Relation Between Ventricular Repolarization Duration and Cardiac Cycle Length During 24-Hour Holter Recordings

Findings in Normal Patients and Patients With Long QT Syndrome

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Background. **The interval from the R wave to the maximum amplitude of the T wave (RTm) contains the heart rate dependency of ventricular repolarization.**

Methods and Results. **A computer algorithm was developed to quantify the RTm and preceding RR intervals for each of more than 50,000 beats on 24-hour ambulatory electrocardiographic (Holter) recordings to evaluate the dynamic relation between repolarization duration and cycle length. The relation of RTm to the preceding RR interval (RTm/RR slope) was determined by the best-fit linear regression equation between these two parameters. Eleven normal subjects and 16 patients with long QT syndrome (LQTS) were investigated. Six of the normal subjects had Holter recordings obtained before and after β-blocker therapy. β-Blockers were associated with a significant ($p=0.005$) reduction in the RTm/RR slope from 0.13±0.02 to 0.10±0.02. The mean value of the RTm/RR slope was significantly ($p=0.003$) larger in the LQTS patients (0.21±0.08) than in normal subjects (0.14±0.03).**

Conclusions. **These findings indicate that 1) quantification of the dynamic relation between ventricular repolarization and RR cycle length can be obtained on a large number of Holter-recorded heart beats; 2) β-blockers reduce the RTm/RR slope in normal patients; and 3) LQTS patients have an exaggerated delay in repolarization at long RR cycle lengths. (*Circulation* 1992;85:1816–1821)**

KEY WORDS • **delayed repolarization** • **arrhythmias** • **sudden cardiac death**

Quantification of ventricular repolarization duration is usually obtained by measurement of the QT interval on a limited number of beats on the 12-lead ECG. Correction for the cardiac cycle length is generally obtained by the Bazett formula,[1] which expresses the linear relation between the log-transformed values of the QT and RR intervals for a single beat. Our previous work on quantification of repolarization in normal individuals[2] and in patients with the long QT syndrome (LQTS)[3] has shown that the cycle length dependency of repolarization duration is concentrated mainly in the first portion of the QT interval (ending at the peak of the T wave) and that the static repolarization duration–cycle length relation is best fit linearly.

The purpose of this work is to determine the dynamic nature of the relation between repolarization duration and cycle length in normal individuals and in patients with LQTS by using a large number of cardiac cycles per patient obtained by computerized analysis of Holter-recorded ECGs. In this context, investigation of the dynamic relation between repolarization duration and cycle length might provide further information into repolarization-related disorders in terms of both diagnosis and therapy.

Methods

Population

The study population consisted of 11 normal volunteers (mean age, 28±4 years; eight men and three women) and 16 patients with LQTS (mean age, 28±15 years; three men and 13 women) who had 24-hour Holter recordings obtained on Marquette series 8500 recorders (Marquette Electronics, Inc.). Normal subjects were asymptomatic, medication-free individuals with no history of cardiovascular or pulmonary disease and a normal physical examination. Six of the 11 normal subjects underwent a second Holter recording while receiving the β-blocker medication nadolol 80 mg/day for 3 days as part of a separate protocol approved by our

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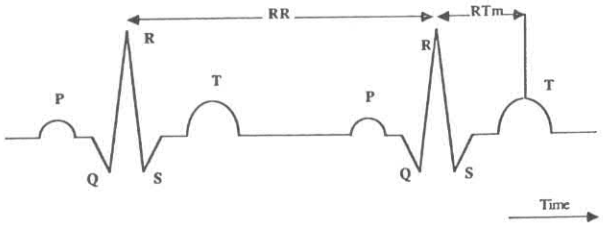

FIGURE 1. *Schematic ECG with parameters of interest.*

institutional human investigation committee. LQTS patients, participants in the International LQTS Study,[4] had a prolonged QT interval on the 12-lead ECG (corrected QT interval [see Reference 1] >0.44 seconds in lead II). Twelve of the LQTS patients had a history of syncope or aborted cardiac arrest, and seven of the LQTS patients were receiving β-blocking medication (five on propranolol and two on nadolol) at the time of the recording.

Electrocardiographic Variables

Cycle length was quantified by the interval between two successive R wave peaks (RR). Repolarization duration was defined as the time interval between the R wave peak and the maximum amplitude of the T wave (RTm). Each RTm interval was coupled to the RR interval of the preceding beat. The RTm measurement avoids the well-known problems associated with the identification of both Q wave onset and T wave offset that are inherent in the measurement of the QT interval. Figure 1 shows a schematic ECG with the parameters of interest.

Electrocardiographic Processing

The analog 24-hour electrocardiographic recording was digitized using the Laser Holter System (Marquette Electronics, Inc.). A validated software package was designed and implemented on a VAX 8350 series Digital Equipment Corporation computer to perform the following three steps of preprocessing of the digitized ECG: 1) recover the digitized electrocardiographic samples from the internal Marquette format; 2) quantify the RR and the subsequent RTm intervals for each heartbeat and successively store these coupled intervals into two separate series; and 3) exclude heartbeats that have RR and RTm intervals that are outside prespecified physiological ranges.

The first step is device dependent. Its purpose is to create an interface between the commercial device used to record and digitize the ECG and the rest of the software, and, in principle, it can be implemented for any recorder.

In the second step, the measurement of RR interval is carried out by an algorithm that looks for the R wave using an adaptive threshold on the amplitude of the first derivative of the ECG signal. Once the threshold is reached, the time of occurrence of the maximum of the R wave is identified. The precision of this measurement is limited by the sampling rate of the commercial Holter system (128 Hz for the Marquette system). The precision can be optimized by fitting a parabola through the maximum value itself and the previous and the successive samples. The parabolic vertices are then used as fiducial points for identifying the peaks of two consecutive R waves. The RR interval is computed as the difference between two consecutive parabolic vertices. After the detection of the second R wave, the algorithm analyzes the post–R wave portion looking for the maximum amplitude of the T wave. One second of the ECG after the peak of the R wave is low-pass filtered (FIR filter, 15-Hz cut-off frequency), and the maximum value of the signal is searched in a time window starting from the previous R wave to 15% and 75% of the mean value of the running RR interval. A parabola is then fit through seven samples centered in correspondence of the found maximum, and its vertex is taken as the fiducial point for the maximum amplitude of the T wave (Tm). Finally, RTm is measured as the difference between two consecutive fiducial points for R and Tm, respectively. The 128-Hz sampling frequency is sufficient to permit accurate and reliable measurement of RR and RTm intervals.[5]

The third step is performed by an algorithm that removes nonphysiological RTm and RR intervals that are not likely to represent physiological components of a heartbeat. We used three parameters to exclude nonphysiological intervals: 1) RR cycle length <350 msec (equivalent to a heart rate >170 beats per minute) or >2,000 msec (equivalent to a heart rate <30 beats per minute); 2) RTm <200 msec or >650 msec; and 3) RTm/RR ratio <0.15 or >0.50. The last two parameters were derived from ranges previously established in normal and LQTS populations.[2,3] A random sample of 100 computer-analyzed heartbeats with RTm and RR intervals that fell inside (n=50) and outside (n=50) these physiological ranges was subjected to beat-by-beat visual edit of the RTm and RR measurements to evaluate the accuracy of this approach. The computer algorithm analysis was 100% (50 of 50) accurate in properly quantifying the RTm and RR intervals of beats that fell within the aforementioned physiological ranges. Artifactual RTm and RR measurements caused by noise and low signal-to-noise ratios were present in 84% (42 of 50) of intervals that were outside the physiological ranges. The overall error rate was 8%, and the computer read-reread repeatability was 100%.

Data Analysis

The Pearson product–moment correlation and the slope (RTm/RR) of the best fit linear regression line for RTm versus RR were computed for each individual using all heartbeats that fell within the prespecified physiological ranges. Statistical analyses used Student's t test and paired t test where appropriate.

Results

The clinical characteristics and Holter findings for the 11 normal subjects are presented in Table 1. The normal subjects ranged in age from 23 to 39 years. A mean of more than 90,000 heartbeats per subject was analyzed. There was a high correlation (r=0.82) for RTm on RR, with an average RTm/RR slope of 0.14±0.03. The findings on a second Holter in six of the normal subjects placed on β-blocker medication (first six subjects listed in Table 1) are presented in Table 2 and Figure 2. β-Blocker therapy was associated with a slowing of the heart rate, a significant (p=0.005) reduction in the RTm/RR slope from 0.13±0.02 to 0.10±0.02

TABLE 1. Clinical Characteristics and Holter Findings in 11 Normal Subjects

Patient/ Sex	Age (years)	ECG (seconds)			24-Hour Holter		
		RR	QT	QT_c	Beats (*n*)	*r**	RTm/RR
1/M	28	1.04	0.38	0.37	90,802	0.69	0.09
2/M	23	1.04	0.42	0.41	94,109	0.79	0.11
3/M	23	0.84	0.39	0.43	102,166	0.86	0.13
4/M	26	0.72	0.36	0.42	77,173	0.84	0.13
5/M	26	0.96	0.40	0.41	90,939	0.84	0.14
6/M	29	0.84	0.38	0.42	75,122	0.89	0.16
7/M	25	0.84	0.40	0.44	114,687	0.84	0.17
8/M	31	0.92	0.40	0.42	93,956	0.77	0.14
9/F	27	0.88	0.40	0.43	83,623	0.81	0.11
10/F	27	0.84	0.36	0.39	102,468	0.82	0.14
11/F	39	0.80	0.39	0.44	97,474	0.92	0.19
Mean	28	0.88	0.39	0.42	92,956	0.82	0.14
±SD	±4	±0.10	±0.02	±0.02	±11,547	±0.06	±0.03

M, male; F, female.
*Pearson product–moment correlation of RTm on RR.

(t=4.72 by paired sample analysis), and a nonsignificant (p=0.11) change in the correlation of RTm on RR (t=1.69 by paired sample analysis).

The clinical characteristics and Holter findings for the 16 patients with LQTS (not age-matched or sex-matched to the normal subjects) are presented in Table 3. The patients ranged in age from 9 to 57 years; seven of the 16 patients were receiving β-blockers at the time of the Holter recording, and the QT_c on the resting ECG averaged 0.52 seconds and ranged from 0.46 to 0.57 seconds. A mean of more than 70,000 heartbeats per patient was analyzed in the LQTS population. There was a high correlation (r=0.68) for RTm on RR, with an average RTm/RR slope of 0.21±0.08. There was no significant difference in the r correlation or RTm/RR slopes (β-blocker, 0.21±0.05; no β-blockers, 0.21±0.10) in those receiving and not receiving β-blockers.

The mean value for the RTm/RR slope (Tables 1 and 3) was significantly (p=0.003) larger in the LQTS patients (0.21±0.08) than in normal subjects (0.14± 0.03). The RTm/RR slope was similarly larger in the nine LQTS patients not receiving β-blockers (0.21±0.10) when compared with the normal subjects. Of note, the correlation coefficient of RTm on RR was smaller in the LQTS patients than in the normal patients (0.68±0.18 versus 0.82±0.06; p=0.008). Mean regression equations were obtained by averaging the slopes and intercepts separately for each population, and this information is graphically presented in Figure 3. These regression lines highlight the observation that LQTS patients have an increasingly exaggerated delay in repolarization at progressively longer RR cycle lengths when compared with normal subjects. Individual RTm versus RR regression lines superimposed on the raw data are presented in Figure 4 for a representative normal subject and a representative LQTS patient.

TABLE 2. Twenty-four–hour Holter Findings for Six Normal Subjects Receiving β-Blockers

Subject	Beats (*n*)	*r**	RTm/RR
1	85,248	0.69	0.08
2	75,349	0.63	0.07
3	91,877	0.81	0.09
4	75,907	0.78	0.10
5	76,847	0.72	0.11
6	78,102	0.81	0.12
Mean	80,555	0.74	0.10
±SD	±6,613	±0.07	±0.02

Subjects are the first six patients listed in Table 1.
*Pearson product–moment correlation of RTm on RR.

Discussion

This study describes a computerized method to automatically analyze the relation between repolarization duration and cycle length on 24-hour electrocardiographic (Holter) recordings. The use of the RTm interval instead of the conventional QT interval has proved to be feasible and has many advantages. Most impor-

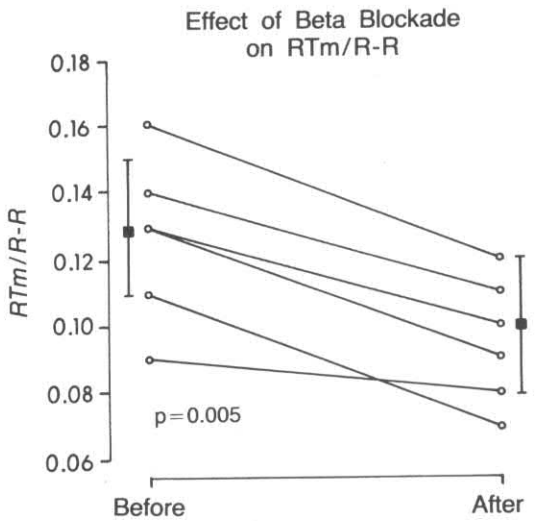

FIGURE 2. *The effect of β-blockade (before vs. after) on the RTm/RR slope in six normal subjects. β-Blockade is associated with a significant reduction in the RTm/RR slope from 0.13±0.02 to 0.10±0.02. Solid box and vertical lines represent mean+SD.*

TABLE 3. Clinical and Holter Characteristics for Long QT Syndrome Patients

Patient/ Sex	Age (years)	β-Blockers	ECG (seconds)			24-Hour Holter		
			RR	QT	QT_c	Beats (*n*)	*r**	RTm/RR
1/M	39	No	1.76	0.76	0.57	67,954	0.97	0.39
2/F	30	Yes	0.60	0.40	0.52	72,664	0.92	0.22
3/F	30	No	0.92	0.44	0.46	88,216	0.87	0.20
4/F	57	Yes	0.94	0.52	0.54	63,757	0.79	0.24
5/F	29	No	1.08	0.58	0.56	73,205	0.78	0.14
6/F	23	No	0.87	0.46	0.49	88,075	0.76	0.32
7/F	26	No	0.96	0.56	0.57	76,779	0.75	0.22
8/F	27	Yes	0.94	0.52	0.54	70,420	0.69	0.30
9/F	27	Yes	0.68	0.40	0.49	85,832	0.68	0.20
10/F	11	Yes	0.64	0.40	0.50	90,116	0.65	0.16
11/F	9	Yes	0.82	0.48	0.53	81,560	0.62	0.15
12/M	43	No	0.72	0.40	0.47	83,156	0.66	0.09
13/F	27	No	0.84	0.42	0.46	63,963	0.53	0.12
14/F	55	Yes	0.72	0.46	0.54	80,419	0.50	0.19
15/M	11	No	1.04	0.56	0.55	62,180	0.45	0.17
16/F	10	No	0.60	0.36	0.47	51,143	0.25	0.25
Mean	28		0.88	0.49	0.52	71,317	0.68	0.21
±SD	±15		±0.28	±0.11	±0.04	±9,779	±0.18	±0.08

M, male; F, female.
*Pearson product–moment correlation of RTm on RR.

tant, RTm is easily identified in the majority of the cases because it is limited by two sharp edges in the ECG (the R deflection and the maximum amplitude of the T wave). The QT interval requires accurate identification of the Q wave and the termination of the T wave, and the latter is often difficult to identify visually and by computer algorithm. The increased accuracy in the repolarization duration measurement that follows from the RTm definition allows the use of noninteractive software to analyze the 24-hour Holter recordings. As a consequence, for each individual, the quantification of the cycle length dependency of the repolarization duration can be obtained on a large number of heartbeats and, taking advantage of the physiological variations during the 24-hour period, over a wide range for both cycle length and repolarization durations. A linear equation describes the relation between repolarization duration and cycle length. An increase in the regression equation complexity by log-transforming the data did not improve the goodness of fit of the relation.

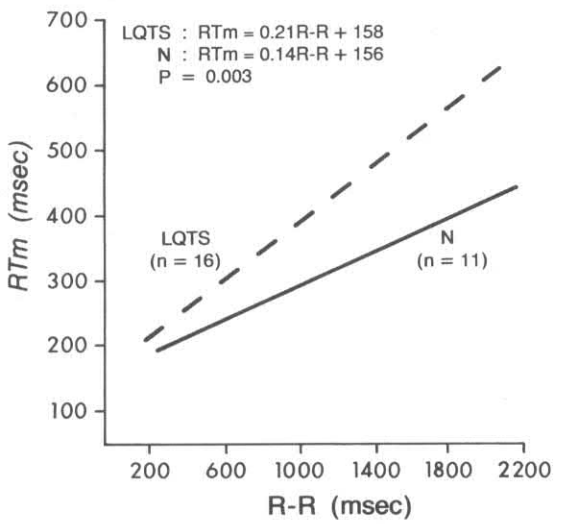

FIGURE 3. *Mean regression RTm/RR lines for 11 normal subjects (N) and 16 patients with long QT syndrome (LQTS). The RTm/RR slope is significantly larger in the LQTS patients than in the normal subjects.*

An important question is the accuracy of the algorithm used to process the electrocardiographic signals. With the extremely large number of beats processed per patient, it is likely that some "noisy" beats with inaccurately quantified RTm and RR intervals were included in the analyses because the intervals were within the prespecified physiological ranges; similarly, some beats with accurately quantified intervals were excluded because the intervals were outside these ranges. These false-positive and false-negative classifications are more likely to occur in beats having RTm and RR intervals near the border zone of the three selected physiological cut points. Our random sample validation indicated that the algorithm worked well. Furthermore, most quantified RTm and RR intervals were in close proximity to the central regression line. The accuracy of the analytical technique is high, with only a small percentage of misclassified intervals (overall error rate 8%).

This study did not involve a match of LQTS and normal subjects by age and sex. The imbalance in these parameters may have contributed to some of the observed difference in the RTm/RR slope between the two groups. We were also concerned that the difference in the RTm/RR slope between the LQTS patients and normal subjects might be influenced by the concomitant β-blocker therapy in seven of the 16

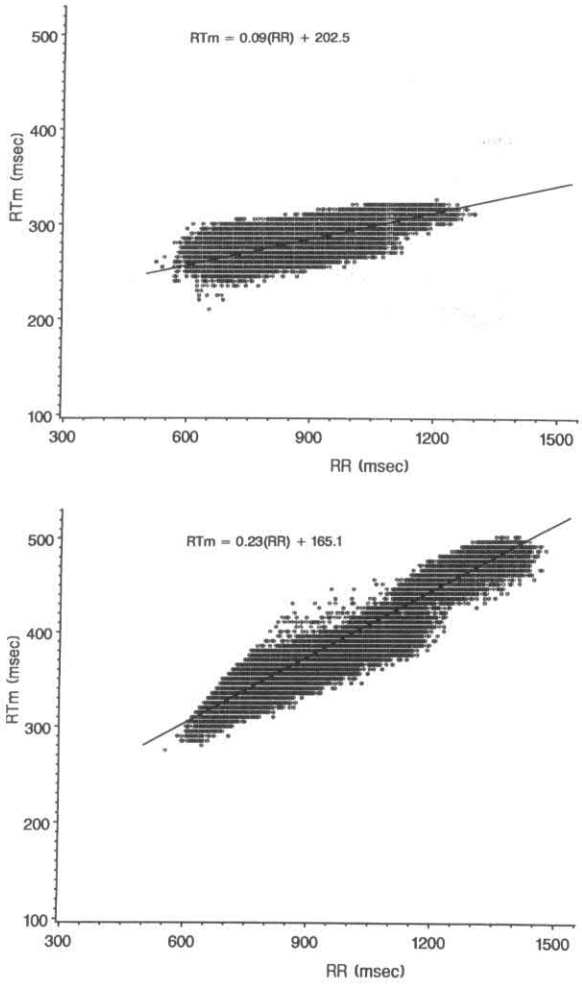

FIGURE 4. *Individual RTm vs. RR regression lines superimposed on the scattergram raw data for a representative normal subject* (top panel) *and a long QT syndrome patient* (bottom panel).

LQTS patients. Because we could not discontinue β-blocker therapy in the LQTS patients, we recorded a second Holter on six of the normal subjects after initiation of the long-acting β-blocker medication nadolol. β-Blocker therapy was associated with a significant 23% reduction in the RTm/RR slope in the normal subjects. We do not know whether other β-blockers with different membrane effects would give the same result. Of note, the RTm/RR slope was essentially the same in the LQTS patients receiving and not receiving β-blockers. Thus, it is unlikely that the increase in the RTm/RR slope observed in the LQTS population relative to the normal patients was related in any way to the β-blocker therapy. Furthermore, the RTm/RR slope in the nine LQTS patients not on β-blockers was significantly larger than the RTm/RR slope in the normal subjects.

The LQTS patients have a significantly increased RTm/RR slope when compared with normal individuals, indicating an exaggerated delay in repolarization with prolonged cycle lengths. This finding may provide additional insight into pause-dependent arrhythmic vulnerability in patients with delayed repolarization.[6,7] In such situations, the repolarization T wave in the beat immediately following a long pause may have a bizarre configuration and accentuated prolongation of the QT interval. This pattern may reflect the presence of afterdepolarizations that contribute to triggered ventricular arrhythmias in patients with prolonged repolarization.[6]

It has been hypothesized that the primary defect in LQTS is an impaired adaptation of the QT interval to abrupt changes in heart rate.[8] Our data suggest a different, more global heart rate–related disorder in LQTS, i.e., an abnormally increasing prolongation in ventricular repolarization at progressively slower heart rates. This pathophysiological aberration may be the substrate for the development of malignant arrhythmias at long cycle lengths.

An interesting finding in this study was the significantly smaller correlation coefficient of RTm on RR for LQTS patients than for normal patients. This lower correlation indicates a lesser dependence between the repolarization interval (RTm) and the preceding RR cycle length in LQTS than in normal subjects. This finding is consistent with partial uncoupling of the repolarization–cycle length relation. This uncoupling may be part of the fundamental electrophysiological abnormality in this disorder.

In the current series of six normal subjects, β-blockers produced a consistent and significant reduction in the RTm/RR slope—a finding indicative of proportionately smaller increases in RTm than RR over a wide range of decreasing heart rates. This pharmacodynamic action of β-blockers would explain the beneficial effect of this class of agents in most patients with LQTS.[8] However, β-blockers can be dysfunctional when an excessive bradycardia is induced by this medication. Recent studies have shown the usefulness of physiological pacing with and without concomitant β-blocker therapy in symptomatic patients with LQTS.[9] The rationale of such therapy is to prevent exaggerated QT prolongation that accompanies profound bradycardia; also, there may be some shortening of the absolute QT interval at augmented pacing rates.[10]

The dynamically recorded RTm/RR slope is a new quantitative measure that may be useful in identifying patients with the delayed repolarization syndrome. This present investigation evaluated patients with the idiopathic (familial) LQTS. The same approach may be useful in studying arrhythmia vulnerability in patients with acquired forms of QT prolongation such as occurs in patients treated with antiarrhythmic agents.[10,11] An increased RTm/RR slope in association with pharmacologically induced QT prolongation may indicate a vulnerability to pause-dependent ventricular arrhythmias. Additional investigation is warranted to explore further the dynamic relation involving repolarization duration, cycle length, and ventricular arrhythmias.

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