolitano C, Cantu F, Towbin JA, Keating MT, Hammoude H, Brown AM, Chen LS. Long QT syndrome patients with mutations of the SCN5A and HERG genes have differential responses to Na+ channel blockade and to increases in heart rate. Implications for gene-specific therapy.[comment]. *Circulation.* 1995;92:3381-6.
40. Groh WJ, Silka MJ, Oliver RP, Halperin BD, McAnulty JH, Kron J. Use of implantable cardioverter-defibrillators in the congenital long QT syndrome. *American Journal of Cardiology.* 1996;78:703-6.
41. Van Langen IM, Birnie E, Alders M, Jongbloed RJ, Le Marec H, Wilde AA. The use of genotype-phenotype correlations in mutation analysis for the long QT syndrome. *Journal of Medical Genetics.* 2003;40:141-5.
42. Brugada J, Brugada R, Antzelevitch C, Towbin J, Nademanee K, Brugada P. Long-term follow-up of individuals with the electrocardiographic pattern of right bundle-branch block and ST-segment elevation in precordial leads V1 to V3. *Circulation.* 2002;105:73-8.
43. Antzelevitch C, Brugada J, Brugada R, Shimizu M, Gussak I, Perez Riera AR. Brugada Syndrome: A decade of progress. *Circulation Research.* 2002;91:1114-1118.
44. Priori SG, Napolitano C, Gasparini M, Pappone C, Della Bella P, Brignole M, Giordano U, Giovannini T, Menozzi C, Bloise R, Crotti L, Terreni L, Schwartz PJ. Clinical and genetic heterogeneity of right bundle branch block and ST-segment elevation syndrome: A prospective evaluation of 52 families. *Circulation.* 2000;102:2509-15.
45. Chen Q, Kirsch GE, Zhang D, Brugada R, Brugada J, Brugada P, Potenza D, Moya A, Borggrefe M, Breithardt G, Ortiz-Lopez R, Wang Z, Antzelevitch C, O'Brien RE,

Schulze-Bahr E, Keating MT, Towbin JA, Wang Q. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. *Nature.* 1998;392:293-6.
46. 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.
47. Brugada R, Brugada J, Antzelevitch C, Kirsch GE, Potenza D, Towbin JA, Brugada P. 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.
48. Priori SG, Napolitano C, Gasparini M, Pappone C, Della Bella P, Giordano U, Bloise R, Giustetto C, De Nardis R, Grillo M, Ronchetti E, Faggiano G, Nastoli J. Natural history of Brugada syndrome: insights for risk stratification and management. *Circulation.* 2002;105:1342-7.
49. Wilde AA, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, Corrado D, Hauer RN, Kass RS, Nademanee K, Priori SG, Towbin JA, Study Group on the Molecular Basis of Arrhythmias of the European Society of C. Proposed diagnostic criteria for the Brugada syndrome: consensus report. *Circulation.* 2002;106:2514-9.
50. Nademanee K, Veerakul G, Mower M, Likittanasombat K, Krittayapong R, Bhuripanyo K, Sitthisook S, Chaothawee L, Lai MY, Azen SP. Defibrillator Versus beta-Blockers for Unexplained Death in Thailand (DEBUT): a randomized clinical trial.[comment]. *Circulation.* 2003;107:2221-6.
51. Priori SG, Napolitano C, Schwartz PJ, Bloise R, Crotti L, Ronchetti E. The elusive link between LQT3 and Brugada syndrome: the role of flecainide challenge. *Circulation.* 2000;102:945-7.
52. Yang P, Kanki H, Drolet B, Yang T, Wei J, Viswanathan PC, Hohnloser SH, Shimizu W, Schwartz PJ, Stanton M, Murray KT, Norris K, George AL, Jr., Roden DM. Allelic variants in long-QT disease genes in patients with drug-associated torsades de pointes. *Circulation.* 2002;105:1943-8.