Heart Rate Influences on Repolarization Duration and Morphology in Symptomatic Versus Asymptomatic KCNQ1 Mutation Carriers

Fabrice Extramiana, MD, Isabelle Denjoy, MD, Fabio Badilini, PhD, Iheb Chabani, MD, Nathalie Neyroud, PhD, Myriam Berthet, MS, Véronique Fressard, PhD, Pascale Guicheney, PhD, Philippe Beaufils, MD, Antoine Leenhardt, MD, Philippe Coumel, MD, and Pierre Maison-Blanche, MD

QT and Tp/Te intervals were longer in patients with LQT1 (n = 67) than in nonaffected subjects (n = 52) but did not differentiate symptomatic (n = 21) from asymptomatic patients (n = 46). At fast heart rate, the time to accumulate the last part of total T-wave area (the t50-97 interval) was longer in symptomatic carriers compared with asymptomatic patients (119 ± 19 vs 106 ± 15 ms, p <0.01). The latter group had significantly longer t50-97 intervals than nonaffected subjects (96 ± 14 ms, p <0.01). ©2005 by Excerpta Medica Inc.

(Am J Cardiol 2005;95:406–409)

Congenital long-QT syndrome (LQTS) is an inherited cardiac disease characterized by the prolongation of ventricular repolarization, susceptibility to Torsades de pointes (TdP), and a risk for sudden death.[1] The mechanism of TdP in LQTS is believed to be related to the transmural dispersion of ventricular repolarization (TDVR).[2,3] Experimental as well as recent clinical data suggest that T-wave morphology could reflect TDVR[4,5] and has been shown to be altered in LQT2 experimental models and in LQT1 and LQT2 mutation carriers.[6,7] IKs malfunction has been linked to a specific QT-rate dependence in patients with LQT1.[8] Moreover, in these patients, TdP appears more frequently during exercise or psychologic stress than in other circumstances.[9] Taken together, these data prompted us to consider rate influences on QT parameters. The aim of this study was to assess QT-interval duration, T-wave morphologic parameters, and their relation to heart rate (HR) changes in symptomatic and asymptomatic patients with LQT1 and in nonaffected family members.

• • •

The study population consisted of 119 genotyped subjects (age range 12 to 70 years) belonging to 23 families. Eighteen mutations in KCNQ1 were identified in 67 patients. Cardiac events (10 men, mean age 33 ± 15 years) included stress or emotion syncope (n = 20) and drug-induced TdP (n = 1). The remaining 46 mutation carriers were asymptomatic (22 men, mean age 39 ± 17 years). The remaining 52 related family members (26 men, mean age 31 ± 15 years), in whom no mutations in KCNQ1 were found, served as a control group.

All patients were free of any other cardiac abnormalities, and electrocardiograms and Holter recordings were obtained before any therapy. Clinical evaluation was performed and blood samples were obtained after the patients provided written informed consent in accordance with the guidelines of the Ethical Committee of Hôpital Pitié-Salpêtrière, Paris, France.

All subjects underwent digital electrocardiograms at rest and 24-hour digital Holter recordings (Elatec Holter system, ELA Medical, Paris, France). QT interval was measured on digital electrocardiograms at rest in lead II and corrected for HR using Bazett's formula. The diurnal and nocturnal circadian periods were defined according to subject diary and mean hourly HRs. To take into account the hysteresis of adaptation of QT interval after HR changes, a selective beat-averaging method extracting sinusal QRS-T complexes preceded by a 1-minute period of stable HR was used.[8,10,11]

The intervals between Q onset and T-wave peak (QTp) and T-wave end (QTe) and T-wave area were automatically measured[10,11] and visually verified. The Tp/Te interval was defined as the difference between the QTe and QTp intervals. The t50-97 interval was defined as the time to accumulate the last part (from 50% to 97% of T) of the total T-wave area[12] (Figure 1). All parameters were measured at different RR intervals (e.g., QT1000 = QT interval at RR = 1000 ms).

Results are given as mean ± SD. Means were compared among groups by analysis of variance with ad hoc post-test and proportions with the chi-square test. Statistical analysis was performed with StatView 5.0 (SAS Institute Inc., Cary, North Carolina).

Gender ratios were not different among the 3 groups. Nonaffected family members were significantly younger than asymptomatic patients with LQT1 (31 ± 15 vs 39 ± 17 years, p <0.05), but no age difference between symptomatic and asymptomatic patients was evident.

From Service de Cardiologie, Groupe Hospitalier Lariboisière, Paris; and INSERM U582, Institut de Myologie, and Service de Biochimie B, IFR No. 14, Groupe Hospitalier Pitié-Salpêtrière, Paris, France. This work was supported by Fondation Leducq, Paris, France, and Dr. Extramiana was the recipient of a grant from Groupe de Réflexion sur la Recherche Cardiovasculaire, Paris, France. Dr. Extramiana's address is: Cardiology Department, Hôpital Lariboisière, 2 rue Ambroise Paré, 75010 Paris, France. E-mail: fabrice.extramiana@lrb.ap-hop-paris.fr. Manuscript received July 27, 2004; revised manuscript received and accepted September 23, 2004.

0002-9149/05/$–see front matter
doi:10.1016/j.amjcard.2004.09.045

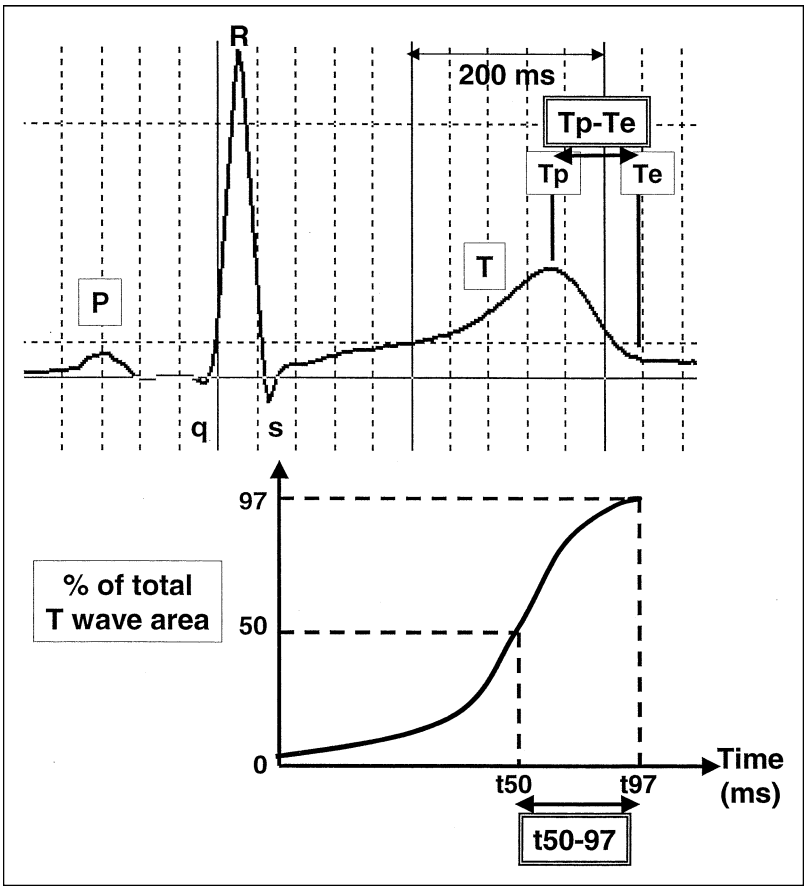

FIGURE 1. Tp/Te and t50-97 interval measurements.

TABLE 1 QT-Interval Duration at Different RR Intervals During the Day and at Night

Variable	Nonaffected Subjects (n = 52)	Asymptomatic Patients with LQT1 (n = 46)	Symptomatic Patients with LQT1 (n = 21)
QTc	402 ± 24	463 ± 34*	460 ± 40*
Day			
QTp700	276 ± 17	325 ± 25*	321 ± 29*
QTe700	354 ± 15	405 ± 34*	402 ± 32*
QTp800	293 ± 18	339 ± 24*	334 ± 30*
QTe800	373 ± 16	422 ± 33*	418 ± 33*
QTp900	311 ± 21	353 ± 25*	346 ± 31*
QTe900	391 ± 19	438 ± 34*	433 ± 34*
QTp1000	328 ± 24	367 ± 27*	358 ± 34*
QTe1000	410 ± 21	455 ± 37*	449 ± 39*
Night			
QTp900	323 ± 21	359 ± 26*	360 ± 34*
QTe900	401 ± 20	443 ± 30*	438 ± 27*
QTp1000	336 ± 23	375 ± 27*	375 ± 35*
QTe1000	417 ± 21	462 ± 32*	458 ± 31*
QTp1100	348 ± 25	390 ± 29*	390 ± 37*
QTe1100	432 ± 23	481 ± 34*	478 ± 36*

*p <0.01 versus nonaffected subjects.

HRs were significantly slower in patients with LQT1 compared with noncarriers, whatever the circadian period considered. For instance, the diurnal RR intervals were 691 ± 89, 761 ± 98, and 772 ± 77 ms in nonaffected subjects, asymptomatic patients, and symptomatic patients, respectively. However, HR was not significantly different between the 2 groups of mutation carriers.

Mean QTc intervals were not different between symptomatic and asymptomatic patients, whereas nonaffected subjects had shorter QTc intervals (Table 1). The proportion of patients with QTc intervals >480 and 500 ms was similar between symptomatic patients (7 of 21 and 2 of 21, respectively) and asymptomatic patients (13 of 46 and 6 of 46, respectively).

QTp and QTe intervals were longer in patients with LQT1 compared with nonaffected subjects, whatever the HR and the circadian period considered, but no significant difference was seen between asymptomatic and symptomatic patients (Table 1).

Tp/Te intervals were longer in patients compared with nonaffected subjects. This difference was significant at the slowest HR. For example, the Tp/Te intervals at RR = 1,000 ms during the day were 82 ± 15 ms in nonaffected subjects and 89 ± 18 ms in patients ($p < 0.05$). Tp/Te intervals were not different between symptomatic and asymptomatic patients except for the nocturnal Tp/Te interval at RR = 900 ms (Table 2).

Table 3 lists the t50-97 intervals measured at different HRs during the 2 circadian periods. At fast HR during the day, t50-97 intervals were significantly longer in symptomatic patients compared with asymptomatic patients. The latter patients had significantly longer t50-97 intervals than nonaffected subjects. This symptom status–related difference was not observed at slower HRs during the day nor during the night. This pattern was related to a lack of t50-97 interval shortening as HR increased in symptomatic patients (Figure 2). In contrast, nonaffected subjects and asymptomatic patients displayed significant decreases in the t50-97 interval as HR increased ($p < 0.0001$ and $p < 0.01$, respectively).

• • •

In this study, we provide evidence that symptomatic patients with LQT1 show a lack of shortening of the late phase of the T wave as HR increases. Symptomatic and asymptomatic patients with LQT1 displayed similar prolonged QT intervals and Tp/Te intervals as opposed to nonaffected family members. However, only symptomatic patients with LQT1 showed abnormal dynamic behavior of ventricular repolarization.

Bazett QTc interval at rest remains the major

TABLE 2 Tp-Te Interval Duration at Different RR Intervals During the Day and at Night

Variable	Nonaffected Subjects (n = 52)	Asymptomatic Patients with LQT1 (n = 46)	Symptomatic Patients with LQT1 (n = 21)
Day			
Tp-Te700	78 ± 11	80 ± 14	81 ± 12
Tp-Te800	79 ± 12	83 ± 15	84 ± 12
Tp-Te900	81 ± 13	85 ± 16	87 ± 14
Tp-Te1000	82 ± 15	88 ± 19	90 ± 17
Night			
Tp-Te900	79 ± 8	84 ± 14*	78 ± 11†
Tp-Te1000	81 ± 9	87 ± 14*	83 ± 11
Tp-Te1100	83 ± 11	90 ± 15*	89 ± 13

*p <0.05 versus nonaffected subjects; †p <0.05 versus asymptomatic patients.

TABLE 3 t50-97 Interval Duration at Different RR Intervals During the Day and at Night

Variable	Nonaffected Subjects (n = 52)	Asymptomatic Patients with LQT1 (n = 46)	Symptomatic Patients with LQT1 (n = 21)
Day			
t50–97 700	96 ± 14	106 ± 15†	119 ± 19†‡
t50–97 800	97 ± 14	109 ± 14†	114 ± 17†
t50–97 900	107 ± 17	125 ± 29*	117 ± 19
Night			
t50–97 900	110 ± 16	116 ± 18	115 ± 15
t50–97 1000	116 ± 17	124 ± 24	130 ± 25*
t50–97 1100	117 ± 17	131 ± 28	135 ± 31

*p < 0.05; †p <0.01 versus nonaffected subjects; ‡p <0.01 versus asymptomatic patients.

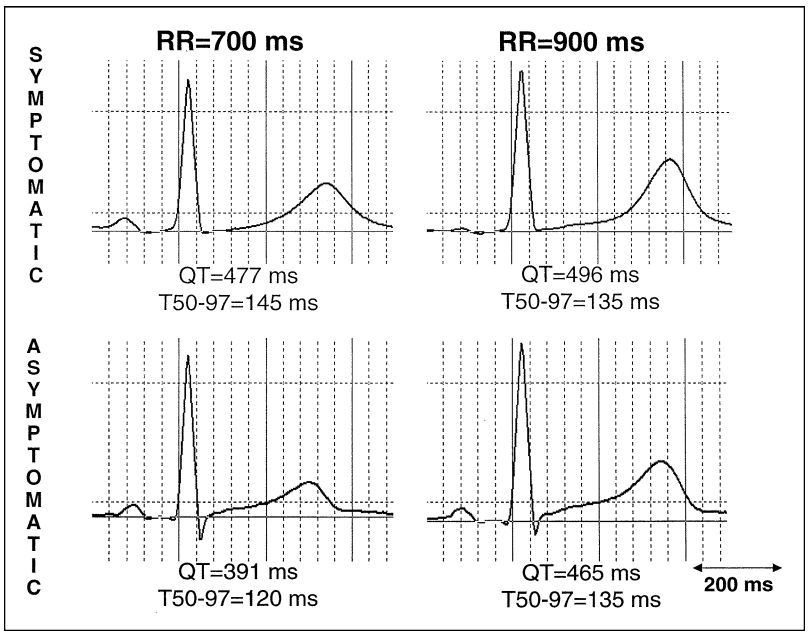

FIGURE 2. QT and t50-97 interval duration at RR = 700 ms *(left panels)* and RR = 900 ms *(right panels)* in 1 symptomatic patient *(top panels)* and 1 asymptomatic patient *(bottom panels).*

LQTS diagnostic criterion.[13] Using a method avoiding the need for a formula to correct for HR, we show that the QT prolongation was observed, whatever the HR and the circadian period considered. Recent data suggest that QTc interval prolongation >480 and 500 ms might have prognostic value in LQTS.[14] However, in the present study, QT intervals were not different between symptomatic and asymptomatic patients, and the proportion of patients with QTc intervals >480 and 500 ms were similar in the 2 groups. It is well established that QTc interval prolongation is absent in 5% to 10% of disease gene carriers and that syncope or cardiac arrest can occur in about 5% of the family members of patients with LQTS who have normal QTc intervals.[1] Therefore, the QT interval duration might not provide sufficient prognostic information.

TDVR plays a critical role in arrhythmogenesis in long QT conditions.[2,6] In addition, the Tp-Te interval has been shown to be the electrocardiographic counterpart of TDVR in the wedge model.[4] This marker has been used in a clinical study showing an increase in the Tp/Te interval as HR increases in patients with LQT1, but without prognostic insight.[7] However, the relation between the human Tp/Te interval and the level of TDVR is not known. Mathematical models suggest that the T-wave area could reflect TDVR.[5] However, this parameter is strongly dependent on T-wave amplitude, which is not constant during long-term recordings (i.e., because of respiration and body position influences). To overcome this problem, we chose to use the t50-97 interval, which represents the time to accumulate the last part of the total T-wave area, thus normalizing the T-wave area and avoiding amplitude change–related biases.

We demonstrate that symptomatic patients with LQT1 show a lack of shortening of the late phase of the T wave as HR increases. The t50-97 interval increase we describe in symptomatic patients at RR = 700 ms was also found at faster HR (RR = 650 ms). Whether the t50-97 interval represents a surrogate of TDVR remains to be demonstrated. However, experimental data show that in the presence of an IKs blocker, TDVR increases when isoproterenol is added to the perfusion.[2] In LQT1, cardiac events occur predominantly in adrenergic conditions, and in our study, the t50-97 interval increased in adrenergic conditions, thus paralleling the behavior of TDVR in the LQT1 experimental model.

Some patients with LQT1 could have been misclassified as asymptomatic because of shorter risk exposure time in young patients. However, this potential selection bias would have blurred the differences between the 2 groups. Because of the relatively small population of the

study and the presence of factors affecting repolarization, such as gender, age, and the electrophysiologic effect of the different mutations, our data do not provide a cut-off value of the t50-97 interval that can be used for risk stratification in patients with LQT1.

We conclude that before therapy, symptomatic patients with LQT1 show a lack of shortening of the late accumulated T-wave area at faster HRs.

1. 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;84:1136–1144.
2. 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. *Circulation* 1998;98:2314–2322.
3. Akar FG, Yan GX, Antzelevitch C, Rosenbaum DS. Unique topographical distribution of M cells underlies reentrant mechanism of Torsade de Pointes in the long-QT syndrome. *Circulation* 2002;105:1247–1253.
4. Yan GX, Antzelevitch C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long-QT syndrome. *Circulation* 1998; 98:1928–1936.
5. Fuller MS, Sandor G, Punske B, Taccardi B, MacLeod RS, Ershler PR, Green LS, Lux RL. Estimates of repolarization dispersion from electrocardiographic measurements. *Circulation* 2000;102:685–691.
6. Di Diego JM, Belardinelli L, Antzelevitch C. Cisapride-induced transmural dispersion of repolarization and Torsade de Pointes in the canine left ventricular wedge preparation during epicardial stimulation. *Circulation* 2003;108:1027–1033.
7. Viitasalo M, Oikarinen L, Swan H, Vaananen H, Glatter K, Laitinen PJ, Kontula K, Barron HV, Toivonen L, Scheinman MM. Ambulatory electrocardiographic evidence of transmural dispersion of repolarization in patients with long-QT syndrome type 1 and 2. *Circulation* 2002;106:2473–2478.
8. Neyroud N, Maison-Blanche P, Denjoy I, Chevret S, Donger C, Dausse E, Fayn J, Badilini F, Menhabi N, Schwartz K, et al. Diagnostic performance of QT interval variables from 24-h electrocardiography in the long QT syndrome. *Eur Heart J* 1998;19:158–165.
9. Schwartz PJ, Priori SG, Spazzolini C, Moss AJ, Vincent GM, Napolitano C, Denjoy I, Guicheney P, Breithardt G, Keating MT, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation* 2001;103:89–95.
10. Badilini F, Maison-Blanche P, Childers R, Coumel P. QT interval analysis on ambulatory ECG recordings: a selective beat averaging approach. *Med Biol Eng Comput* 1999;37:71–79.
11. Extramiana F, Maison-Blanche P, Badilini F, Pinoteau J, Deseo T, Coumel P. Circadian modulation of QT rate-dependence in healthy volunteers: gender and age differences. *J Electrocardiol* 1999;32:33–43.
12. Benhorin J, Merri M, Alberti M, Locati E, Moss AJ, Hall WJ, Cui L. Long QT syndrome: new electrocardiographic characteristics. *Circulation* 1990;82: 521–527.
13. Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long QT syndrome: an update. *Circulation* 1993;88:782–784.
14. Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, Vicentini A, Spazzolini C, Nastoli J, Bottelli G, et al. Risk stratification in the long-QT syndrome. *N Engl J Med* 2003;348:1866–1874.

Epidemiology of Pacemaker Procedures Among Medicare Enrollees in 1990, 1995, and 2000

David W. Brown, MSPH, MSc, Janet B. Croft, PhD, Wayne H. Giles, MD, MSc, Robert F. Anda, MD, MSc, and George A. Mensah, MD

Using Medicare hospital claims records and beneficiary enrollment data, the investigators describe the epidemiology of inpatient pacemaker procedures (*International Classification of Diseases*, Ninth Revision, Clinical Modification codes 37.80 to 37.89) in Medicare enrollees. From 1990 to 2000, the age-standardized inpatient pacemaker procedure prevalence (per 100,000 enrollees) increased from 325.4 to 504.4 in all Medicare beneficiaries. The prevalence increased significantly with age; was less for women than for men; and was less for blacks, Hispanics, and Asians than for whites. ©2005 by Excerpta Medica Inc.

(Am J Cardiol 2005;95:409–411)

This report describes the prevalence of inpatient pacemaker procedures in Medicare beneficiaries in the United States during 1990, 1995, and 2000. We address several shortcomings of the current body of research[1]: current trend data are derived from mailed surveys[1–4] that are subject to nonresponse-related problems and may not reflect a true national prevalence[2]; the most recent data are from 1993[3]; racial and ethnic differences are not well described[4]; and we are unaware of any studies conducted specifically in Medicare beneficiaries, a group that may account for 85% of pacemaker procedures.

• • •

The Medicare Provider Analysis and Review file is created from billing information for hospital claims and is a record of inpatient care for Medicare beneficiaries. We obtained Medicare Provider Analysis and Review data and modified beneficiary enrollment data for 1990, 1995, and 2000 from the Centers for Medicare and Medicaid Services. The hospital claims file included admission and discharge information on patients, including their age at admission, race or ethnicity, and gender, as well as 6 codes for hospital procedures from the *International Classification of Diseases*, Ninth Revision, Clinical Modification (ICD-9-CM). Beneficiary enrollment data contained a record for each patient eligible for Medicare benefits that included race or ethnicity, age, and gender.

We searched the hospital claims records in the Medicare Provider Analysis and Review file for ICD-9-CM codes indicating the insertion, replacement, removal, or revision of pacemaker leads or devices (codes 37.80 to 37.89). We identified 87,050 eligible hospital claims records for 1990, 112,824 for 1995, and 138,102 for 2000. We do not display data for

From the Emerging Investigations and Analytic Methods Branch and the Cardiovascular Health Branch, Centers for Disease Control and Prevention, Atlanta, Georgia.

Mr. Brown was supported by a Career Development Award through the Association of Teachers of Preventive Medicine, Washington, DC.

Mr. Brown's address is: 4770 Buford Hwy NE (MS K67), Atlanta, Georgia 30341. E-mail: dbrown6@cdc.gov.

Manuscript received August 10, 2004; revised manuscript received and accepted September 20, 2004.

0002-9149/05/$–see front matter
doi:10.1016/j.amjcard.2004.09.046