DISTINGUISHED SCIENTIST GOLDEN LIONEL AWARD

LECTURE
History never looks like history when you are living through it

SAMi VIskin
A TALE OF TWO DISEASES: THE HISTORY OF LONG QT SYNDROME AND BRUGADA SYNDROME.

Sami Viskin, M.D.
Tel Aviv Medical Center
Israel
2015

Rejected by NEJM, Lancet, Ann Intern Med (without peer review) Accepted to the Journal of the American College of Cardiology
60 year old woman after receiving sotalol

Avoid quinidine and QT-prolonging drugs

40 year old man after receiving ajmaline

Electrophysiologic study

ICD if VF is induced
Long QT syndrome is diagnosed "in the presence of QTc>500 ms ... when a secondary cause for QT prolongation is absent."

Brugada syndrome is diagnosed” in patients with type 1 ECG... either spontaneously or after provocative drug test with a Class I antiarrhythmic drug.”
CONGENITAL DEAF-MUTISM, FUNCTIONAL HEART DISEASE
WITH PROLONGATION OF THE Q-T INTERVAL,
AND SUDDEN DEATH

ANTON JERVELL, M.D., AND FRED LANGE-NIELSEN, M.D.
TÖNSBERG, NORWAY

A COMBINATION of deaf-mutism and a peculiar heart disease has been observed in 4 children in a family of 6. The parents were not related, and normal hearing.

All were healthy, suffered from "fainting attacks." By clinical and roentgen-ray examinations, no signs of heart disease, however, revealed a significant arrhythmia.

In the ages of 4, 5, and 9

A repeated "fainting attacks" occurred, up to 6 months, and they never cleared following efforts. His relatives, and partly with cyanosis, but not with the typical symptoms of the bladder, however, slight congestions and precordial pains.

Central Hospital (Dr. Kloster).
CONGENITAL DEAF-MUTISM, PROLONGED QT INTERVAL, SYMPTOMATIC ATTACKS AND SUDDEN DEATH

SAMUEL A. LEVINE, M.D.,† AND CLYDE R. WOODWORTH, M.D.,‡

BEVERLY AND BOSTON, MASSACHUSETTS

The case reported below represents a new and very distinct clinical entity. The young patient was observed by us for some years. It was hoped that a similar case might meet with a happy issue.

This patient had no family history of deaf-mutism, but his mother had had transient cardiac arrhythmias and syncopal attacks during pregnancy. The patient developed symptoms of deaf-mutism, with prolongation of the QT interval on electrocardiogram. He died suddenly at the age of 39. One brother, 9 years of age, was well. The family history of epilepsy or any condition similar to the one affecting the patient was negative.

An 8-year-old boy was admitted to the hospital with a history of sudden death. He was well and active. On physical examination, his blood pressure was normal. The electrocardiogram showed prolongation of the QT interval. The patient died suddenly during sleep.

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O. C. Ward, M.D., F.R.C.P.I., D.C.H.,

A NEW FAMILIAL CARDIAC SYNDROME IN CHILDREN

1964
Quinidine Syncope
Paroxysmal Ventricular Fibrillation Occurring during Treatment of Chronic Atrial Arrhythmias

By Arthur Selzer, M.D., and H. Wesley Wray, M.D.

Quinidine occupies an almost unique place in the therapy of cardiac arrhythmias. In the 45-odd years of its clinical use only very few drugs possessing similar pharmacologic properties have been found, but arrhythmias is not known, it is estimated that the figure is between 200 and 300.

Quinidine therapy has been administered with slight modifications, as follows: A priming dose of 0.2 Cm. of quinidine sulfate every 4 hours was frequently given for 1 or 2 days. As a rule,
Thioridazine (Mellaril®)-induced Ventricular Tachycardia Controlled with an Artificial Pacemaker

Fred W. Schoonmaker, M.D., Robert T. Osteen, A.B., and Joseph C. Greenfield, Jr., M.D.

Durham, North Carolina

Since its introduction as a neuroleptic agent, thioridazine (Mellaril®) has shown therapeutic safety (1). Although it has antipsychotic properties (2), ventricular tachycardia occurred rarely during treatment (3, 4). In this paper, a case of ventricular tachycardia secondary to thioridazine and its response to an artificial pacemaker is presented. Treatment with procainamide (5, 6) was ineffective. Use of this arrhythmiagraphic tracing is offered for use in cases of ventricular tachycardia after failure of the drug and electrical cardioversion.

Case Report

Patient E. E. S., a 50-year-old woman, was admitted to the Durham Veterans Administration Hospital on October 30, 1966, complaining of shortness of breath and hemoptysis. She had been treated with thioridazine for the previous 3 months.

Figure 1. Lead II of the electrocardiogram demonstrating frequent premature nodal contractions and episodic ventricular tachycardia. The Q-T interval is 0.52 sec."

Prevention of Tetanus

This statement was issued from the International Conference on Tetanus, sponsored by the Swiss Academy of Medical Sciences with the support of the World Health Organization and held on 5-6 October 1966 in Paris, France.

The statement was prepared by the Committee on Control of Tetanus and the World Health Organization.
La tachycardie ventriculaire a deux foyers opposés variables.

_F. Dessertenne._
Arch Mal Coeur Vaiss 1966;59:263.
Something is missing...
THE EFFECTS OF THE ORAL ADMINISTRATION OF QUINIDINE SULPHATE ON PATIENTS WITH TRANSIENT VENTRICULAR FIBRILLATION DURING ESTABLISHED ATRIOVENTRICULAR DISSOCIATION.

SIDNEY P. SCHWARTZ, M.D., M. PRICE MARGOLIES, M.D., AND ANTHONY FIRENZE, M.D.

NEW YORK, N. Y.

Am Heart J 1953;45:404-415
Transient ventricular fibrillation.
Sidney P. Schwartz. Am Heart J 1953

Before quinidine
Transient ventricular fibrillation.
Sidney P. Schwartz. Am Heart J 1953

After quinidine


Krikler DM, Curry PV. Torsade De Pointes, an atypical ventricular tachycardia. British Heart Journal 1976
Long QT syndrome

**Congenital form**
- 1957 – Jervell-Lange Nielsen
- 1964- Romano - Ward

**Drug-induced**
- 1964 – Seltzer
- 1966 - Schoonmaker
Functional Distribution of Right and Left Stellate Innervation to the Ventricles:

PRODUCTION OF NEUROGENIC ELECTROCARDIOGRAPHIC CHANGES BY UNILATERAL ALTERATION OF SYMPATHETIC TONE

Right stellate ganglionectomy OR left stellate stimulation
⇒ QT prolongation

Left stellate ganglionectomy OR right stellate stimulation
⇒ No change in QT interval
Unilateral Cervicothoracic Sympathetic Ganglionectomy for the Treatment of Long QT Interval Syndrome

Left Cardiac Sympathetic Denervation in the Therapy of Congenital Long QT Syndrome
A Worldwide Report

Peter J. Schwartz, MD; Emanuela H. Locati, MD; Arthur J. Mons, MD; Richard S. Crampton, MD; Rinaldo Trazeri, MD; and Ugo Ruberti, MD

Background. Long QT syndrome (LQTS) is a congenital disorder accompanied by a high incidence of sudden cardiac death. β-Adrenergic blockade is the therapy of choice, and it is successful in 75–80% of patients. For those in whom cardiac events (syncope or cardiac arrest) are not prevented by β-blockade, experimental studies suggest that left cardiac sympathetic denervation (LCSD) may be useful.

Methods and Results. We identified 85 LQTS patients worldwide who underwent LCSD, and we provide here the first large-scale evaluation of its efficacy. The time interval between the first cardiac event and LCSD and the follow-up period after LCSD were similar (5.6±6.1 versus 5.9±5.7 years). The mean age of the patients at surgery was 20±13 years. LCSD was followed by highly significant (p<0.0001) decreases in the number of patients with cardiac events (from 99% to 45%), in the number of cardiac events per patient (from 22±32 to 1±3), and in the number of patients with five or more cardiac events (from 71% to 10%). There were seven sudden deaths (8%), and the 5-year survival rate was 94%. The marked reduction in the incidence of tachyarrhythmic syncope suggests that LCSD has also reduced the risk for sudden death in this high-risk population.

Conclusions. The present findings demonstrate that for LQTS patients who continue with syncope or cardiac arrest despite the use of β-blockers, LCSD is a very effective therapy.
Linkage of a Cardiac Arrhythmia, the Long QT Syndrome, and the Harvey ras-1 Gene

MARK KEATING,* DONALD ATKINSON, CHRISTINE DUNN, KATHERINE TIMOTHY, G. MICHAEL VINCENT, MARK LEIPPERT

Genetic factors contribute to heart disease. In this study, linkage analyses have been performed in a family that is predisposed to sudden death from cardiac arrhythmias, the long QT syndrome (LQT). A DNA marker at the Harvey ras-1 locus (H-ras-1) was linked to LQT with a logarithm of the likelihood ratio for linkage (lod score) of 16.44 at θ = 0, which confirms the genetic basis of this trait and localizes this gene to the short arm of chromosome 11. As no recombination was observed between LQT and H-ras-1, and there is a physiological rationale for its involvement in this disease, ras becomes a candidate for the disease locus.

Cardiovascular disease is a major cause of morbidity and mortality in the industrialized world. Over the last 10 years, it has become increasingly apparent that inherited traits are involved in the pathogenesis of most cardiovascular disorders. Much attention has been and continues to be focused on the genes that regulate lipid metabolism and their role in atherogenesis. In this study, we have begun to investigate the genetic basis of a type of cardiovascular disease that is not directly linked to lipid abnormalities, that of cardiac arrhythmias.

Ventricular arrhythmias are a common cause of cardiac arrest and death (1). The pathogenesis of these arrhythmias is poorly understood, but predisposing factors include myocardial ischemia and infarction, metabolic abnormalities, and genetic factors. In this study we have examined a large...
A Molecular Basis for Cardiac Arrhythmia: HERG Mutations Cause Long QT Syndrome

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Eric D. Green,‡ and Mark T. Keating*†‡
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National Institutes of Health
Bethesda, Maryland 20892

Summary

To identify genes involved in cardiac arrhythmia, we investigated patients with long QT syndrome (LQT), an inherited disorder causing sudden death from a ventricular tachycardia, torsade de points. We previously mapped LQT loci on chromosomes 11 (LQT1), 7 (LQT2), and 3 (LQT3). Here, linkage and physical mapping therefore, provides a unique opportunity to study life-threatening cardiac arrhythmias at the molecular level. A molecular basis for LQT was not previously known. In 1991, we discovered tight linkage between autosomal dominant LQT and a polymorphism at H-RAS (Keating et al., 1991a). This discovery localized an LQT gene (LQT1) to chromosome 11p15.5 and made genetic testing possible in some families. Autosomal dominant LQT was previously thought to be genetically homogeneous, and the first seven families that we studied were linked to 11p15.5 (Keating et al., 1991b). In 1993, however, several laboratories, including our group, identified families that were not linked to chromosome 11p15.5 (Benhorin et al., 1993; Curran et al., 1993a; Tobin et al., 1994). In 1994, we identified two additional LQT loci, LQT2 on chromosome 7q35-36 (nine families) and LQT3 on chromosome 3p21-22 (three families) (Jiang et al., 1994). Since three families in our study remained unlinked, at least one more LQT locus exists. This degree of heterogeneity suggests that distinct LQT genes may encode proteins that interact to modulate cardiac repolarization and arrhythmia risk. Since LQT is associated with abnormal cardiac repolarization, genes that encode ion channels (or their modulators) are reasonable candidates. H-RAS, which was localized to chromosome 11p15.5, was excluded as a candidate for LQT1 based on direct DNA sequence analysis.

Introduction

Long QT syndrome (LQT) is an inherited disorder that causes sudden death from cardiac arrhythmias, specifically torsade de points and ventricular fibrillation. We previously mapped three LQT loci: LQT1 on chromosome 11p15.5, LQT2 on 7q35-36, and LQT3 on 3p21-22. These data are consistent with a likely cellular role for HERG, a gene encoding the ether-a-go-go-related gene (HERG), which encodes the LQT1 ion channel (Jiang et al., 1994). A key role for HERG may be exerted through the modulation of potassium currents, which are known to be important in the generation of action potentials and the regulation of cardiac repolarization.

Figure 3. HERG Intragenic Deletions Associated with LQT in Two Families

SCN5A Mutations Associated with an Inherited Cardiac Arrhythmia, Long QT Syndrome

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Summary

LQT (Romano–Ward syndrome) is more common and is not associated with other phenotypic abnormalities. A disorder very similar to inherited LQT can also be acquired, usually as a result of pharmacologic therapy (Schwartz et al., 1975; Zipes, 1987).

We have used two strategies to identify LQT genes, a candidate gene approach and positional cloning. P3


tional information is now available for three LQT loci, as we have mapped LQT1 to chromosome 11p15.5 (Keating et al., 1991a, 1991b), LQT2 to 7q35-36, and LQT3 to 3p21-22 (Jiang et al., 1994). The candidate gene approach relies on likely mechanistic hypotheses based on physiology. Although little is known about the physiology of LQT, the disorder is associated with prolongation of the QT interval on electrocardiograms, a sign of abnormal cardiac repolarization. This association suggests that genes encoding ion channels (or their modulators) are reasonable candidates for LQT. This hypothesis is now supported by our recent discovery that chromosomes 7-linked LQT results from mutations in the human ether-a-go-go-related gene (HERG), a putative cardiac potassium channel gene (Curran et al., 1995 [this issue of Cell]). A neuroendocrine calcium channel gene (CACNL1A2; Chin et al., 1991; Sbino et al., 1992) and a gene encoding a GTP-binding protein that modulates potassium channels (GNA12; Weinstein et al., 1988; Magovcic et al., 1992) became candidates for LQT3 based on their chromosomal location. Subsequent
Brief Communication

Quinidine Delays $I_k$ Activation in Guinea Pig Ventricular Myocytes

Dan M. Roden, Paul B. Bennett, Dirk J. Snyders, Jeffrey R. Balser, and Luc M. Hondeghem

A major action of the antiarrhythmic agent quinidine is prolongation of cardiac repolarization. In these experiments, the time-dependent effects of quinidine on the delayed rectifier potassium current, $I_k$, a current contributing to cardiac repolarization, were investigated in acutely disaggregated guinea pig ventricular myocytes using the whole-cell recording configuration of the patch-clamp method. The effect of quinidine on $I_k$ was dependent on the duration of depolarization. After long (2,000 msec) pulses, $I_k$ was reduced by 30 ± 27% (SD; $n=8$, paired) by 10 μM quinidine; in contrast, after short (100 msec) pulses, the drug decreased $I_k$ 65 ± 35% ($p<0.05$). This effect was found both in paired experiments as well as when quinidine-pretreated cells were compared to non-pretreated cells. Quinidine significantly delayed $I_k$ activation (9 ± 20 msec at baseline but did not alter the subsequent time course of activation (till findings are consistent with the hypothesis that quinidine promotes which opening does not occur. (Circulation Research 1988;62:1

The widely used antiarrhythmic agent quinidine prolongs cardiac repolarization both in patients

Baseline 5/2/86 #4

Quinidine

Figure 4. $I_k$ tail amplitudes elicited in the same fashion as shown in Figure 2 in quinidine-pretreated ($n=6$) and non-pretreated ($n=9$) preparations. As in the paired data shown in Figures 2 and 3, the effect of quinidine on $I_k$ tails was greater after short depolarizing pulses.
Electrocardiographic and Clinical Predictors of Torsades de Pointes Induced by Almokalant Infusion in Patients with Chronic Atrial Fibrillation or Flutter: A Prospective Study

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From the Department of Medicine, Sahlgrenska University Hospital, Göteborg, Sweden; *Department of Cardiology, Karolinska Hospital, Stockholm, Sweden; †Division of Cardiology, Sahlgrenska University Hospital, Göteborg, Sweden; ‡Division of Cardiology, Uppsala University Hospital, Uppsala, Sweden; and the Department of Cardiology, Medical University Hospital, Heidelberg, Germany; §Department of Cardiology, University Grensien, The Netherlands; ‖Department of Cardiology, Umeå University Hospital, Umeå, Sweden; and ||Department of Medicine, Hudiksvall University Hospital, Hudiksvall, Sweden.

HULTZ, B. ET AL.; Electrocardiographic and Clinical Predictors of Torsades de Pointes: Almokalant Infusion in Patients with Chronic Atrial Fibrillation or Flutter: A Prospective Study.

The aim of this study was to identify predictors of torsades de pointes (TDP) in patients with atrial fibrillation (AF) or flutter exposed to the Class III antiarrhythmic drug almokalant. TDP can be caused by prolonged myocardial repolarization. One hundred patients received almokalant infusion (daily dose 1) and 62 of the patients during sinus rhythm (SR) on the following day (infusion 2) patients converted to SR. Six patients developed TDP. Among AF, T wave alternans was worsened to infusion (baselines) in patients developing TDP (60% vs 44%, P < 0.01). After 30 minutes of infusion, the TDP patients exhibited a longer QT interval (409 ± 114 vs 443 ± 54 ms; mean ± SD), a prolonged QT dispersion (50 ± 24 vs 27 ± 26 ms; P < 0.05), and a lower T wave amplitude (0.24 ± 0.16 mV; P < 0.01). After 30 minutes of infusion, they exhibited a longer QT (26 ± 469 ± 74 ms; P < 0.001), a larger QT dispersion in preeclampsia (82 ± 7 vs 54 ± 52 ms; P < 0.001), and more ventricular tachyarrhythmies (163 ± 0 vs 40 ± 34 ms; P < 0.001), and T wave alternans was more common (0%; P < 0.001). Risk factors for development of TDP were at baseline: female gender, in trystates, and treatment with diuretics; and, after 30 minutes of infusion: sequential heart block, ventricular extrastoles in bigeminy, and a biphasic T wave. Patients exhibited early during almokalant infusion a prolonged QT prolongation, increased QT dispersion, and T wave marked morphological T wave changes. (PACE 1998; 21:1044-1057)

antiarrhythmics, almokalant, torsades de pointes, atrial fibrillation, prediction, electrocardiographic variables

GUEST EDITORIAL

Taking the “Idio” out of “Idiosyncratic”:
Predicting Torsades de Pointes

DAN M. RODEN
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Adverse reactions to drug therapy are the bane of the practitioner, and all the more so when they occur in an idiosyncratic, or apparently unpredictable, fashion. The occurrence of torsades de pointes during treatment with action potential prolonging drugs has long fallen into this category. Progress toward understanding mechanisms underlying torsades de pointes and identifying patients at risk would go a long way to rationalizing therapy with currently available antiarrhythmic drugs and perhaps directing development of new agents.

History and Incidence

Syncpe during initiation of quinidine therapy was recognized in the 1920s but it was not until 1994 that polymorphic ventricular fibrillation was described. The points (1) probably tachycardia occurring in a hypomagnesemic patient. 2 It is interesting that the estimated incidence of torsades de pointes with quinidine (0.5%-8%), with sotalol (0.5%-6%), and with ibutilide (up to 6%) are all quite similar, 3 despite the fact that trials have been conducted in different patient populations using different approaches to drug dosing. These figures refer to the incidence during the first several hours or days of therapy although it is well recognized that torsades de pointes can occur during long-term treatment. In our own studies gathered alternately, the heterogeneity of action potential durations (APDs) across the wall of the heart creates the substrate for transient functional block (particularly in the mid-myocardium, or M-cell layer) with scroll or spiral wave(s) meandering across the wall of the heart to maintain the arrhythmia. 10-12 The latter mechanism is also consistent with an increasing body of evidence suggesting that dispersion of repolarization times (i.e., a substrate favoring reentry) is a very frequent accompaniment of torsades de pointes. 13,14

What Is Known about Risk?
Previous and New Data

Supported in part by grants from the United States Public Health Service HL46581 and HL49691. Dr. Roden is the...
Long QT syndrome

**Congenital form**
- 1957 – Jervell-Lange Nielsen
- 1964 – Romano - Ward

**Drug-induced**
- 1964 – Seltzer
- 1966 - Schoonmaker

1995

I_{Kr}

1988
The spectrum of symptoms and QT intervals in carriers of the gene for the long-QT syndrome

G. Michael Vincent, M.D., Katherine W. Timothy, B.S., Mark Leppert, Ph.D., and Mark Keating, M.D.

Abstract. Background. The familial long-QT syndrome is characterized by a prolonged QT interval on the electrocardiogram, ventricular arrhythmias, and sudden death. It is caused by mutations in the gene encoding the cardiac ion channel proteins. QTc intervals of the gene carriers ranged from 0.41 to 0.59 second (mean, 0.49). By contrast, the QTc intervals of the noncarriers ranged from 0.38 to 0.43 second (mean, 0.40). This study illustrates the use of QTc interval to identify asymptomatic carriers of the gene. The distribution of QTc intervals among carriers and noncarriers is shown in the graph.
Diagnostic tests in LQTS

1997

Hysteresis of the RT Interval With Exercise
A New Marker for the Long-QT Syndrome?
Andrew D. Krahm, MD; George J. Klein, MD; Raymond Yee, MD

Abstract
The diagnosis of the long-QT syndrome (LQTS) may be difficult to establish, particularly with normal or borderline prolongation of the Q-T interval on routine electrocardiograms.

2002

Epinephrine-Induced QT Interval Prolongation: A Gene-Specific Paradoxical Response in Congenital Long QT Syndrome
Michael J. Ackerman, MD; Anant Khossettieh, MD; David J. Tester, BS; Joseph B. Heilik, RN; Win-Kuang Shen, MD; and Co-been J. Porter, MD

- Objective: To determine the effect of epinephrine on the QT interval in patients with genotyped long QT syndrome (LQTS).
- Patients and Methods: Between May 1999 and April 2001, 37 patients (23 females) with genotyped LQTS (LR1) or LQT2 or LQT3 tended to have shortened QT intervals (P<.001). The maximum mean ± SD change in QT (30TQ [epinephrine QT minus baseline QT]) was -5±4 ms (controls), +94±51 ms (LQTS), and +87±67 ms (LQTS and LQT2 patients). Of 27 controls, 6 had functional mutations in their LQTS genes.

2003

Epinephrine Unmasks Latent Mutation Carriers With LQT1 Form of Congenital Long-QT Syndrome
Wataru Shimizu, MD, PhD; Takashi Noda, MD; Hiroshi Takaki, MD; Takashi Kunita, MD, PhD; Hitoshi Nagaya, MD, PhD; Kazuhiro Satomi, MD; Kazuhiro Suyama, MD, PhD; Noboru Aihara, MD; Shigyuki Ichigo, MD; Kazuo Fujita; Katsumasa Nakamura, MD, PhD; Tohru Ohkawa, MD, PhD; Federico Ducci, Carlo Napolitano, MD, PhD; Silvia G. Priori, MD, PhD

- Objective: This study was designed to test the hypothesis that epinephrine infusion may be a provocative test able to unmask nonpenetrant KCNQ1 mutation carriers.
- Details: The LQTS form of congenital long QT syndrome is associated with high vulnerability to sympathetic stimulation and appears with incomplete penetrance.
- Methods: The 12-lead electrocardiographic parameters before and after epinephrine infusion were compared with baseline values in patients with LQTS and in unaffected family members. The study was performed in 22 patients (15 males, 7 females, mean age 35 years, range 9-78 years) with LQTS and 30 unaffected family members (19 males, 11 females, mean age 40 years, range 11-67 years). The mean QT interval decreased by 2.7±2.3 ms (P<.05) in LQTS patients and increased by 1.4±1.5 ms (P<.05) in unaffected family members. The mean corrected QT interval (QTc) decreased by 2.0±1.7 ms (P<.05) in LQTS patients and increased by 1.3±1.6 ms (P<.05) in unaffected family members.

Graphs and tables showing results before and after epinephrine infusion.
Provocation of sudden heart rate oscillation with adenosine exposes abnormal QT responses in patients with long QT syndrome: a bedside test for diagnosing long QT syndrome

Sami Viskin1*, Raphael Rosso1, Ori Rogowski1, Bernard Belhassen1, Aviva Levitas2, Abraham Wagshal1, Amos Katz2, Dana Fourey1, David Zeitser1, Antonio Oliva3, Guido D. Pollevick3, Charles Antzelevitch1, and Uri Rozovski1

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Received 8 July 2005; accepted 25 July 2005

Eur Heart J 2005

KEYWORDS
Long QT syndrome; Adenosine; Sudden death;
Porcine model of QT prolongation

Aims Is arrhythmias in the long QT syndrome (LQTS) are triggered by heart rate deceleration or acceleration, we speculated that the sudden bradycardia and subsequent tachycardia that follow adenosine injection would unveil QT changes of diagnostic value in patients with LQTS.

Methods and results Patients (11 LQTS and 10 controls) received intravenous adenosine during sinus tachycardia at supine and standing position. A significant QT prolongation was found at both heart rate conditions in patients. QTc prolongation was significantly greater at supine position. In control subjects, a similar but smaller effect was seen only at supine position.

Results In response to brief standing, patients and control subjects responded with similar heart rate acceleration of 26

The Response of the QT Interval to the Brief Tachycardia Provoked by Standing
A Bedside Test for Diagnosing Long QT Syndrome

Sami Viskin, MD,* Pieter G. Postema, MD,§ Zahuri A. Bhuiyan, MD, PhD,§ Raphael Rosso, MD,|| Jonathan M. Kalman, MBBS, PhD,|| Jitendra K. Vohra, MD,|| Milton E. Guevara-Valevda, MD,¶ Maniio F. Marquez, MD,¶ Exgeni Kogan, MD,* Bernard Belhassen, MD,* Michael Glikson, MD,† Boris Strauss, MD,‡ Charles Antzelevitch, PhD,‖ Arthur A. M. Wilde, MD§

Tel Aviv, Israel: Amsterdam, the Netherlands; Melbourne, Australia; Miami, Miami, and Utica, New York

JACC 2010

Objectives This study was undertaken to determine whether the short-lived acute increase in heart rate during standing, will expose changes in the QT interval that are of diagnostic value.

Background The QT interval shortens during heart rate acceleration, but this response is not instantaneous. We tested whether the transient, sudden sinus tachycardia that occurs during standing would expose abnormal QT interval prolongation in patients with long QT syndrome (LQTS).

Methods Patients (8 with LQTS [QTc 46%], LQT2 41%, LQT3 4%, not genotyped 9%) and 80 control subjects underwent baseline electrocardiogram (ECG) while resting in the supine position and were then asked to get up quickly and stand still during continuous ECG recording. The QT interval was studied at baseline and during maximal sinus tachycardia, maximal QT interval prolongation, and maximal QT interval stretching.

Results In response to brief standing, patients and control subjects responded with similar heart rate acceleration of 26
**Cellular Basis for the Normal T Wave and the Electrocardiographic Manifestations of the Long-QT Syndrome**

Gan-Xin Yan, MD, PhD; Charles Antzelevitch, PhD

**Background**—This study probes the cellular basis for the T wave under arterially perfused canine left ventricular (LV) wedge preparation, transmembrane and ECG events.

**Methods and Results**—Floating microelectrodes were used to record simultaneously from epicardial, M-region, and endocardial sites or subepicardial areas recorded concurrently. Under baseline and LQI conditions, repolarization and repolarization coincided with the peak of the T wave; repolarization

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**Sotalol testing unmaps altered repolarization in patients with suspected acquired long-QT-syndrome—a case-control pilot study using i.v. sotalol**

Stefan Käab*, Martin Hinterseer, Michael Näbauer, Gerhard Steinbeck

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**A** Control Group

**B** Study Group

**QTc (ms)**

- **Control Group**
  - Before: 300
  - After: 400

- **Study Group**
  - Before: 300
  - After: 450

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*Eur Heart J 2003*
Intravenous erythromycin challenge-test to diagnose CONGENITAL long QT.

I_{Kr} channel blockade to unmask occult congenital long QT syndrome

Darwin Jeyaraj, MD, Denise P. Abernethy, BA, Rupa N. Natarajan, BA, Mary M. Dettmer, RN, BSN, Maria Dikshteyn, MS, Diana M. Meredith, BSE, Kevin Patel, MD, Raghavendra R. Allareddy, MD, Steven A. Lewis, MS, Elizabeth S. Kaufman, MD
About 264,000 results (0.35 sec)

About 107,000,000 (0.46 sec)
RIGHT BUNDLE BRANCH BLOCK, PERSISTENT ST SEGMENT ELEVATION AND SUDDEN CARDIAC DEATH: A DISTINCT CLINICAL AND ELECTROCARDIOGRAPHIC SYNDROME

A MULTICENTER REPORT

PEDRO BRUGADA, MD, JOSEP BRUGADA, MD

Aalst, Belgium and Barcelona, Spain

Objectives. The objectives of this study were to present data on eight patients with recurrent episodes of aborted sudden death whom ventricular biopsies were performed. The arrhythmia leading to (aborted) sudden death was a rapid polymorphic
Brugada syndrome

From first description to identification of culprit genetic mutation in 6 years (30 years for LQTS).

It’s the sodium channel
And it only took 6 years!

SCN5A mutation

Male predominance in Brugada syndrome

Male predominance in Ashley Madison

Mizusawa & Wilde, Circ-EP 2012
Brugada syndrome: The ECG changes from day to day
Sodium Channel Block Produces Opposite Electrophysiological Effects in Canine Ventricular Epicardium and Endocardium

Subramaniam C. Krishnan and Charles Antzelevitch

Using microelectrode techniques we compared the effects of tetrodotoxin (TTX, 2–3 μM), DL-propranolol (1–3 μg/ml), and flecainide acetate (10–15 μM) on isolated canine ventricular epicardial (epicardium) and endocardial (endocardium) tissues. Propranolol, TTX, and flecainide decreased V_{max} and phase 0 amplitude in a use-dependent manner in both tissues. The effects of propranolol were slow to develop and wash out. TTX and propranolol always abbreviated action potentials by 23.8±5.6 msec and 10.8±12.9 msec after 1 and 1 amplitudes led to the epicardial action potential. 4 hours of exposure to TTX terminated at more all-or-none repolarization potential. In some epicardium, prolongation at other foundization was often attenuated to endocardium to sodium, 4-aminopyridine or epicardial notch. Action sodium blockade in endocardium occurred in epicardium. The data indicate that current, may exert an epicardial spanning the ventricle, not in endocardium. 

Flecainide 15 μM 30 min
Flecainide 15 μM 40 min
Control

Autonomic and Antiarrhythmic Drug Modulation of ST Segment Elevation in Patients With Brugada Syndrome

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Objectives. We examined autonomic nervous system and antiarrhythmic drug modulation of ST segment elevation in patients with Brugada syndrome.

Background. Right bundle branch block with pseudo-normal axis and ventricular tachyarrhythmia are characterized by the electrocardiographic (ECG) features of Brugada syndrome. However, the mechanism of ST segment elevation in patients with Brugada syndrome is unknown.

Methods. The study included 10 patients with Brugada syndrome without heart or coronary artery disease. Thirty-three invasive and non-invasive tests, including high take-off of the atrioventricular node, were performed. The ECGs of the patients were recorded on a digital multichannel recorder. The ECGs were analyzed for the characteristics of ST segment elevation and the relationship to the autonomic nervous system.
Sodium Channel Blockers Identify Risk for Sudden Death in Patients With ST-Segment Elevation and Right Bundle Branch Block but Structurally Normal Hearts

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Background — A mutation in the cardiac sodium channel gene (SCN5A) has been described in patients with the syndrome of right bundle branch block, ST-segment elevation in leads V1 to V3, and sudden death (Brugada syndrome). These
Introduction

BrugadaDrugs.org is a non-profit initiative developed by physicians from the University of Amsterdam Academic Medical Center, department of Cardiology, in collaboration with a panel of world-renowned experts on Brugada syndrome as an aid to physicians who treat patients with Brugada syndrome and as an aid to patients with Brugada syndrome and their families with the goal to provide free, worldwide accessible and up-to-date information on safe drug use in Brugada syndrome.

Please read our request for donations to support this initiative.

This website is up to date through September 2, 2015. The last drug update has been communicated on January 24, 2015, there are currently no new drugs under consideration.

Worldwide, the Brugada syndrome has been recognized as an important cause of sudden cardiac death at a relatively young age. However, many or most patients with Brugada syndrome are asymptomatic and will also not experience malignant arrhythmias. This knowledge base can result in a challenge for both physicians and patients. Brugada syndrome is diagnosed in the presence of specific electrocardiographic abnormalities (known as the type-1 Brugada syndrome ECG) combined with an absence of gross structural abnormalities and several other criteria. Furthermore, Brugada syndrome often shows familial aggregation. The presence of this type-1 ECG in particular has been linked to an increased risk...
“Asymptomatic, drug-induced type I Brugada” is THE most common indication for ICD implantation for Brugada syndrome in Europe. 

Sacher, Circulation 2006
History never looks like history when you are living through it.
~John W. Gardner (1912-2002)