at distinguishing what is related to the HR as such and what has to deal with the ANS. At variance from HR variability, which provides information on the ANS through the normal sinoatrial node, investigating QT dynamicity yields a direct information on the normal or abnormal ventricular myocardium and the effect of the ANS. This explains why this approach is probably even more important; not only is it technically more difficult, but the interpretation of the results will be difficult. We are just at the beginning of this fruitful era.

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Automatic Detection of Spatial and Dynamic Heterogeneity of Repolarization

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Abstract: Heterogeneity of ventricular repolarization is associated with the development of life-threatening ventricular arrhythmias. Temporal heterogeneity of repolarization may be manifest in an individual beat (spatial heterogeneity) or in a sequence of beats (dynamic heterogeneity). Spatial inhomogeneity of repolarization throughout the myocardium may be expressed electrocardiographically as dispersion of repolarization durations computed in simultaneously recorded leads. The beat-to-beat changes in the repolarization pattern (duration and/or amplitude) may account for a dynamic (time-dependent) dimension of heterogeneity, occasionally seen as T-wave alternans. A visual detection of heterogeneous repolarization is a time-consuming, observer-dependent, and frequently inaccurate process. Therefore, we developed computer algorithms designed to detect automatically (1) dispersion of repolarization and (2) nonvisible T-wave alternans from digitally recorded (1,000 Hz) X, Y, and Z electrocardiogram leads. This automatic approach was subsequently tested in 10 patients with idiopathic long QT syndrome and in 10 age-matched normal subjects. Long QT syndrome patients presented with significantly higher indices of heterogeneity in comparison with the control subjects; the dispersion of repolarization was 44 ± 11 and 13 ± 6 ms, respectively ($P < .01$), and T-wave alternans index was 0.40 ± 0.37 and 0.03 ± 0.06, respectively ($P < .01$). Simultaneous evaluation of spatial (dispersion of repolarization) and dynamic (T-wave alternans) aspects of repolarization provides new insight into heterogeneity of electrical recovery after myocardial depolarization. The automatic detection of repolarization dispersion and T-wave alternans in digital electrocardiogram recordings provides a practical method to evaluate heterogeneity of repolarization and may be useful for stratifying patients at risk of ventricular arrhythmias. **Key words:** ventricular arrhythmia, T-wave alternans, repolarization, heterogeneity, long QT syndrome, dispersion.

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Primary or secondary QT prolongation is a known factor predisposing to the occurrence of ventricular arrhythmias. Many experimental and clinical investigations indicate that an overall prolongation of repolarization duration can be associated with the development of life-threatening ven-

tricular arrhythmias.[1–5] Prolongation of repolarization may significantly increase the risk of arrhythmias but is not an obligate factor for ventricular arrhythmias to occur. Rather, a nonuniform recovery of excitability in the myocardium appears to be essential for arrhythmia triggering. In 1964, Han and Moe[6] documented an association between nonuniform recovery of excitability and lowered ventricular fibrillation threshold. Further electrophysiologic studies confirmed a significant contribution of nonuniform recovery of excitability to arrhythmia induction.[7–9] A nonuniform recovery of excitability can be more prominent in patients with prolonged repolarization but may also occur in patients with normal repolarization duration, usually caused by pathologic (eg, necrosis, ischemia) changes in the myocardium or mediated by an imbalance of the autonomic nervous system.[8–10] Experimental and clinical studies have demonstrated that the duration of repolarization measured in surface electrocardiogram (ECG) leads may be considered representative of the duration of recovery of myocardial excitability.[6–11] Therefore, heterogeneity of repolarization evaluated in surface ECG leads may be used to evaluate the magnitude of nonuniform recovery of excitation.

Spatial and Dynamic Heterogeneity of Repolarization

Figure 1 shows a three-channel Holter recording of a long QT syndrome patient with marked heterogeneity of repolarization expressed by interlead changes in repolarization duration and beat-to-beat alterations in T-wave configuration. This example clearly indicates that heterogeneity of repolarization should be considered a (at least) two-dimensional phenomenon. A spatial heterogeneity may be defined by the dispersion of repolarization durations computed in simultaneously recorded leads (QT dispersion). The beat-to-beat changes in the repolarization pattern (duration and/or amplitude) may account for a dynamic (time-dependent) dimension of heterogeneity, as manifest by T-wave alternans. Both QT dispersion and T-wave alternans seem to be precipitated by an interregional variation in repolarization pattern throughout the myocardium.

Interregional heterogeneity of repolarization may be explained by a variability in the shape and duration of action potentials throughout the myocardium (eg, epicardial-endocardial or anterior-posterior differences).[8,10,12–14] An additional meaningful contribution to repolarization variability has been the identification of M cells that were found to have an excessive prolongation of action potential duration in comparison to the endo- or epicardial cells.[15] Because the M cells may account for a large part of midmyocardium, their role in heterogeneity of repolarization is probably even larger that expected.

Hypothesized Ionic Mechanisms of Heterogeneous Repolarization

Interregional differences in ionic channel distribution and kinetics may account for the spatial heterogeneity (dispersion of repolarization). A distinct distribution in the kinetics of ionic (mainly potassium) channels throughout the myocardium was documented by Antzelevich's group for a potassium transient outward current.[14,15] However,

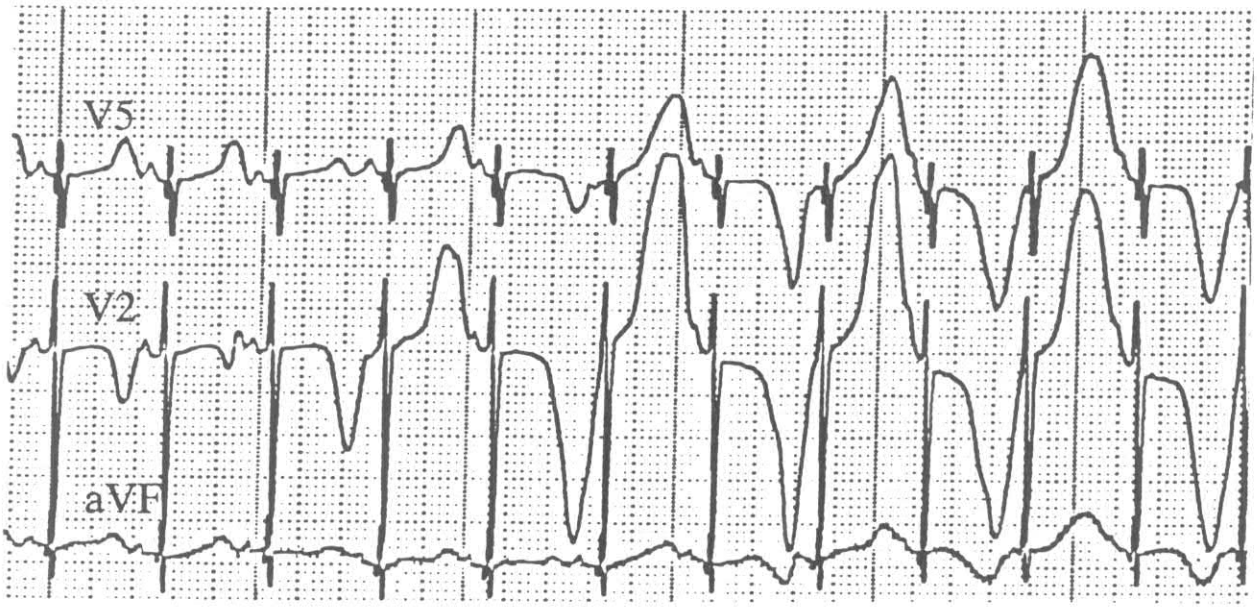

Fig. 1. Continuous Holter recording of heterogenous repolarization in a 2-year-old patient with long QT syndrome. Note interlead changes in repolarization duration and beat-to-beat changes in T-wave configuration.

the mechanisms responsible for T-wave alternans, a feature of dynamic heterogeneity, appear to be more complex. Because the occurrence of T-wave alternans is significantly related to the heart rate[16] and to the repolarization duration,[17] the cycle length–repolarization durations relationship[18] may play a crucial role for the initiation of T-wave alternans. The beat-by-beat changes in ionic channel kinetics may be an essential mechanism underlying the conditions for this phenomenon.

Current passing through slow delayed rectifier potassium channels (I_{Ks}) is particularly important in determining the time at which repolarization begins and the rate at which it occurs. It is entirely possible that delayed ventricular repolarization as manifest by a prolonged QTc interval may be due to slower than normal channel kinetics for I_{Ks} or any other channel that contributes to the time course of the change in the balance of inward and outward membrane currents during phases 1, 2, and 3 of the action potential.[19–21] The presence of very slow I_{Ks} kinetics relative to the cycle length could contribute to the beat-to-beat T-wave changes that characterize T-wave alternans (Fig. 2). With prolonged repolarization of an action potential (beat 1 in a sequence), it is hypothesized that I_{Ks} channels return to the closed state with a slower than normal time course. The next action potential (beat 2) would be stimulated when a fraction of I_{Ks} channels has not yet returned to the closed state. Because some I_{Ks} channels are still open, the time to reach a critical number of open I_{Ks} channels to begin phase 3 repolarization during beat 2 will be shorter than for beats in which all these channels had been closed at the onset of depolarization. Hence, action potential of beat 2 will be shorter than the first. After this briefer period of activation, provided the heart rate is constant, there will be a longer diastolic period during which a larger fraction of I_{Ks} channels can return to the closed state. Then, at the time the next action potential starts (beat 3 in this sequence), almost all the I_{Ks} channels would be closed; the time to reach the critical number of open channels during the next action potential would be similar to that of action potential 1, resulting in a more prolonged action potential and, in turn, a longer QTc interval. This sequence of repetitive short and long action potential durations (with alternating repolarization length) may eventually subside when a steady-state relationship is reached for a fixed heart rate. Alternans is reinitiated when a change in channel kinetics or cycle length occurs. In such a hypothetical scheme, the probability of developing alteration in T-wave duration would be influenced by the critical relationship between repolarization duration and cycle length—the two components of QTc ($QT\sqrt{RR}$). The various magnitudes of T-wave alternans[18] may be related to the duration of the prolonged repolarization and to the amount of involved myocardium. With minor (monophasic) T-wave alternans, the heterogeneity of the delayed channel kinetics may involve only a small amount of myocardium, whereas in the case of marked (biphasic) T-wave alternans, the beat-to-beat polarity change may reflect more extensive heterogeneity of delayed ionic kinetics. These hypotheses need to be proved in future experimental studies.

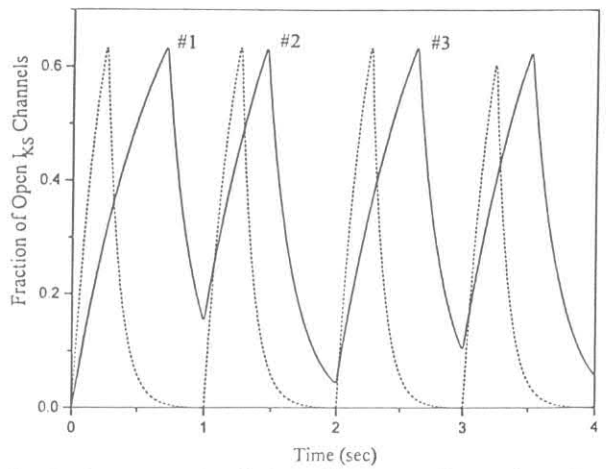

Fig. 2. Computer simulation of the hypothesized mechanism of T-wave alternans: time course of delayed rectifier potassium channels (I_{Ks}) opening at a fixed cycle length (1 second) in relation to the fraction of opened channels. Dashed line, normal-channel kinetics; solid line, slow-channel kinetics.

Dispersion of Repolarization in Clinical Studies

Experimental investigations, which proved a meaningful contribution of nonuniform recovery of myocardial excitability for arrhythmia generation,[6–11] established the foundation for further clinical studies. Primarily, dispersion of repolarization was analyzed from body surface maps.[22–24] In 1984, Sylven et al.[22] recorded 120-lead body surface maps in 14 patients with mainly secondary QT prolongation and demonstrated significantly increased QT interval variability in comparison to the normal subjects. Similar findings, based on 117-lead ECG recordings, were also reported by DeAmbroggi et al.[23] in patients with idiopathic long QT syndrome. A marked spatial variation in QT intervals measured by 150-electrode mapping was also demonstrated by Mirrvis[24] in 30 patients with acute myocardial infarction.

The body surface mapping, although excellent for electrophysiologic investigations, is not a practical approach to evaluate larger groups of patients. Therefore, a standard 12-lead ECG recording has been considered as a fundamental method to evaluate (either manually or automatically) dispersion of repolarization in clinical settings.[25–27] In 1989, Merri et al.[26] reported preliminary observations on automatic measurements of heterogeneity from a standard (digital Marquette [Milwaukee, WI]) 12-lead ECG in normal subjects, further enhanced in long QT syndrome patients.[28] An increased dispersion of QT intervals, measured manually on a standard 12-lead ECG in patients with long QT syndrome, was also observed by others.[29,30]

Patients with ischemic heart disease are the other population in whom dispersion of repolarization should be considered as a potential risk factor for cardiac death. Recently,

we investigated the prognostic significance of dispersion of repolarization measured on a 12-lead ECG after an acute coronary event in a group of 68 coronary patients, 17 of whom died from arrhythmic cardiac death during a mean 2-year follow-up period.[31] In that study, an increased dispersion of repolarization made an independent and significant contribution to the risk of arrhythmic cardiac death in patients with ischemic heart disease. A significant association between QT dispersion and sudden death was also recently found in patients with chronic heart failure.[32]

A visual detection of dispersion of repolarization is a time-consuming, observer-dependent, and frequently inaccurate process. An automatic analysis of repolarization duration and configuration may overcome these difficulties. Recently, Bhullar et al.[33] proposed a computerized method to detect automatically dispersion of repolarization from a hard-copy ECG. This approach, despite some limitations, can be valuable if there is no access to digital ECG recordings (or for retrospective analyses of hard-copy ECGs). Currently, most ECG machines provide the ability to record and store ECG signals in digital form. A direct analysis of digitalized signals (particularly if recorded with a high sampling frequency) can be carried out. Previously, our group[26,27] showed that the duration of repolarization can be reliably measured by applying a designated computer algorithm. Subsequently, we developed a computerized approach to detect automatically dispersion of repolarization from a three-channel Holter recording.[34]

Visible and Nonvisible T-wave Alternans

T-wave alternans was described in literature from the beginning of electrocardiography but mainly as case report studies, with some of them demonstrating that this occasionally recorded ECG phenomenon may be associated with subsequent episodes of torsades de pointes or ventricular fibrillation.[10,35,36] Recently, in our large International Long QT Syndrome Registry, we identified a series of 30 patients with T-wave alternans recorded on a 12-lead ECG.[17] We observed that the development and the pattern of T-wave alternans in long QT syndrome patients was strongly associated with the magnitude of repolarization delay. Long QT syndrome patients with recorded T-wave alternans had an increased risk of cardiac events, but the risk was primarily associated with QTc prolongation. Interestingly, the ECG recording of biphasic beat-to-beat changes in T-wave configuration indicated an increased likelihood of frequent (more than five in a patient) episodes of cardiac events, confirming again that T-wave alternans should be treated as a marker of electrical instability. However, the number of patients with recognized T-wave alternans in this population was limited, because only visible (on 12-lead ECG) forms of T-wave alternans were analyzed. Based on the observed association between occurrence of T-wave alternans and QTc prolongation, we may speculate that much larger numbers of long QT syndrome patients probably have T-wave alternans, but in most of them, the T-wave changes were too discrete (nonvisible) to be detected by the naked eye. A computer detection of nonvisible T-wave alternans has been reported previously in animal studies by Adam et al.[37] and Nearing et al.,[38] who confirmed a significant relationship between the magnitude of T-wave alternans and decreased ventricular fibrillation threshold. Recently, Rosenbaum et al.[39] confirmed in a clinical study of 69 patients referred to electrophysiologic testing that T-wave alternans (evaluated during atrial pacing) was an independent predictor of inducibility of ventricular arrhythmias and subsequent arrhythmic events. Independently, we developed (see below) a dedicated computer algorithm to detect nonvisible forms of T-wave alternans from three-lead Holter ECG recordings, further validated in long QT syndrome patients.[40]

Computerized Approach for Complex Evaluation of Heterogeneous Repolarization

Large and complex heterogeneity of repolarization (as in Fig. 1) is unusual. In most patients, the magnitude of heterogeneous repolarization is much more subtle, thus requiring automatic and more precise techniques of measurements. To evaluate ECG features of nonuniform recovery of excitability automatically, we decided to analyze simultaneously the spatial and dynamic heterogeneity of repolarization, applying our recently developed computerized algorithms designated to detect dispersion of repolarization and nonvisible T-wave alternans.[34,40] The long QT syndrome patients, who are particularly predisposed to present with bizarre repolarization patterns,[1,28] were chosen to test this approach.

Thus, in 10 patients with long QT syndrome with Bazett's heart rate corrected QTc of 520 ± 78 $ms^{1/2}$, and in 10 control subjects with normal QTc values (QTc of 372 ± 14 $ms^{1/2}$), short-term digital ECG recordings were made. Electrocardiograms were acquired using a digital, three-channel DMI AltairDisc Holter recorder (Diagnostic Medical Instrument, Inc., Syracuse, NY) set at a sampling frequency of 1,000 Hz per channel.[41] The X, Y, and Z bipolar, orthogonal ECG leads, which are likely to demonstrate three-dimensional changes in repolarization pattern, were chosen for recordings. After ECG acquisition, the digital data were transferred to a SUN Server (Mount View, CA) 4/470, for further analyses.

Four-minute time series of acquired ECG signals were analyzed to evaluate the duration and configuration of repolarization in X, Y, and Z leads. After QRS detection, a beat-specific baseline was estimated[42] for low-frequency drift adjustment, and the repolarization segment (1-second window after the peak of R wave) was smoothed with a moving average filter (main lobe cutoff 20 Hz). Thereafter, first and second derivatives of the filtered signals within the repolarization segment were computed to define the peak, the beginning, and the end of the T wave. The dura-

tion of repolarization was computed in each lead from the peak of the R wave to the end of the T wave (RT). The heart rate-adjusted (with preceding RR interval) RTc was also calculated for each beat. U wave, when apparent, was not included in the measured duration of repolarization.

Dispersion of repolarization was evaluated computing a maximal difference in repolarization durations between simultaneously recorded X, Y, and Z leads for each recorded beat. The median values of a maximal RT difference (RTd) were used as measures of the dispersion magnitude.

For T-wave alternans analysis, beat-by-beat baseline-adjusted T-wave areas were computed in each lead. Thereafter, the autocorrelation function of the T-wave area time series was applied to quantify the magnitude of T-wave alternans by means of a T-wave alternans index (TWAI). This index was calculated by adding the "upstrokes" of the autocorrelation function lasting at most 1 lag in the first 10 lags of the function. The median of maximal TWAI values in any of three leads was used to measure the extent of T-wave alternans.

Heterogeneity of Repolarization in Long QT Syndrome Patients

The long QT syndrome patients compared with the 10 control subjects showed a similar heart rate (mean RR interval, 1,019 ± 192 and 925 ± 114 ms, respectively) and, as expected, demonstrated significantly longer RTc values (Table 1). All long QT syndrome patients had increased values of repolarization dispersion, a mean RTd of 44 ± 11 ms (23–56 ms). Control subjects presented with a significantly lower magnitude of dispersion with a maximal RTd of 22 ms (mean, 13 ± 11 ms). All long QT syndrome patients showed higher values of dispersion than controls, despite the fact that during ECG recordings they were treated with beta-blockers, drugs likely to influence the magnitude of dispersion of repolarization.[43]

T-wave alternans index (Table 1) was equal to zero in eight control subjects, and in the other two, the values of TWAIs were 0.08 and 0.18. The long QT syndrome patients showed remarkably higher values of TWAI (0.40 ± 0.34); in two patients, T-wave alternans was equal to zero.

Complex evaluation of the heterogeneity of repolarization, performed by a simultaneous assessment of the above ECG parameters of dispersion and T-wave alternans in each studied subject, showed that all long QT syndrome patients demonstrated a marked heterogeneity of repolarization. In six of them, both the dispersion of repolarization and T-wave alternans indices were increased, whereas in the other four patients, either of the two parameters of heterogeneity (RTd or TWAI) were elevated.

Clinical Implications of Automatic Analysis of Heterogeneous Repolarization

A nonuniform recovery of excitability in myocardium, which contributes significantly to the risk of ventricular

Table 1. Dispersion of Repolarization (RTd) and T Wave Alternans (TWAI) in Long QT Syndrome Patients Compared to Control Subjects

Group	QTc ($ms^{1/2}$)	RTc ($ms^{1/2}$)	RTd (ms)	TWAI
Control subjects				
1	390	321	7	0.00
2	375	354	21	0.00
3	360	331	11	0.00
4	377	345	9	0.00
5	379	323	10	0.08
6	357	315	9	0.00
7	389	334	9	0.00
8	381	325	11	0.00
9	362	311	19	0.18
10	351	322	22	0.00
Mean ± SD	372 ± 14	328 ± 13	13 ± 6	0.03 ± 0.06
LQTS patients				
1	696	516	54	1.29
2	505	435	41	0.36
3	450	418	54	0.00
4	542	492	56	0.63
5	605	443	53	0.40
6	494	487	23	0.31
7	452	376	41	0.39
8	478	439	35	0.00
9	462	414	38	0.19
10	527	475	41	0.42
Mean ± SD	521 ± 78*	450 ± 43*	44 ± 11*	0.40 ± 0.34*

* Significantly higher than in the control subjects ($P < .01$).

arrhythmias, can be evaluated in clinical settings by a simultaneous analysis of spatial (dispersion of repolarization) and dynamic (T-wave alternans) heterogeneity of repolarization. The automatic detection of repolarization dispersion and T-wave alternans from surface ECG leads may become a practical method to evaluate heterogeneity of repolarization in various patient populations. This innovative approach may provide an opportunity not only to stratify patients at risk of ventricular arrhythmias but also to evaluate spontaneous or triggered (by ischemia or drugs) changes in heterogeneity of repolarization during long-term ECG monitoring.

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Sex Differences in the Rate of Cardiac Repolarization

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Although the rate-corrected QT interval and early duration of repolarization (S-offset to T-wave apex) are typically longer in women than in men, it is not clear whether these differences are due to disparate rates of early and/or later phases of cardiac repolarization. Accordingly, we quantitated and compared maximum instantaneous rates of repolarization in the ascending and descending limbs of the T waves in women and men.

We studied 617 normal subjects (481 men, 136 women; mean age, 37 years). All subjects had normal histories and physical examinations, were on no cardiac medication, and were in normal sinus rhythm at 60, 70, or 80 beats/min. None had evidence of bundle branch block, left ventricular hypertrophy, intraventricular conduction defect, or myocardial infarction. Electrocardiograms (ECGs) were recorded as digitized data on MAC-12 ECG machines (Marquette Electronics, Milwaukee, WI). Surface lead V_5 was chosen for measuring repolarization variables. Before variables were measured, ECG recordings were excluded from further analysis when T-wave amplitude was lower than 0.10 mV, the T waves were negative or had humps, or the recorded data file was incomplete. A computer algorithm running on a PC-486 machine was designed to interactively process and analyze these digitized ECG data. Electrocardiogram variables in our analysis consisted of QT, maximum dV/dt, minimum dV/dt, QTm, JTm, time from Q to maximum dV/dt, time from Q to minimum dV/dt, time from J to maximum dV/dt, and time from J to mini-

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