Korean J Physiol Pharmacol
Vol 6: 1–7, February, 2002

Congenital LQT Syndromes: From Gene to Torsade de Pointes

Edward Carmeliet

Department of Physiology, K.U.L. University Leuven, Belgium

Congenital Long QT syndrome (LQTs) is a relatively rare pathologic disorder but results frequently in sudden cardiac death. Of the six LQTs that have been clinically described, five have been worked out for their genetic and biophysical profile. Most are generated by mutations which cause a loss of function in two delayed K^+currents, i_{Ks} and i_{Kr}. One syndrome is generated by mutations in the Na^+ channel which causes essentially a gain of function in the channel. Clinically the syndromes are characterized by slowed repolarization of the cardiac ventricular action potential and the occurrence of typical arrhythmias with undulating peaks in the electrocardiogram, called Torsade de Pointes. Arrhythmias are initiated by early or delayed afterdepolarizations and continue as reentry. Triggers for cardiac events are exercise (swimming; LQT1), emotion (arousal; LQT2) and rest/sleep (LQT3). β-blockers have a high efficacy in the treatment of LQT1 and LQT2. In LQT3 their use is questionable. The study of congenital LQTsyndromes is a remarkable example of how basic and clinical science converge and take profit of each other's contribution.

Key Words: Arrhythmia, Congenital LQT, Delayed K^+ currents, Persistent Na^+ current, Torsade de pointes, β-block

INTRODUCTION

The first congenital Long QT syndrome (LQTs), later known as the Jervell, Lange-Nielsen syndrome, was described for an Norwegian family with 6 children and consisted of deaf-mutism, long QT interval in the electrocardiogram (ECG) and sudden death (Roden et al, 1995). The ECG of the parents was normal; 4 children were born deaf-mute, had an ECG with prolonged QT, frequent syncopes and in 3 cases these were lethal before the age of ten. Heredity is autosomal recessive. The second syndrome, known as Romano-Ward syndrome is also characterized by a long QT and sudden death but no deaf-mutism; heredity is autosomal dominant.

The lethal effects are caused by typical ventricular arrhythmias known as torsade de pointes arrhythmia (TdP). This arrhythmia, first described by Dessertenne (Dessertenne, 1966), a French cardiologist, has a very typical ECG signature. The ventricular complexes are polymorphous in nature and show characteristic undulating peaks, forming a torsade. In many cases the arrhythmia spontaneously stops with return to normal sinus rhythm. In some however, the situation worsens and the arrhythmia evolves into ventricular fibrillation and syncope.

Genetics and biophysical profile

Information on the genes and biophysical correlates is available for the different clinical syndromes with the exception of LQT4. In four LQT syndromes (LQT 1, 2, 5 and 6), mutations are present in K^+ channels; in the LQT3 syndrome mutations are situated in the Na^+ channel.

The autosomal dominant Romano-Ward syndrome corresponds to mutations on 5 different genes (Schwartz et al, 1995). In four of these syndromes (LQT 1, 2, 5 and 6) mutations are present in K^+ channels and affect two delayed K^+ currents, i_{Ks} and i_{Kr}, which play an important role in the repolarization process of the cardiac action potential. The K^+ channel mutations for the i_{Ks} current affect the *K_vLQT1*- or *KCNQ1*-gene (LQT1) and the *MinK*- or *KCNE1*-gene (LQT5), for the i_{Kr} current the *HERG*- or *KCNH2*-gene (LQT2) and the *MiRP1*- or *KCNE2*-gene (LQT6) are mutated. Mutations in the K^+ channels are usually, but not always, accompanied by a decrease of function caused by a variety of underlying mechanisms. A summary of the biophysical changes and corresponding mutations is given in Table 1 (the list of the mutations is not exhaustive). As major changes distinction is made between absence of function or change in function. Absence of function can be due to the presence of non-conducting channels in the plasma membrane or deficiency in the processing, i.e. retention of the proteins in the endoplasmic reticulum or less synthesis and increased proteolysis. A change in function is evident as changes in gating (activation, inactivation) or in permeation (fall in unitary current or shift in selectivity from K^+ to Na^+).

In the LQT3 syndrome mutations are present in the Na^+ channel. In most cases the mutations result in an augmentation or gain of function, which is due to the existence of a late or persistent current (see (Balser, 2001) and Table 2). A typical example is a mutation in which the KPQ

Corresponding to: Edward Carmeliet, Department of Physiology, K.U.L. University Leuven, Gasthuisberg, Herestraat, 49, 3000 Leuven, Belgium. (Tel) 32 16 402823, (Fax) 32 16 347139, (E-mail) edward.carmeliet@med.kuleuven.ac.be.

ABBREVIATIONS: LQTs, long QT syndrome; ECG, electrocardiogram; TdP, torsade de pointes; EAD, early afterdepolarization; DAD, delayed afterdepolarization; APD, action potential duration.

Table 1. Biophysical changes in K^+ channels induced by mutations (examples)

1. Absence of function		Gene mutation
Non-conducting channel protein in plasma membrane		*KCNH2*-G628S (1)
		KCNE1-T59P/L60P (2)
		KCNQ1-Y281C (3)
Abnormal channel processing	Retention in endoplasmic reticulum	*KCNH2*-A561V (4)
		KCNH2-R752W (5)
		KCNH2-Y611H (6)
	Less synthesis, increased proteolysis	*KCNH2*-A561V (7)
2. Change in function		
Gating	Negative shift inactivation, causing more inward rectification	*KCNH2*-T474I, -A614V, -V630L (8)
	Accelerated activation and deactivation	*KCNH2*-S818L (9)
	Positive shift activation and faster deactivation	*KCNQ1*-R555C (10)
	Induced inactivation	*KCNQ1*-L273F (11)
	Slow opening, fast deactivation	*KCNE2*- Q9E (12)
Permeation	Decrease in single channel conductance	*KCNE1*-S74L (13)
	Change in selectivity, increase in Na^+ permeability	*KCNH2*-N629D (14)
Blocking properties	Increased block by antibiotics	*KCNE2*-Q9E (15)

(1) (Zhou et al, 1998), (2) (Huang et al, 2001), (3) (Bianchi et al, 2000), (4) (Ficker et al, 2000a), (5) (Ficker et al, 2000b), (6) (Zhou et al, 1998), (7) (Kagan et al, 2000), (8) (Nakajima et al, 1998), (9) (Nakajima et al, 2000), (10) (Chouabe et al, 1997), (11) (Seebohm et al, 2001), (12) (Abbott et al, 1999), (13) (Sesti & Goldstein, 1998), (14) (Lees-Miller et al, 2000), (15) (Abbott et al, 1999)

Table 2. Mutations in Na^+ channel *SCN5A* and associated biophysical changes

Persistent current combined with accelerated rate of inactivation and of recovery	△KPQ (1)
Positive shift of inactivation leading to more window current	L619F (2)
Slow inactivation and slow recovery from inactivation leading to less current at elevated rates	1795insD (3)
Decrease in fast Na^+ current during upstroke leads to increased Ca^{2+} influx and Ca^{2+} load at low rates, with stimulation of Na^+,Ca^{2+} exchange current	D1790G (4)
Positive shift of window current due to positive shift of inactivation and activation	E1295K (5)
Increased sensitivity to lidocaine block	R1623Q (6)
to flecainide block	△KPQ (7, 8)
	1795insD (7)
to pilsicainide	△KPQ (9)

(1) (Chandra et al, 1998), (2) (Wehrens et al, In preparation), (3) (Veldkamp et al, 2000), (4) (Wehrens et al, 2000), (5) (Abriel et al, 2001), (6) (Kambouris et al, 2000), (7) (Viswanathan et al, 2001), (8) (Nagatomo et al, 2000), (9) (Ono et al, 2000)

aminoacids in the linker between domain 3 and 4 of the channel protein are deleted. It is known that this linker plays an important role in the inactivation process. The cardiac Na^+ current i_{Na} in these mice is characterized by the existence of a slowly inactivating component which persists during the plateau of the action potential; at the same time the fast component is largely increased. The action potential is prominently lengthened at slow rates and the slope of the QT-RR relation is increased. At the same time the tendency to develop early afterdepolarizations (EADs) is enhanced and spontaneous polymorphous arrhythmias resembling TdPs occur (Nuyens et al, 2001).

In the L619F mutation the persistent current is combined with a positive shift of steady state inactivation resulting in a broader voltage range of increased window current (Wehrens et al, In preparation). The QT interval is markedly prolonged and causes a functional 2 : 1 auriculoventricular block because of excessive prolongation of the action potential in the specialized conduction system. In the 1795insD mutation (Veldkamp et al, 2000) the persistent current is associated with slow recovery from inactivation. The combination of these two functional changes in current is of special importance. The persistent current is responsible for the long QT at low rates of stimulation but the

slow recovery causes fall in fast Na^+ current at high rates, simulating the Brugada syndrome (Brugada & Brugada, 1992).

Not all mutations of the *SCN5A* generate persistent current. The mutation (D1790G) instead causes a reduction in fast Na^+ current, due to a speeding-up of inactivation and a negative shift of the inactivation curve (An et al, 1998). And yet QT is prolonged. A theoretical study based on the Luo-Rudy model provides a possible explanation (Wehrens et al, 2000): the slower upstroke velocity and smaller overshoot of the action potential leads to a larger Ca^{2+} inward movement, extra Ca^{2+} load of the sarcoplasmic reticulum, a rise in the Ca^{2+} transient and an increase of the inward Na^+, Ca^{2+} exchange current. At the same time the smaller depolarization also causes less I_{Ks} activation anf thus less outward current. The final effect is marked prolongation of the action potential duration (APD) especially at low rates. In another mutation (E1295K), both activation and inactivation are shifted in the positive direction (Abriel et al, 2001). As a consequence the window current, although not increased, occurs at more positive potentials. At these potentials the inward rectifier K^+ current, I_{K1}, and the delayed K^+ current, I_{Kr}, show stronger inward rectification and thus carry less outward current. The fall in outward current is responsible for the prolongation of the APD.

The autosomal recessive Jervell and Lange-Nielsen syndrome is generated by mutations on *KCNQ1* or *KCNE1* present in the two alleles with resultant loss of function of I_{Ks} current. The I_{Ks} current plays an important role not only in the heart but also in the inner ear (Casimiro et al, 2001; Vetter et al, 1996), in intestinal and renal epithelia and in zona glomerulosa cells of the adrenal cortex (Arrighi et al, 2001) (see section clinical and physiological phenotypes).

Genesis of arrhythmia: triggered activity and reentry

Distinction should be made between the initiation and the continuation of an arrhythmia. As initiating stimulus for TdP arrhythmia, early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs) play an important role. EADs usually are grafted on a slowed and prolonged repolarization. The slowed repolarization (long QT) is due to a fall in outward current or a rise in inward current (Kass & Davies, 1996; Shimizu & Antzelevitch, 1999). Prolongation of APD is especially pronounced at low rates or following a pause. The onset of TdP has been associated with bradycardia or pauses of sinus rhythm. When the rate of repolarization falls below a critical level, a secondary depolarization can ensue due to reactivation of the L-type Ca^{2+} current. When of sufficient amplitude the result is a propagated extrasystole. Experimental as well as modeling studies (Viswanathan & Rudy, 1999) have shown that pause-induced EADs develop preferentially in midmyocardial M cells. Abnormal slowing of the heart rate can be avoided by pacing with algorithms preventing pauses (Viskin, 2000) and is especially indicated in LQT3 patients who are particularly prone to develop TdP at rest or during sleep when the heart rate is low.

In contrast to EADs, which are pause-related, DADs are more probable when heart rate is high. As shown in table 3, TdP arrhythmia is frequently associated with exercise and stress, situations in which the sympathetic system is overactive. β-receptor stimulation leads to increased levels of intracellular Ca^{2+}, indirectly via the enhanced heart rate and directly via activation of the L-type Ca^{2+} current. A higher intracellular Ca^{2+} load is accompanied by an enhanced propensity to generate DADs (Wu et al, 1999a; Wu et al, 1999b; Burashnikov & Antzelevitch, 2000).

The extra beat triggered by EAD or DAD excites cells in which excitability has sufficiently recovered. However this recovery is inhomogeneous, because of the existence of dispersion in the repolarization process. Dispersion is accompanied by a longer vulnerable period and a greater probability of unidirectional conduction, conditions favourable for reentry. In LQT3, dispersion is especially pro-

Table 3. Clinical phenotypes, triggers, sympathetic agonists and antagonists

	LQT1	LQT2	LQT3
Gene mutated	*KCNQ1*	*KCNH2*	*SCN5A*
Current affected	Loss of i_{Ks}	Loss of i_{Kr}	Gain i_{Na}
Events with (1)			
Exercise	62%	13%	13%
Emotion	26%	43%	19%
Sleep/rest	3%	29%	39%
Other	9%	15%	29%
Specific triggers	Swimming	Noise (arousal)	
β-Blockers (1,2) efficacy in patients	High	Medium	Questionable
In animal models (3,4,5)	Antiarrhythmic	Antiarrhythmic	Proarrhythmic
Isoproterenol (cellular and animal models)	Proarrhythmic: increased dispersion (4,5)	Proarrhythmic: transient increase of dispersion (5)	Antiarrhythmic (6): block of transient prolongation APD Proarrhythmic: EAD

Based on data published in (1) (Schwartz et al, 2001), (2) (Moss et al, 2000), (3) (Shimizu & Antzelevitch, 1999), (4) (Shimizu & Antzelevitch 1998), (5) (Shimizu & Antzelevitch, 2000), (6) (Nuyens et al, 2001)

nounced when the action potential is abnormally lengthened at low rates (Viskin, 2000) but also occurs during rate acceleration. In a transgenic △KPQ-LQT3 mouse model sudden acceleration is accompanied by transient prolongation of APD with EADs and induction of runs of extrasystoles and polymorphous arrhythmia (Nuyens et al, 2001). TdP-like arrhythmia was also induced in this model by extrasystolic or long-short-long pacing.

The typical torsade-type changes in the QRS axis during TdP has been attributed to the existence of a rather long reentry pathway. It is most of the time accompanied by T-wave alternans. According to a tridimensional analysis of the anthopleurin model (LQT3 model) the initial beat consistently arose as a subendocardial focal activity, whereas subsequent beats were due to reentrant excitation in the form of rotating scrolls (El-Sherif et al, 1997). In most cases the transition in QRS axis coincided with the transient bifurcation of a predominantly single rotating scroll into two simultaneous scrolls involving both the right and left ventricle separately. In 4 of 26 episodes a single circuit changed its location from beat to beat.

Clinical and physiological phenotypes

LQT1: The majority of the cardiac events (62%) (Schwartz et al, 2001) in LQT1 patients occurs during exercise, 26% during emotional stress and only 3% during rest or sleep. Swimming as a trigger is particularly frequent (33%). Most cardiac events occur during young age (60% before the age of 15 year). Elevation of the sympathetic tone seems to play an important role and β-blocker therapy is efficient (Schwartz et al, 2001). Intravenous injection of epinephrine markedly prolongs the QT interval in LQT1 patients (Noda et al, 2001). In animal and cellular models dispersion is sensibly increased in the presence of isoproterenol, the effect being due to prolongation of the action potential in midmyocardial cells while shortening occurs in subepicardial and subendocardial cells. The disparate effects on subepicardial cells and midmyocardial cells cause increased dispersion and enhanced probability of unidirectional conduction (Shimizu & Antzelevitch, 1998; Shimizu & Antzelevitch, 2000). An explanation can be found in the fact that sympathetic stimulation stimulates i_{Ks} and thus exerts a shortening effect on the action potential duration. This last effect however, only occurs when i_{Ks} is sufficiently present. When i_{Ks} is less expressed (as in LQT1 and LQT5), the repolarization reserve will be much less, especially in midmyocardial cells.

In these cells then, instead of the shortening by increased i_{Ks}, a stimulatory effect on the the L-type Ca^{2+} current causes prolongation of the action potential.

The association of deafness in the Jervell, Lange-Nielsen syndrome has found an explanation in the fact that the i_{Ks} current in the stria vascularis plays an important role in the formation of the endolymph in the middle ear (Table 4). Studies on transgenic mice with knockout for the *KCNE1* (Vetter et al, 1996) or *KCNQ1* (Casimiro et al, 2001), have shown deficient production of endolymph, a solution which normally contains an elevated K^+ concentration. In these mice, auditory cells undergo a secondary degeneration caused by the absence of the secretion of endolymph, resulting in deafness.

Recent findings in this mouse model have shown (Arrighi et al, 2001) that *KCNE1*-deficient mice have also lower K^+ plasma concentration, which can be considered an arrhythmogenic compounding factor. Aldosterone levels are increased and probably the main reason for the hypokalemia by promoting K^+ secretion in the kidney and intestine. The high aldosterone levels are the consequence of activation of the renin-angiotensin axis. In the zona glomerulosa cells of the adrenal cortex, excessive aldosterone production is normally prohibited by activation of I_{Ks} current. This protective mechanism is absent in the mice, lacking the *KCNE1* peptide.

LQT2: In LQT2 patients most of the cardiac events (43%) occur during emotional stress, with 26% elicited by auditory stimuli, 13% during exercise (Schwartz et al, 2001). Intravenous injection of epinephrine causes a transient prolongation of the QT interval (Noda et al, 2001). Also in animal cellular models, in which i_{Kr} is blocked by E-4031 or dofetilide, isoproterenol transiently prolongs the action potential (Priori et al, 1996) and increases dispersion (Shimizu & Antzelevitch, 2000). An elevated sympathetic tone is thus proarrhythmic in the LQT2 syndrome. It should be noted however that 29% of the cardiac events also occur during rest/sleep.

LQT3: LQT3 syndrome is rare but the severity of cardiac events is greater than in the other syndromes: death occurs in 20% of the first event in contrast to only 4% in the other syndromes. LQT3 complications also occur later in life (less than 10% at the age of 15 year). The syncopes occur for 39% of the genotypic patients during the night or at rest (Schwartz et al, 2001) when cardiac frequency is very low. QT interval lengthening is then most pronounced (Stramba-Badiale et al, 2000). Excessive prolongation of the action potential is accompanied by an increased probability to develop EADs, responsible for the initiation of the arrhythmia. Pacing to avoid abnormal prolongation of APD is therefore a useful therapeutic intervention. An increase in rate causes acceleration of the repolarization process which is more pronounced in LQT3 patients (Schwartz et al, 1995) and in LQT3 cellular models (Priori et al, 1996) than in LQT2.

It should be stressed that a non-negligible fraction of cardiac events in the LQT3 occurs during exercise (13%) or emotion (19%) (Ali et al, 2000; Schwartz et al, 2001), situations in which sympathetic tone and heart rate may be expected to increase. The question thus raises to what extent the higher probability of arrhythmias under these conditions is due to the enhanced sympathetic tone or to the rate as such. In vitro experiments on heterozygotic mice preparations with △KPQ mutation have shown that sudden

Table 4. Multiple organs affected in the Jervell, Lange-Nielsen LQTs (KCNQ1 and KCNE1)

Cardiac cells	Inner ear	Intestine and kidney	Adrenal cortex
Fall in i_{Ks} current LQT and TdP arrhythmia	Deafness, insufficient K^+ secretion in stria vascularis	Loss of K^+, enhanced Na^+ absorption	Increased production of aldosterone

acceleration of the rate causes a transient lengthening of the action potential. This paradoxical lengthening is frequently accompanied by EADs and generation of TdP arrhythmias. When the rate is increased in the presence of isoproterenol however, the transient lengthening and the EADs are prevented. A further indication that isoproterenol exerts antiarrhythmic activity in this model was shown by the higher maximum following frequency and the low efficiency of long-short-long pacing in eliciting reentry arrhythmia. From these observations it can be concluded that an increase in sympathetic drive which results in an enhanced sinus rate alone without neurosecretion at the ventricular level should be considered dangerous. Such situation occurs when activity of the right stellate ganglion dominates the activity of the left stellate ganglion. The sinus node is selectively innervated by postganglionic nerves of the right stellate ganglion while most of the ventricular myocardium is governed by the left stellate ganglion (Ben-David & Zipes 1988; Fujiki et al, 1999).

A note on therapy

β-blockers are the mainstay therapy for LQT1 and LQT2 patients. This is reasonable since most of the arrhythmias in these patients (Schwartz et al, 2001) occur in the presence of sympathetic overdrive: emotion and exercise together account for 88% of the cardiac events in LQT1 and for 56% in LQT2. Consistent with this observation β-receptor stimulation has been shown to cause prolongation of APD and enhanced dispersion in cellular models of LQT1 and LQT2 (Priori et al, 1996; Shimizu & Antzelevitch, 2000), and should be considered arrhythmogenic.

For LQT3 patients however the usefulness of β-receptor blocker therapy has been questioned (Moss et al, 2000). During rest or sleep, when most cardiac events occur, β-receptor antagonism may further slow heart rate and promote arrhythmias. At elevated heart rates on the other hand, β-receptor agonism (isoproterenol) exerts antiarrhythmic activity in the ΔKPQ transgenic mouse model (Nuyens et al, 2001). In LQT3 patients (Noda et al, 2001) and in LQT3 cellular models (Priori et al, 1996; Shimizu & Antzelevitch, 2000) β-receptor stimulation antagonizes LQT and causes shortening of the APD, independent of the rate. In a cellular model of LQT3 propranolol on the other hand has been shown to facilitate the occurrence of arrhythmias (Shimizu & Antzelevitch, 1999).

The use of β-blockers in the therapy of LQT3 thus remains questionable and other therapeutic interventions should be considered, such as defibrillators, pacemakers and Na^+ channel blockers. It has been known for a long time that the late or persistent Na^+ current is very sensitive to Na^+ channel block by tetrodotoxin (Coraboeuf et al, 1979). Mutations in the Na^+ channel are accompanied by important changes in the sensitivity to drugs. The late (persistent) Na^+ current of the LQT3 mutant channel (ΔKPQ) for instance is more sensitive to flecainide (Nagatomo et al, 2000) and pilsicainide (Ono et al, 2000) block than the peak Na^+ current (normal and mutant channel). In patients with a D1790G mutation, flecainide was highly effective while lidocaine was not (Benhorin et al, 2000). In another LQT3 mutant (R1623Q) however, an unusual high sensitivity to inactivated state block by lidocaine has been demonstrated. These changes in sensitivity should be taken into account when planning drug therapy.

CONCLUSION

The study of congenital LQT syndromes is a remarkable example of how basic and clinical science converge and take profit of the each other's contribution. This type of research has not only helped clinicians to direct more carefully their therapy but has importantly facilitated the understanding of how ionic channels function and how they are modulated. The results have amplified our knowledge in basic and applied electrophysiology. The impact is not restricted to the congenital LQT syndrome but implies also acquired forms of LQT, hypertrophy and heart failure. It is hoped that this knowledge may improve therapy based on a more efficient modulation of ionic channels or even by directly interfering with their genetic expression.

REFERENCES

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* 97: 175–187, 1999

Abriel H, Cabo C, Wehrens XH, Rivolta I, Motoike HK, Memmi M, Napolitano C, Priori SG, Kass RS. Novel arrhythmogenic mechanism revealed by a long-QT syndrome mutation in the cardiac Na^+ channel. *Circ Res* 88: 740–745, 2001

Ali RH, Zareba W, Moss AJ, Schwartz, PJ, Benhorin, J, Vincent GM, Locati EH, Priori S, Napolitano C, Towbin JA, Hall WJ, Robinson JL, Andrews ML, Zhang L, Timothy K, Medina A. Clinical and genetic variables associated with acute arousal and nonarousal-related cardiac events among subjects with long QT syndrome. *Am J Cardiol* 85: 457–461, 2000

An RH, Wang XL, Kerem B, Benhorin, J, Medina A, Goldmit M, Kass RS. Novel LQT-3 mutation affects Na^+ channel activity through interactions between α- and β_1-subunits. *Circ Res* 83: 141–146, 1998

Arrighi I, Bloch-Faure M, Grahammer F, Bleich M, Warth R, Mengual R, Drici MD, Barhanin J, Meneton P. Altered potassium balance and aldosterone secretion in a mouse model of human congenital long QT syndrome. *Proc Natl Acad Sci USA* 98: 8792–8797, 2001

Balser JR. The cardiac sodium channel: gating function and molecular pharmacology. *J Mol Cell Cardiol* 33: 599–613, 2001

Ben-David J, Zipes DP. Differential response to right and left ansae subclaviae stimulation of early afterdepolarizations and ventricular tachycardia induced by cesium in dogs. *Circulation* 78: 1241–1250, 1988

Benhorin J, Taub R, Goldmit M, Kerem B, Kass RS, Windman I, Medina A. Effects of flecainide in patients with new SCN5A mutation: mutation-specific therapy for long-QT syndrome? *Circulation* 101: 1698–1706, 2000

Bianchi L, Priori SG, Napolitano C, Surewicz KA, Dennis AT, Memmi M, Schwartz PJ, Brown AM. Mechanisms of I_{Ks} suppression in LQT1 mutants. *Am J Physiol* 279: H3003–3011, 2000

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* 20: 1391–1396, 1992

Burashnikov A, Antzelevitch C. Block of I_{Ks} does not induce early afterdepolarization activity but promotes beta-adrenergic agonist-induced delayed afterdepolarization activity. *J Cardiovasc Electrophysiol* 11: 458–465, 2000

Casimiro MC, Knollmann BC, Ebert SN, Vary JC Jr, Greene AE, Franz MR, Grinberg A, Huang SP, Pfeifer K. Targeted disruption of the Kcnq1 gene produces a mouse model of Jervell and Lange-Nielsen Syndrome. *Proc Natl Acad Sci USA* 98: 2526–2531, 2001

Chandra R, Starmer CF, Grant AO. Multiple effects of KPQ deletion mutation on gating of human cardiac Na^+ channels

expressed in mammalian cells. *Am J Physiol* 274: H1643–1654, 1998

Chouabe C, Neyroud N, Guicheney P, Lazdunski M, Romey G, Barhanin J. Properties of KvLQT1 K^+ channel mutations in Romano-Ward and Jervell and Lange-Nielsen inherited cardiac arrhythmias. *Embo J* 16: 5472–5479, 1997

Coraboeuf E, Deroubaix E, Coulombe A. Effect of tetrodotoxin on action potentials of the conducting system in the dog heart. *Am J Physiol* 236: H561–567, 1979

Dessertenne F. La tachycardie ventriculaire à deux foyers opposés variables. *Arch Mal Coeur Vaiss* 59: 263–272, 1966

El-Sherif N, Chinushi M, Caref EB, Restivo M. Electrophysiological mechanism of the characteristic electrocardiographic morphology of torsade de pointes tachyarrhythmias in the long-QT syndrome: detailed analysis of ventricular tridimensional activation patterns. *Circulation* 96: 4392–4399, 1997

Ficker E, Dennis AT, Obejero-Paz CA, Castaldo P, Taglialatela M, Brown AM. Retention in the endoplasmic reticulum as a mechanism of dominant-negative current suppression in human long QT syndrome. *J Mol Cell Cardiol* 32: 2327–2337, 2000a

Ficker E, Thomas D, Viswanathan PC, Dennis AT, Priori SG, Napolitano C, Memmi M, Wible BA, Kaufman ES, Iyengar S, Schwartz PJ, Rudy Y, Brown AM. Novel characteristics of a misprocessed mutant HERG channel linked to hereditary long QT syndrome. *Am J Physiol* 279: H1748–1756, 2000b

Fujiki A, Masuda A, Inoue H. Effects of unilateral stellate ganglion block on the spectral characteristics of heart rate variability. *Jpn Circ J* 63: 854–858, 1999

Huang L, Bitner-Glindzicz M, Tranebjaerg L, Tinker A. A spectrum of functional effects for disease causing mutations in the Jervell and Lange-Nielsen syndrome. *Cardiovasc Res* 51: 670–680, 2001

Kagan A, Yu Z, Fishman GI, McDonald TV. The dominant negative LQT2 mutation A561V reduces wild-type HERG expression. *J Biol Chem* 275: 11241–11248, 2000

Kambouris NG, Nuss HB, Johns DC, Marban E, Tomaselli GF, Balser JR. A revised view of cardiac sodium channel "blockade" in the long-QT syndrome. *J Clin Invest* 105: 1133–1140, 2000

Kass RS, Davies MP. The roles of ion channels in an inherited heart disease: molecular genetics of the long QT syndrome. *Cardiovasc Res* 32: 443–454, 1996.

Lees-Miller JP, Duan Y, Teng GQ, Thorstad K, Duff HJ. Novel gain-of-function mechanism in K^+ channel-related long-QT syndrome: altered gating and selectivity in the HERG1 N629D mutant. *Circ Res* 86: 507–513, 2000

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 β-blocker therapy in congenital long-QT syndrome. *Circulation* 101: 616–623, 2000

Nagatomo T, January CT, Makielski JC. Preferential block of late sodium current in the LQT3 KPQ mutant by the class I_c antiarrhythmic flecainide. *Mol Pharmacol* 57: 101–107, 2000

Nakajima T, Furukawa T, Tanaka T, Katayama Y, Nagai R, Nakamura Y, Hiraoka M. Novel mechanism of HERG current suppression in LQT2: shift in voltage dependence of HERG inactivation. *Circ Res* 83: 415–422, 1998

Nakajima T, Kurabayashi M, Ohyama Y, Kaneko Y, Furukawa T, Itoh T, Taniguchi Y, Tanaka T, Nakamura Y, Hiraoka M, Nagai R. Characterization of S818L mutation in HERG C-terminus in LQT2. Modification of activation-deactivation gating properties. *FEBS Lett* 481: 197–203, 2000

Noda T, Takaki H, Kurita T, Taguchi H, Suyama K, Aihara N, Kamakura S, Nakamura K, Ohe T, Towbin JA, Priori SG. Differential response of dynamic ventricular repolarization to sympathetic stimulation in LQT1, LQT2 and LQT3 forms of congenital Long QT syndrome. *PACE* 24: 589, 2001

Nuyens D, Stengl M, Dugarmaa S, Rossenbacker T, Compernolle V, Rudy Y, Smits JF, Flameng W, Clancy CE, Moons L, Vos MA, Dewerchin M, Benndorf K, Collen D, Carmeliet E, Carmeliet P. Abrupt rate accelerations or premature beats cause life-threatening arrhythmias in mice with long-QT3 syndrome. *Nat Med* 7: 1021-1027, 2001

Ono K, Kaku T, Makita N, Kitabatake A, Arita M. Selective block of late currents in the $\triangle$KPQ Na^+ channel mutant by pilsicainide and lidocaine with distinct mechanisms. *Mol Pharmacol* 57: 392–400, 2000

Priori SG, Napolitano C, Cantu F, Brown AM, Schwartz PJ. Differential response to Na^+ channel blockade, β-adrenergic stimulation, and rapid pacing in a cellular model mimicking the SCN5A and HERG defects present in the long-QT syndrome. *Circ Res* 78: 1009–1015, 1996

Roden DM, George AL, Bennett PB. Recent advances in understanding the molecular mechanisms of the long QT syndrome. *J Cardiovasc Electrophysiol* 6: 1023–1031, 1995

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. *Circulation* 92: 3381–3386, 1995

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* 103: 89–95, 2001

Seebohm G, Scherer CR, Busch AE, Lerche C. Identification of specific pore residues mediating KCNQ1 inactivation. A novel mechanism for long QT syndrome. *J Biol Chem* 276: 13600–13605, 2001

Sesti F, Goldstein SA. Single-channel characteristics of wild-type I_{Ks} channels and channels formed with two minK mutants that cause long QT syndrome. *J Gen Physiol* 112: 651–663, 1998

Shimizu W, Antzelevitch C. Cellular basis for the ECG features of the LQT1 form of the long-QT syndrome. Effects of β-adrenergic agonists and antagonists and sodium channel blockers on transmural dispersion of repolarization and torsade de pointes. *Circulation* 98: 2314–2322, 1998

Shimizu W, Antzelevitch C. Cellular basis for long QT, transmural dispersion of repolarization, and torsade de pointes in the long QT syndrome. *J Electrocardiol* 32: 177–184, 1999

Shimizu W, Antzelevitch C. Differential effects of β-adrenergic agonists and antagonists in LQT1, LQT2 and LQT3 models of the long QT syndrome. *J Am Coll Cardiol* 35: 778–786, 2000

Stramba-Badiale M, Priori SG, Napolitano C, Locati EH, Vinolas X, Haverkamp W, Schulze-Bahr E, Goulene K, Schwartz PJ. Gene-specific differences in the circadian variation of ventricular repolarization in the long QT syndrome: a key to sudden death during sleep? *Ital Heart J* 1: 323–328, 2000

Veldkamp MW, Viswanathan PC, Bezzina C, Baartscheer A, Wilde AA, Balser JR. Two distinct congenital arrhythmias evoked by a multidysfunctional Na^+ channel. *Circ Res* 86: E91–97, 2000

Vetter DE, Mann JR, Wangemann P, Liu J, McLaughlin KJ, Lesage F, Marcus DC, Lazdunski M, Heinemann SF, Barhanin J. Inner ear defects induced by null mutation of the isk gene. *Neuron* 17: 1251–1264, 1996

Viskin S. Cardiac pacing in the long QT syndrome: review of available data and practical recommendations. *J Cardiovasc Electrophysiol* 11: 593–600, 2000

Viswanathan PC, Bezzina CR, George AL, Jr, Roden DM, Wilde AA, Balser JR. Gating-dependent mechanisms for flecainide action in SCN5A-linked arrhythmia syndromes. *Circulation* 104: 1200–1205, 2001

Viswanathan PC, Rudy Y. Pause induced early afterdepolarizations in the long QT syndrome: a simulation study. *Cardiovasc Res* 42: 530–542, 1999

Wehrens XH, Abriel H, Cabo C, Benhorin J, Kass RS. Arrhythmogenic mechanism of an LQT-3 mutation of the human heart Na^+ channel α-subunit: A computational analysis. *Circulation* 102: 584–590, 2000

Wehrens XHT, Rossenbacker T, Jongbloed RJ, Gewillig M, Heidbühel

H, Doevendans PA, Vos MA, Wellens HJJ, Kass RS. Heterozygous *SCN5A* mutation in the domain I-II linker causes long QT syndrome with 2 : 1 atrioventricular block. In preparation.

Wu Y, MacMillan LB, McNeill RB, Colbran RJ, Anderson ME. CaM kinase augments cardiac L-type Ca^{2+} current: a cellular mechanism for long Q-T arrhythmias. *Am J Physiol* 276: H2168–2178, 1999a

Wu Y, Roden DM, Anderson ME. Calmodulin kinase inhibition prevents development of the arrhythmogenic transient inward current. *Circ Res* 84: 906–912, 1999b

Zhou Z, Gong Q, Epstein ML, January CT. HERG channel dysfunction in human long QT syndrome. Intracellular transport and functional defects. *J Biol Chem* 273: 21061–21066, 1998