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Tracking Repolarization Dynamics in Real-Life Data

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Abstract: Ambulatory (Holter) electrocardiographic recordings provide the tools for tracking temporal instabilities of repolarization during various daily activities. However, analysis of low-amplitude repolarization changes in this setting is challenging due to the presence of multiple artifacts, variable activity levels, and other uncontrolled factors. Here we compare performance of different methods for continuous analysis of repolarization dynamics using simulated signals and real-life Holter recordings. Selection of relatively stable segments with a low baseline drift and accurate correction of baseline wander constitute the first step in repolarization analysis. We describe application of adaptive filtering, which yields more accurate results than non-adaptive techniques. Because small (microvolt-level) residual baseline drifts can be a source of error in tracking repolarization changes, stability of isoelectrical segment has to be controlled. To compare robustness of spectral and time-domain techniques for tracking temporal repolarization instabilities (T-wave alternans, TWA), we used simulated signals with changing heart rate, variable levels of TWA, noise, phase shifts, spurious artifacts, and period-four oscillations. In addition, we compared performances of the inter-beat and intra-beat averaging techniques for tracking dynamics of T-wave alternans. Using the simulated signals and real-life Holter data, we showed that analysis of information both in time and frequency domains combined with control of baseline drifts (surrogate analysis) gives a more reliable estimate of the low-amplitude repolarization dynamics than each of these techniques alone. To summarize, dynamic tracking of low-amplitude repolarization changes in ambulatory recordings is possible during most of the recording time but requires accurate control of baseline wander and stability of isoelectrical segments. Analysis of time-frequency distributions embedded in repolarization dynamics facilitates detection of abrupt and transient repolarization instabilities, including changes in the level of T-wave alternans and slower periodicities. **Key words:** Cardiac repolarization, dynamic analysis, T-wave alternans.

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Tracking cardiac repolarization instabilities has proved useful for identification of subjects at a high risk of arrhythmic events (1). Analysis of beat-to-beat alterations in the T-wave morphology (T-wave alternans, TWA) has become a clinical test of arrhythmia vulnerability and a predictor of future arrhythmic events in some patient populations (2). An increase in repolarization instability has also been reported prior to the initiation of ventricular fibrillation in an ischemic dog model (3). These clinical and experimental data, although obtained in a controlled setting, suggested that dynamic repolarization analysis could be extended to real-life conditions, which include regular daily activities and sleep, to uncover the instabilities and transients that precede and, possibly, facilitate the initiation of spontaneous events. However, analysis of small (microvolt-level) changes in electrocardiographic (ECG) signals in an ambulatory setting represents a major challenge due to the presence of multiple uncontrolled factors, including physical activity, variable respiration frequency, motion artifacts, noise, and changes in body position. Since repolarization instability is a dynamic phenomenon, which could be elicited or aggravated by changes in autonomic nervous system activity, physical exercises or mental stress, an ideal analytical approach has to be dynamic as well (4,5).

The signal processing methods that have been developed for analysis of repolarization instabilities include both frequency and time-domain techniques. The frequency-domain approach has an advantage of representing the entire spectrum of frequency elements, so that the impact of each element on repolarization instability can be assessed. This approach, however, has several limitations. Because of the requirements of signal stationarity during each time interval, this method is not appropriate for quantifying transients and abrupt changes; it is usually applied to signals obtained in controlled conditions (2). The time-domain techniques have lesser sensitivity to non-stationarities but cannot discriminate between T-wave alternans and slower periodicities (6).

Thus, uncertainty exists regarding whether and how repolarization instability can be analyzed in real-life ambulatory (Holter) recordings. The goal of this study was to compare the performance of different methods for analysis of repolarization dynamics using simulated signals with various noises and artifacts as well as real-life Holter data. We show that analysis of information both in time and frequency domains (time-frequency distributions) as well as the surrogate analysis (baseline control) is useful for quantification of transient changes in the level of T-wave alternans and slower periodicities.

Materials and Methods

Analysis of Simulated Data

To probe the accuracy of different methods in detecting repolarization instabilities, we used the methodology described by Nearing and Verrier (7). A simulated ECG signal was constructed by concatenating a single normal cardiac complex to produce a signal with a zero-level TWA and 1 sec-long RR intervals. Next, we simulated consecutively: 1) increasing levels of TWA (10,20,50, 100, 200, 500, and 1000 μV); 2) increasing (as above) levels of solitary spikes during T-waves (representing motion artifacts); 3) heart rate increasing from 60 to 180 bpm in 10-bpm increments with the length of cardiac complexes adjusted to the change in heart rate according to the following formula $N=S\times60/HR$; $L_x= L_{x-1}$(1 : where S is the sampling frequency, HR denotes heart rate, and N is the length of the current cardiac complex, and 4) multiple phase-reversals in TWA (frequency: 5 phase-shifts/min)*. In addition, performance of the methods was tested on simulated period-four oscillations in the T-wave morphology. Oscillations at this frequency can be generated by respiratory movements and can represent a confounding source of variations in the repolarization segment. Importantly, these oscillations can interfere with the detection of other periodicities, such as period-three oscillations, which can herald an imminent onset of chaos (8). Finally, to examine robustness of each method to different levels of random noise, the above-described simulations were repeated after addition of 5, 10, 25, 50, 100, 200, and 300 μV random noise.

Inter-Beat and Intra-Beat Averaging

We applied 2 time-domain approaches to the analysis of repolarization instabilities: the inter-beat averaging (the modified moving average, MMA) as described by Nearing and Verrier (7) and the intra-beat averaging (IBA) approach. In the MMA approach, TWA is first determined for each point in the JT-segment and then averaged over all points in

**A phase reversal in the sequence of alternating (larger-smaller-larger-smaller) T-waves occurs when some T-waves in the sequence are out of phase with the previous beats, for example: larger-smaller-smaller-larger-smaller T-waves.*

the entire JT-segment. In the IBA, the intra-beat averaging is applied first by calculating the mean T-wave amplitudes (between the onset and offset of the T wave) in each beat, and then TWA is calculated by serial subtraction of these mean T-wave amplitudes for all consecutive cardiac complexes in the 5-min segment.

Real-Life Data Analysis

Baseline Correction

Removal of the low-frequency elements of baseline drift is difficult in the context of repolarization analysis, because the frequency of repolarization waveforms lies in the low-frequency range. Since any filtering of the ECG signal causes certain distortion of the cardiac complexes in general, and repolarization waveforms in particular, an ideal filter for baseline correction must identify the periods that have minimal or no baseline artifacts and avoid filtering of those segments.

A number of filters and correction techniques have been developed, but due to the changing frequency of baseline wander, adaptive filtering can be advantageous compared to non-adaptive approaches. One can estimate the magnitude of baseline drift using an RMS error of fitting a straight line to a cumulative squared signal (9). Using this method, Holter recordings were shown to have a low RMS error (corresponding to a low-amplitude baseline drift) during approximately 75% of the recording time. Since the lowest frequency components of the cardiac complexes in more than 99% of adults, 99% of the time are greater than 0.67 Hz, the spectral energy in the range 0-0.67 Hz can be assumed to represent total energy of baseline wander (10). Therefore, the cutoff frequency for the baseline filter can be taken as the higher border of the frequency range that contains 99% of the total energy in the 0-0.67 Hz range. Compared to high-pass filtering, these adaptive procedures allow two-fold reduction in the error of the T-wave amplitude estimation (9). The filtering, however, cannot remove the baseline completely, and a piece-wise linear correction of residual wander is required afterwards locally (in the vicinity of each cardiac complex) (9).

Although the above-described filtering approach makes the baseline substantially more stable, a small (5–20 μV) residual baseline drift can still exist in the signal after the filtering (9). This residual baseline variation can introduce significant errors into the analysis of low-amplitude (microVolt level) changes in repolarization and requires additional control (surrogate analysis) as described below.

Selection of Fiducial Points

Fiducial points were detected as previously described (11). In short, the algorithm selected the largest number of QRS complexes with a >.85 correlation in each 5-min interval. Then, the selected QRS complexes were averaged over the 5 minutes to construct an average template, on which the algorithm determines the onset, peak, and the offset of P, Q, R, S, and T-waves using adaptively adjusted thresholds that depend on the local amplitude and derivative of the corresponding waveform and the local baseline. If the points were not found, the program requested a manual input from an operator.

To exclude spurious (motion) artifacts, which may contaminate analysis of repolarization, the algorithm also required that the amplitudes of the individual T-waves are within the range of mean ± standard deviation of the average template.

Testing the Quality of Local Baseline

To separate low-amplitude repolarization changes from residual baseline wander and motion artifacts, we used the approach described by Nearing and Verrier (7). In particular, the algorithm determined the maximum displacement from the zero-level and the standard deviation of the TP segment in each beat. If the maximum displacement or the standard deviation of the TP segment was greater than the predefined thresholds (50 μV), the corresponding beats were excluded from the analysis.

In addition, temporal stability of isoelectric segment was tested by applying the beat-to-beat T-wave alternans analysis to the isoelectric part of the TP-segment. (This method was referred to as the surrogate TWA.) The time series of the surrogate TWA were compared to those of the "true" TWA.

Analysis of Repolarization Instability

The MMA and IBA methods described above were applied to Holter ECG data. In addition, spectral analysis of the time series comprised from the mean T-wave amplitudes was performed to test for the presence of slower periodicities in the signal. The integrated power between 0.15–0.4 cycles/beat, the peak frequency, and the peak magnitude

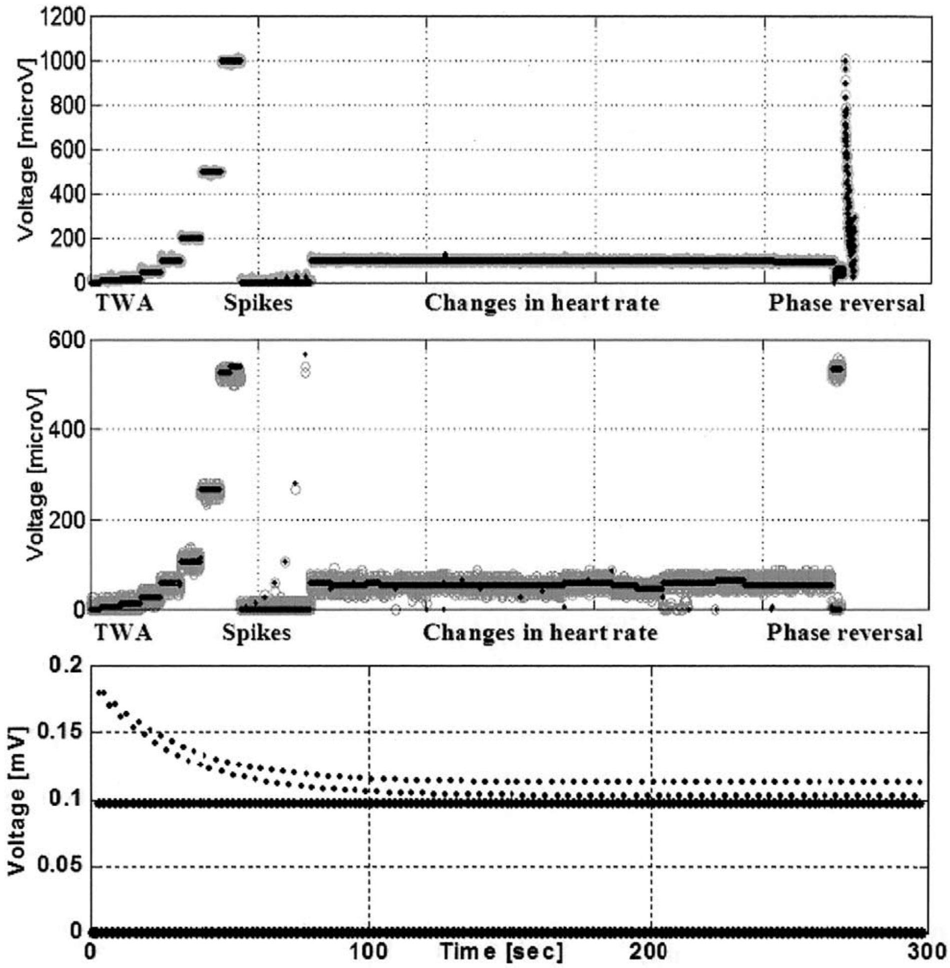

Fig. 1. Simulated ECG signals (see Materials and Methods for details) with added 25-μV random noise (light-gray) and without noise (black) were analyzed using the (A) Modified Moving Average and (B) Intra-Beat Averaging. Each point represents the magnitude of TWA in a 15-sec interval; the total length of the simulated signal is approximately 4 hours. Note that the MMA is more robust to the spurious artifacts [the spread of the light-gray area along the y-axis is smaller in (A) compared to the (B)]. On the other hand, during the last period of a constant-level TWA with phase-reversals, MMA inaccurately shows that the level of TWA is changing both in the noisy (light-grey) and clean (black) ECG signal. (C) Estimation of T-wave alternans in the presence of period-4 oscillations using MMA (dotted lines) and IBA (solid lines at 0 and 0.1 mV). See text for details.

in this frequency range were analyzed in each 5-min interval.

Selection of the Time Window

Choice of an appropriate time window for repolarization analysis is not simple. Selection of a long scale may obscure detection of short transients, whereas selection of a short scale would increase the impact of local artifacts and noise. The 5-min intervals that we used for analysis have also been previously used in a number of studies, because 1) autonomic activity is relatively stable over this period, which makes the signal more stationary and simplifies the analysis, and 2) this time window provides enough data for averaging and filtering out of spurious artifacts (11).

Results

Repolarization Dynamics in the Simulated Signals

Figure 1 shows application of MMA (top panel) and IBA (middle panel) to the simulated signals with added 25-μV random noise and without noise. Note that because MMA limits the impact of variations in the data points, the effect of spurious artifacts on the estimated TWA is smaller with MMA than with IBA. However, due to the slower "time-response" of MMA, it leads to inaccurate estimation of the TWA during the last section of the signal, when phase-reversals in the sequence of alternating T waves occur. Although the 2 methods show similar trends in the level of TWA, the output values (y-scales) are different. Since MMA shows the maximum amplitude difference, a 1000-μV TWA in the test signal would yield a 1000-μV output value. However, the same test signal would give an almost two-times smaller output with the IBA, which estimates differences between the mean amplitudes of the T waves. Note also that both MMA and IBA methods may erroneously represent the period-four oscillations as the period-two TWA (Fig. 1, bottom panel). The IBA shows two co-existing levels of TWA (at 0 and 0.1 mV), which suggest the presence of slower periodicities. With MMA, the period-four oscillations are more difficult to detect because of the time-smoothing properties of this method.

Figure 2, top panel, shows the RMS error of TWA estimation using MMA and IBA in the presence of different levels of random noise. Although the 2 methods produce similar trends of the RMS curves, MMA gives a smaller error due to the restricted impact of variations in the data points as discussed earlier (7).The greater robustness to noise of the MMA is of particular importance when low-amplitude TWA is studied.

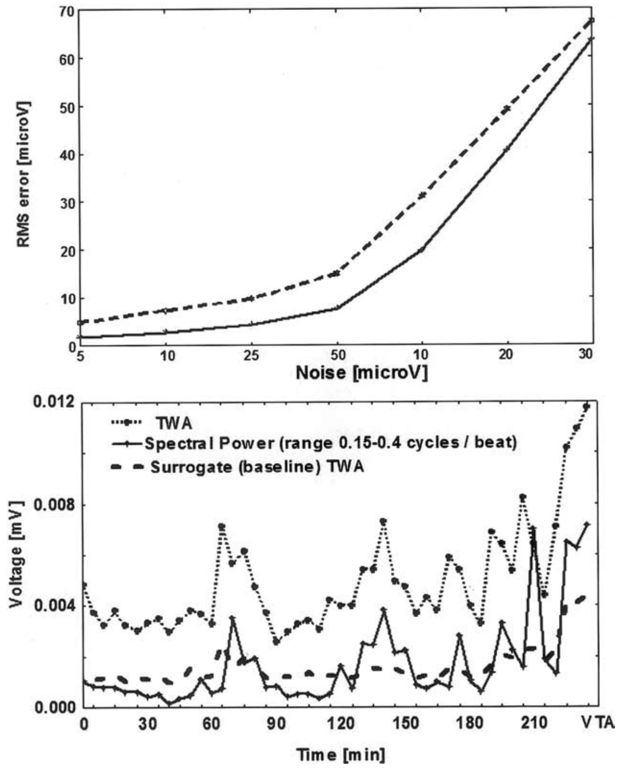

Fig. 2. (A) RMS error of the T-wave alternans estimation using the Modified Moving Average (solid line) and the Intra-Beat Average (dashed line) analysis for different levels of random noise. The trends of the RMS curves are similar for the 2 methods, however, the MMA gives a smaller error due to the limited impact of variations in the data points. (B) Dynamics of T-wave alternans (TWA), spectral power (range: 0.15-0.4 cycles/beat), and surrogate (baseline) TWA in a subject during 4 hours before the onset of spontaneous sustained ventricular tachyarrhythmia (VTA). VTA starts at the end of the 4-hour period. Note that most of the time, the dynamics of the three indices are similar, because the baseline drift (surrogate TWA) is included in the estimated "true" TWA and because the dynamics of the spectral energy and that of TWA obtained over 5-min intervals are correlated. However, approximately 15 min before the arrhythmia, the 3 indices become dissociated because of the predominant rise in TWA. See text for details.

Repolarization Changes in Real-Life Holter ECG Signals

Figure 2, bottom panel, shows changes in the T-wave alternans (measured by IBA), surrogate (baseline) TWA, and the spectral energy (range: 0.15–0.4 cycles/beat) in a Holter ECG during 4 hours before the onset of spontaneous sustained (>30 sec) monomorphic ventricular tachycardia. Note that all 3 indices mirror each other most of the recording time because: 1) the baseline drift is included in the estimated amplitude of the T wave, and 2) the time series of TWA and the spectral power computed over the 5-min intervals are correlated. However, approximately 15 minutes before the event, the dynamics of these indices become dissociated. A surge in the magnitude of the T-wave alternans is greater than that of the spectral power or the surrogate (baseline) TWA. This dissociation shows the predominant rise in the level of T-wave alternans before the onset of arrhythmia. Furthermore, the increase in the spectral power concomitant with the increase in TWA indicates that the temporal repolarization instabilities include a number of frequency elements in addition to TWA. A modest increase in the level of surrogate (baseline) TWA could be related to greater physical or psychological activity, which is usually associated with enhanced motion and respiratory artifacts as well as changes in the skin resistance (under the electrodes) due to the enhanced perspiration. Further support for this hypothesis comes from an observa-

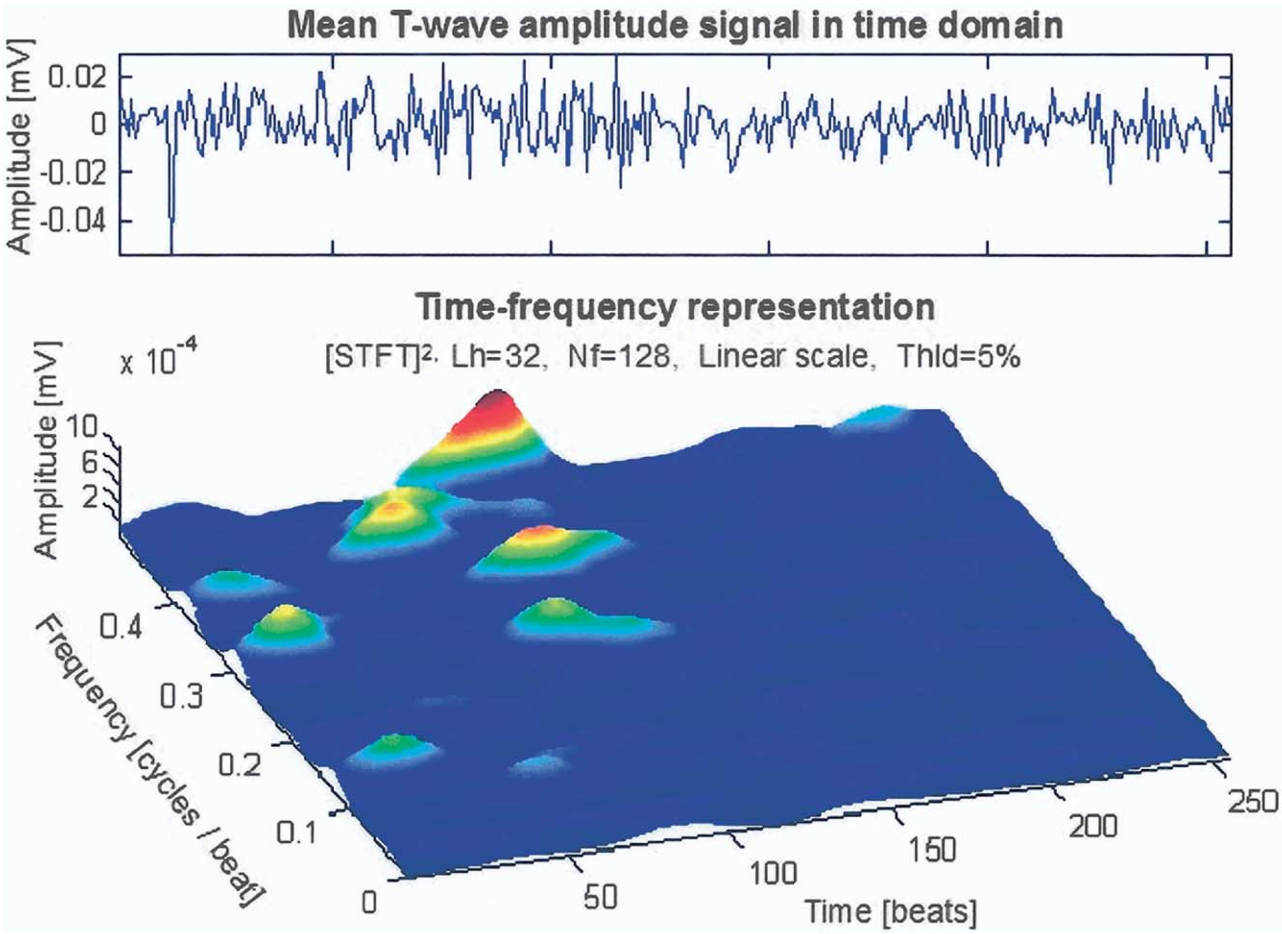

Fig. 3. Dynamics of the mean amplitudes of the T waves during 2 min before the onset of ventricular tachyarrhythmia in a subject whose 4-hour dynamics was shown in Figure 2, bottom panel. The corresponding time series of the mean T-wave amplitudes is shown at the top. The time-frequency representation was obtained using the short-time Fourier transform. Note the predominant energy concentration in the high-frequency part of the spectrum with the highest peak at the frequency of the T-wave alternans (0.5 cycles/beat). During arrhythmia-free periods, the energy was predominantly concentrated in the low-frequency parts of the spectrum.

tion of increased heart rate (from 80 to 100 bpm) during the same period of time.

Time-frequency Representation of Repolarization Dynamics

To further investigate the patterns of repolarization dynamics in the time-frequency plane, we applied time-frequency analysis based on the short-time Fourier Transform to the series of T-wave amplitudes recorded over 2 minutes before the onset of ventricular tachyarrhythmia in the subject whose 4-hour dynamics was shown in Figure 2. The corresponding time series of the T-wave amplitudes is shown in Figure 3 (above the time-frequency distribution). Note that most of the energy is concentrated in the higher frequency part of the spectrum with the greatest peak at the frequency of T-wave alternans (0.5 cycles/beat). This energy concentration in the high-frequency part of the spectrum before the onset of arrhythmia was different from the predominantly low-frequency energy concentration during arrhythmia-free periods.

Discussion

Dynamic analysis of repolarization instability and its role in arrhythmogenesis has become an area of intensive experimental and clinical research. A growing number of studies is exploring various analytical approaches to real-life ECG recordings. Since the spectral and time-domain techniques that have been applied to the analysis of repolarization dynamics have a number of limitations, analysis of information both in time and frequency domains could be useful for examining the time course and structure of abrupt changes and transients in the level of T-wave alternans and slower periodicities. In addition, controlling residual baseline drift by applying surrogate analysis to the isoelectric segment and comparing time series of the surrogate data with the "true" repolarization dynamics is needed to ensure reliable control of the low-amplitude baseline drift.

We compared performance of different time-domain and spectral methods for tracking temporal instability of cardiac repolarization using simulated signals and real-life Holter recordings. The inter-beat (Modified Moving Average) analysis (7) and the intra-beat averaging showed similar accuracy with respect to detection and quantification of T-wave alternans and robustness to various levels of random noise. This result is not in disagreement with the previous reports of successful application of these techniques to analysis of the T-wave alternans during various functional tests (5,6,12). The advantage of the Modified Moving Average analysis was its lower sensitivity to random noise and spurious artifacts at the expense of a slower time response. The inter-beat averaging may lead to inaccurate estimation of TWA when the number of phase shifts is increased (Fig. 1). On the other hand, the intra-beat averaging showed higher sensitivity to random noise and abrupt solitary artifacts but a faster response time and a greater sensitivity to the amplitude modulation, which can occur during changes in the autonomic nervous system activity or functional tests (5,6).

Analysis of information in the time and frequency domains (or in the time-frequency plane) may also provide insights into the cascade of instabilities that ultimately leads to the initiation of arrhythmia. In experimental studies, an increase in complexity of the T-wave oscillations preceded the onset of imminent ventricular fibrillation (6). Theoretical studies in nonlinear dynamics suggested that the increased complexity of oscillations might represent a route to chaos through a chain of period-doubling bifurcations (8). Tracking repolarization dynamics in real-life data might help to reveal the patterns of destabilization that are related to the mechanisms of initiation of spontaneous arrhythmias.

Perspectives. Risk of cardiovascular events, such as arrhythmias or sudden cardiac death, is a dynamic factor, which varies over time. Information about the temporal and spatial evolution of repolarization patterns, heart rate, and other physiological data, tracked continuously, is necessary for dynamic assessment of the individual patient's risk profile. Recent advancements in wireless communication technology and portable computing devices provide the platform for the implementation of this information exchange. This information, in turn, will allow timely optimization of diagnostic and treatment strategy, early detection of high-risk periods, and initiation of preventive therapies.

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