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Detection of T-Wave Beat-By-Beat Variations prior to Ventricular Arrhythmias Onset in ICD-Stored Intracardiac Electrograms: The Endocardial T-Wave Alternans Study (ETWAS)

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Background: *The aim of the Endocardial T-Wave Alternans Study was to prospectively assess the presence of T-wave alternans (TWA) or beat-to-beat repolarization changes on implantable cardioverter-defibrillator (ICD)-stored electrograms (EGMs) immediately preceding the onset of spontaneous ventricular tachycardia (VT) or fibrillation (VF).*

Methods: *Thirty-seven VT/VF episodes were compared to 116 baseline reference EGMs from the same 57 patients. A Bayesian model was used to estimate the T-wave waveform in each cardiac beat and a set of 10 parameters was selected to segment each detected T wave. Beat-by-beat differences in each T-wave parameter were computed using the absolute value of the difference between each beat and the following one. Fisher criterion was used for determining the most discriminant T-wave parameters, then top-M ranked parameters yielding a normalized cumulative Fisher score > 95% were selected, and analysis was applied on these selected parameters. Simulated TWA EGMs were used to validate the algorithm.*

Results: *In the simulation study, TWA was detectable even in the case of the smallest simulated alternans of 25 μ V. In 13 of the 37 episodes (35%) occurring in nine of 16 patients, significant larger beat-to-beat variations before arrhythmia onset were detected compared to their respective references (median one positive episode per patient). Parameters including the T-wave apex amplitude seem the more discriminant parameters.*

Conclusions: *Detection of beat-by-beat repolarization variations in ICD-stored EGMs is feasible in a significant subset of cases and may be used for predicting the onset of ventricular arrhythmias. (PACE 2014; 00:1–10)*

T-wave alternans, sudden death, implantable cardioverter defibrillator, intracardiac electrogram, ventricular tachycardia

Introduction

T-wave alternans (TWA) refers to subtle beat-to-beat alternations in amplitude, shape, or duration of the repolarization waves, which have been shown to be linked with the occurrence of spontaneous malignant ventricular arrhythmias.^{1–3} Experimental works have demonstrated a causal mechanistic relationship between TWA and the occurrence of ventricular fibrillation (VF).^{4–6} Moreover, a close temporal relationship between periodic variations in repolarization and the onset of ventricular tachyarrhythmia has been observed in animal models^{7,8} and also in humans using ambulatory electrocardiogram (ECG) recordings.⁹

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Electrograms (EGMs) stored in implantable cardioverter-defibrillator (ICD) memories represent an unique opportunity for detecting T-wave changes immediately before arrhythmia onset in patients prone to malignant ventricular arrhythmias. Short-term prediction of ventricular arrhythmia onset by detecting increasing levels of TWA or of periodic T-waves changes is an interesting area for the development of future preventive therapeutic options in this setting.

Detection of intracardiac TWA has been shown to be feasible in animals using simple manual calculations or time-domain method^{7,10} and in humans using spectral analysis with a good concordance with surface ECG TWA.^{11–14} However, analysis of ICD-stored signals suffers some important limitations due to the short periods of recordings currently available (usually 10–15 seconds—i.e., 10–20 beats) which hinder usual spectral and temporal analysis,¹⁵ and because of the fixed filtering, amplification, and sampling rate preventing upstream tailored signal processing. To date, TWA or beat-to-beat T-wave variations have been reported to be detectable in ICD-stored EGMs before episodes of ventricular tachycardia (VT) in an isolated case report¹⁶ and in two recent retrospective studies^{15,17} before being prospectively demonstrated to increase before VT/VF onset.¹⁸

However, the techniques used in these studies are either limited to the detection of alternating variations in T-wave amplitude only—and therefore cannot evaluate other possible periodic repolarization changes or variations unrelated to T-wave amplitude—or either incompatible with the currently very short available durations of recorded EGMs before arrhythmia onset. Moreover, a high-quality beat-to-beat T-waveform extraction is required for the reliability of the results.

The aim of the Endocardial T-Wave Alternans Study (ETWAS) was to prospectively assess the presence of increasing levels of TWA or periodical beat-to-beat repolarization changes on ICD-stored EGMs immediately preceding the onset of spontaneous VT/VF. The originality of the proposed approach relies on a beat-to-beat Bayesian model to estimate successive T waveforms along the EGMs and on a multivariate detection of repolarization changes based on the absolute differences of several well-defined T-wave parameters between successive cardiac beats.

Methods

We conducted a prospective multicenter trial including consecutive patients referred for ICD implantation at the French University Hospitals of Toulouse, Montpellier, Nîmes, and Aix-en-

Provence. The protocol was approved by the local Ethics Committee. Signed informed consent was obtained from each participant.

Patient Selection

Patients implanted with single-chamber, dual-chamber, or biventricular ICD (St. Jude Medical, Sylmar, CA, USA) according to the current international guidelines for device implantation were included. Patients presenting with paroxysmal atrioventricular block or permanent atrial fibrillation with spontaneous atrioventricular conduction were not included in the study because of potential alternation between paced and spontaneous QRS complexes.

EGM Acquisition

Stored EGMs were filtered and recorded in a similar fashion in every ICD model (1.5–300 Hz, rolloff slope 40 db/decade, sampling rate of 128 Hz with 8-bit resolution, leading to 7.8-ms and 29–83- μ V time and voltage steps according to the programmed amplification). These values were considered to be acceptable for detecting beat-to-beat changes in intracardiac T waves as reported in the literature.^{11,14,15,17}

Each patient was discharged with a specific ICD programming. First, to collect the largest amount of signal before the onset of each arrhythmia, the pre-trigger duration for stored EGM was programmed to its maximal value—that is, 32 seconds. Second, the recorded intracardiac lead was programmed to be “ring-to-can” (between the proximal pole of the distal pacing/sensing dipole of the ICD lead as the cathode and the can as the anode). This configuration yields high levels of TWA¹¹ and is suggested to explore wider myocardial areas (far-field bipolar recording). Third, the setting of amplification was tailored for each patient to record T waves as large as possible while avoiding clipping of the signal; this was usually programmed to a value of ± 7.4 mV, but was sometimes programmed to ± 3.7 mV (when T wave < 3 mV) or to ± 10.6 mV (for T wave > 7 mV). Other device programming, especially VT/VF detection and ICD therapies, was left at the physician discretion.

Episode EGMs were automatically stored in the device memory upon detection of a spontaneous ventricular arrhythmia. Patients were followed during 12 months with interim visits at 3 months, 6 months, and 9 months per the standard practice of each center. All episode EGMs were retrieved from device memory at each follow-up visit. At the 12-month visit, standard programming of the device was done.

Reference EGMs consisted of baseline EGMs, which were real-time intracardiac electrograms

streamed from the programmer to an external computer via an analog-to-digital acquisition card and a custom software (DAQcard 6062E and LabWindows CVI, National Instruments, Austin, TX, USA). These real-time EGMs were sampled at 1 kHz and 12-bit resolution in order to ensure signal quality. These EGMs were recorded at rest during sinus rhythm at implantation (prior to anesthesia for ICD testing) and/or during follow-up visits.

Thus, the clinical data consisted of two sets: a set of “reference” EGMs and a set of “episode” EGMs from the same patients.

EGM Selection

Episode and reference EGMs featuring major artifacts, clipping of the T wave, atrial fibrillation, alternation between intrinsic and paced ventricular beats, or including more than one premature ventricular or supraventricular beats were eliminated from the analysis. The remaining episodes were then carefully reviewed by an electrophysiologist (PM) and those whose ventricular origin could not be formally proved were also excluded.

Processing

The processing consisted in two steps. First, a Bayesian model^{19,20} was used to estimate simultaneously the T-wave location and waveform in each cardiac beat. Second, a set of 10 parameters was computed to characterize each detected T wave.

Step 1: T-Wave Segmentation

In brief, beat-to-beat T-waveform estimation was performed using a Bayesian model to estimate on a beat-by-beat basis simultaneously with the T-wave position, the T waveform, and the baseline. The used algorithm²⁰ is a beat-by-beat version of the one previously detailed,¹⁹ which was originally designed for being applied to a bloc of successive beats (10–20 beats). This technique has been proven to be reliable in defining waveform positions and morphologies on surface ECG with almost 100% sensitivity and specificity even in the presence of noise or wandering baseline²⁰ since modeling provides a denoised estimation of each T wave.

Step 2: T-Wave Parameter Extraction

Six landmarks were then positioned on each segmented beat (Fig. 1)—five on the T wave and one corresponding to the R peak—leading to calculation and extraction of 10 parameters exploring the whole repolarization for each cardiac beat (Fig. 2).

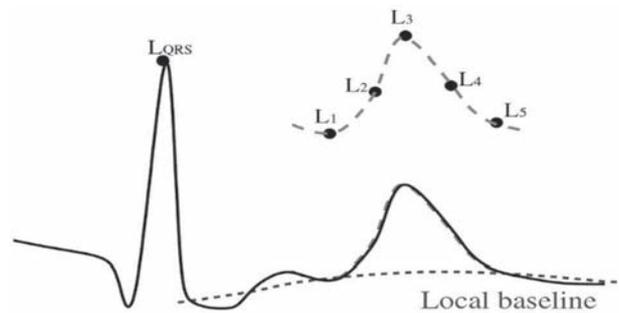


Figure 1. T-wave landmarks. Representation of the five fiducial points calculated on each T wave for defining the studied 10 T-wave parameters. P_{QRS} is the point related to the apex of the QRS complex. $P1$ is the point related to the onset of T wave. $P2$ is the point of maximal ascending slope of the T wave. $P3$ is the point related to the T wave apex. $P4$ is the point of maximal slope of the descending part of the T wave. $P5$ is the point related to T-wave end. These points were calculated independently of the morphology of the T wave although T-wave morphology was very similar in most of the EGMs (T waves are biphasic due to ICD filtering¹⁵).

Validation on Simulated Data and Validation of the References

Synthetic data were first used to validate the algorithm using simulated TWA EGMs. Among the set of selected references, 10 EGMs (approximately 500 beats) from six patients were selected as representative reference signals. TWA was simulated by adding or subtracting alternatively (on an every-other-beat basis) a Hanning window to the successive delineated T waves as already done,²¹ which provides very realistic data. Different T-wave amplitude values of 25 μV and 50 μV have been chosen for these evaluations, based on the threshold TWA level of 29 μV showing the best discrimination value according to Swerdlow et al.¹⁸ The above detailed two steps processing was applied on the different EGMs with synthetic TWA.

Evaluation of TWA or T-Wave Beat-to-Beat Variations

We evaluated beat-to-beat differences of each T wave in a slightly different way as the technique developed by Swerdlow et al.¹⁵: each T wave was characterized by a set of 10 parameters. For each parameter, we computed the absolute value of the difference between each beat and the following one. Premature beats and the following beat were eliminated.

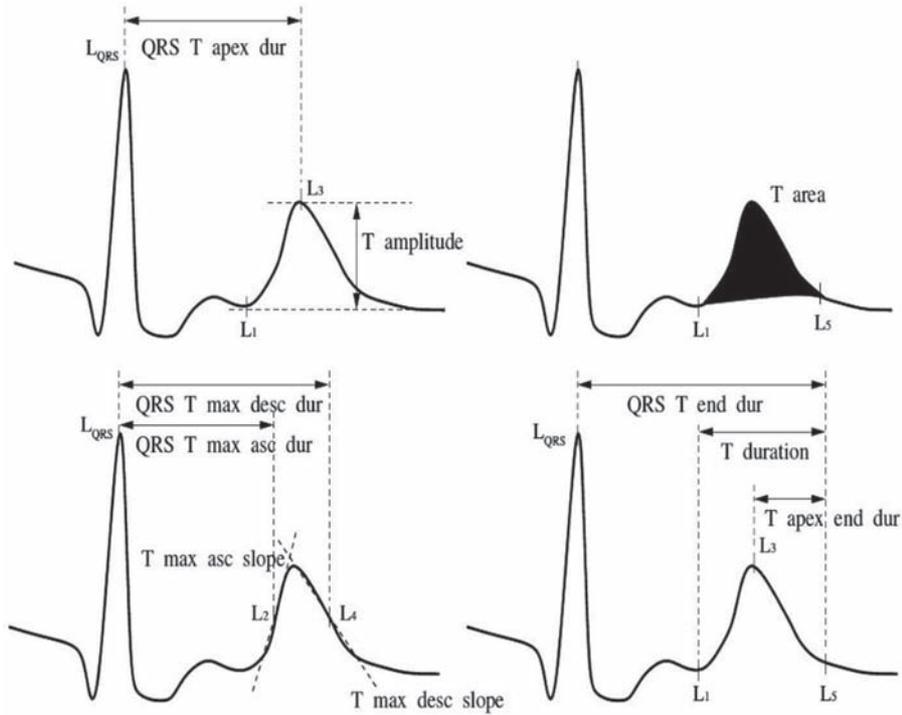


Figure 2. Parameters exploring the whole repolarization. Schematic representation of the 10 T-wave parameters exploring the whole repolarization included in the study.

Statistical Analysis

Numerical values were expressed as mean \pm standard deviation, or as median and interquartile range as suitable. Categorical variables were reported as percents. Comparisons of continuous variables between groups were performed with the two-sample multivariate t -test,²² as detailed in the following paragraph. Categorical variables were compared with χ^2 test.

Each episode was tested against each reference of the same patient by using a statistical test able to take into account the successive beat-to-beat differences in each of the 10 parameters characterizing the T-wave changes. Given the beat-to-beat differences of the 10 parameters related to the considered episode and the corresponding references, TWA/T-wave variations were formulated as a multivariate two-class problem: H0 (= no significant beat-to-beat T-wave parameter variation) and H1 (= significant beat-to-beat T-wave parameter variation). The chosen hypothesis test was the two-sample multivariate t -test—that is, Hotelling's T^2 test.²² This test is the multivariate generalization of the two-sample univariate t -test and tests the means of beat-to-beat differences of the two samples, assuming a Gaussian distribution of the T-wave parameter differences.

However, the 10 T-wave parameters may contribute unequally to the characterization of the beat-to-beat T-wave variations. For example, if the TWA relies on an amplitude alternation, the amplitude-related parameters would be more discriminant than wave shape-related parameters or duration-related parameters. Moreover, since TWA detection algorithms are studied with the aim of implementing in ICD and performing real-time processing, it is of great importance to study any implementation cost reduction. The Fisher criterion^{23,24} aims at finding the most discriminant parameters to distinguish between the two hypotheses, H0 and H1. Furthermore, it allows to know which parameters are more discriminant when the alternation/variations occur, which may be interesting from a clinical point of view. After computing the Fisher score for each parameter, we selected the top-M ranked parameters, which yield a normalized cumulative Fisher score superior to a given predefined value (95% in this study). This means that these M parameters carry more than 95% of the information necessary to discriminate between both hypotheses. Finally, the multivariate two-sample t -test is applied on the reduced set of these selected parameters at 5% significance level. Moreover, successive beat-to-beat values of each parameter were plotted

against the beat number and visual checking of each of these graphs was performed for excluding beat-to-beat variations not caused by periodic or nonperiodic pattern—that is, monotonic linear increase or decrease of T-wave parameter values.

Once the method has been validated to be able to detect small TWA levels and before applying it to real EGM episodes, each reference has been tested against the other references of the same patient with the same method. Then episodes were compared to references. An episode was considered “positive” when TWA/T-wave variations were significantly larger compared to any reference from the same patient.

Analysis was performed using Matlab software (Matlab Version 7.10.0.499—[®] 2010a; The MathWorks, Natick, MA, USA) and associated statistical toolbox.

Results

Fifty-seven patients had been included. Clinical characteristics of the patient population are summarized in Table I.

A full data set could not be obtained in five patients, because three patients died during the follow-up, one patient was explanted, and one was lost to follow-up after implantation. At 1-year follow-up, 16 of 57 patients (29%) experienced at least one episode of VT/VF leading to a total of 37 episodes (median one episode/patient, range 1–13, mean 19 ± 26 beats), whereas 116 references have been selected (median six references/patient, range 2–16, mean 86 ± 73 beats). Compared to patients without VT, there was no difference in age, ejection fraction, gender, New York Heart Association (NYHA) class, primary or secondary prevention indication for ICD, underlying heart disease, therapy with amiodarone, or implantation of biventricular devices. Only β -blockers were more often prescribed in patients with recurring arrhythmias during the follow-up (13/16 vs 22/41, $P = 0.05$).

Selected episodes comprised monomorphic VT ($n = 31$), polymorphic VT ($n = 5$), and VF ($n = 1$) with a mean cycle length of 243 ± 56 ms, among which 13 were successfully and two were unsuccessfully treated by antitachycardia pacing, while 22 spontaneously reverted to sinus rhythm (nonsustained episodes). Two patients had biventricular-paced rhythm before episodes and in references. Mean heart rate was 71 ± 18 beats/min before ventricular arrhythmia onset and 67 ± 17 beats/min during baseline recordings ($P = ns$).

Simulation Study

In both cases of simulated TWA levels, the Fisher score selected four parameters among the 10 to be the most discriminative (having a cumulative Fisher score superior to 0.95) and these four

parameters were the ones related to the amplitude (T-wave max ascending and descending slopes, T-wave area, and T-wave amplitude), which is coherent with the technique used for simulated TWA (see “Methods” section). Then, in both of the cases, the multivariate two-sample *t*-tests carried out on these four discriminant parameters led to a positive decision of the presence of TWA, even in the case of the smallest simulated alternans of 25 μV . Figure 3 shows an example of EGM portions with synthetic 25 μV and 50 μV TWA.

Clinical Study

Among these 37 episodes, 13 (35%) episodes have been found to have significant beat-to-beat variations before arrhythmia onset compared to their respective references. Among the 116 references, eight (7%) were considered “positive” compared to the other references from a given patient. The difference in “positive” EGMs between episodes and references was significant ($P < 0.0001$). There was a median of one positive episode and zero positive reference for each patient presenting with VT/VF during the follow-up. Nine patients demonstrated at least one “positive” episode (median one, 1–4). Significant beat-to-beat variations were observed before 2/5 polymorphic VT, 10/31 monomorphic VT, and 1/1 VF ($P = ns$), and before 8/22 nonsustained episodes and 5/15 treated episodes ($P = ns$). From the two patients with biventricular-paced rhythm, one had a “positive” episode and one had a “negative” episode.

Examples of baseline and pre-trigger ICD-stored EGM and of beat-to-beat variations in T-wave amplitude drawn from the baseline and pre-trigger EGM are shown in Figures 4 and 5. The 95% most discriminant parameters for each patient and the mean Fisher score for each parameter are depicted in Figure 6. Parameters including the T-wave apex amplitude appear to be the more discriminant parameters (T-wave max ascending and descending slopes, T-wave area, and T-wave amplitude). There was a median of six discriminant parameters per patient (5–8) (6 per positive episode, 5 to 8).

Beat-by-beat averaged differences for the most discriminant parameters in positive episodes are shown in Table II, together with the averaged magnitude of increase of beat-to-beat variations compared to references. There was no difference in beat-by-beat variations for RR intervals between references (22.9 ± 41.6 ms) and episodes (31 ± 28.5 ms; $P = ns$). There were no significant differences in heart rate (79 ± 22 vs 66 ± 14 beats/min, $P = 0.09$) or in beat-by-beat variations in RR intervals (43 ± 32 ms vs 46 ± 41 ms, $P = 0.8$) before positive and negative episodes.

Table I.

Clinical Characteristics of the Study Population

Gender	45 men (79%)		
Age	64 ± 12 years old (31–83)		
Ejection fraction (%)	34 ± 15% (15–70)		
NYHA class			
	I	21	37%
	II	23	40%
	III	12	21%
	IV	1	2%
Indication	Primary prevention	28	49%
	Secondary prevention	29	51%
Cardiac resynchronization devices		9	16%
Underlying heart disease			
Coronary artery disease		35	61%
Dilated cardiomyopathy		13	23%
Primary electrical disease		4	7%
Hypertrophic cardiomyopathy		2	3.5%
Arrhythmogenic right ventricular cardiomyopathy		2	3.5%
Sarcoidosis/myocarditis		1	2%
Antiarrhythmic medications	β-blockers	35	61%
	Amiodarone	18	32%

NYHA = New York Heart Association.

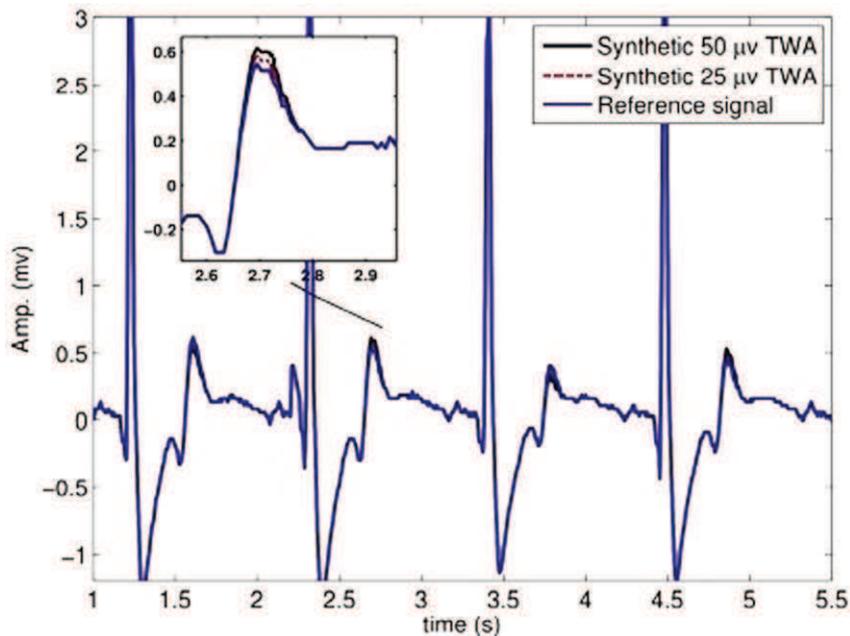


Figure 3. Example of EGM portions with synthetic 25- μ v and 50- μ v TWA. EGM = electrogram; TWA = T-wave alternans.

Compared to patients with recurring arrhythmias without significant T-wave variations, there was no difference in age, ejection fraction, gender, NYHA class, primary or secondary prevention indication for ICD, therapy with amiodarone

or β -blockers, or implantation of biventricular devices. Patients with ischemic heart disease have less often T-wave variations compared with patients with dilated cardiomyopathy (3/8 vs 5/6, $P = 0.08$).

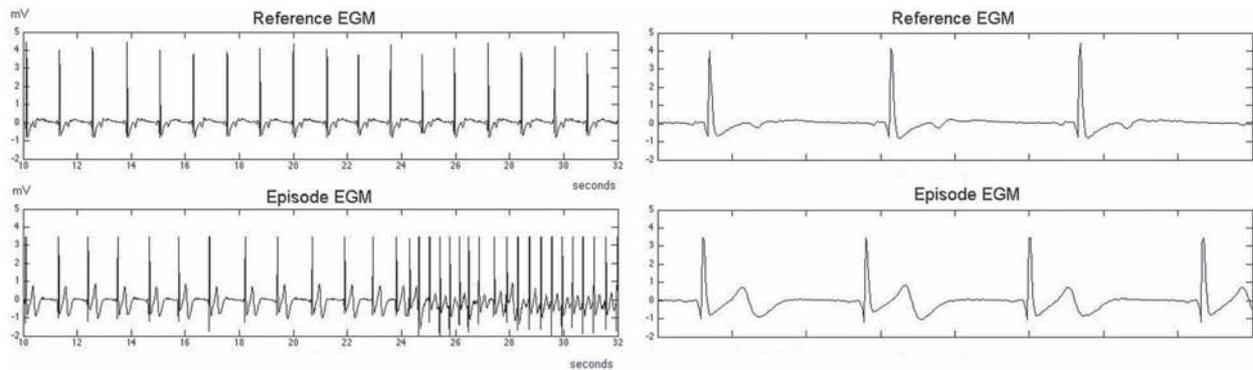


Figure 4. Examples of baseline and pre-trigger ICD-stored EGM in the same patient. EGM = electrogram; ICD = implantable cardioverter-defibrillator.

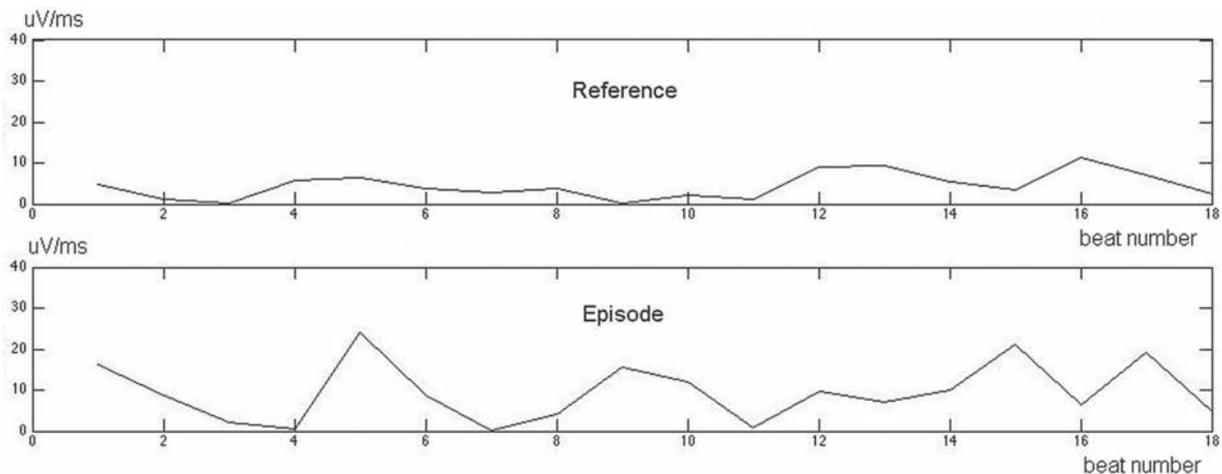


Figure 5. Beat-to-beat variations in T-wave maximal descending slope drawn from the baseline and pre-trigger EGM seen in Figure 4. Although there were no clear beat-to-beat changes at visual inspection of the T waves in baseline and pre-onset recordings in Figure 4, there were some beat-to-beat variations in T-wave maximal descending slope that were significantly higher before VT than at baseline ($P < 0.05$). EGM = electrogram; VT = ventricular tachycardia.

Discussion

In this study, we proposed a beat-to-beat Bayesian approach together with discriminant analysis to analyze the ICD-stored EGM recordings. First, the beat-to-beat Bayesian approach was used to delineate and reduce the noise of the T waveforms from the stored EGM. Then, beat-to-beat variations of various T-wave parameters extracted from the estimated waveforms were subjected to discriminant analysis to reduce the dimensionality. Finally, a two-sample multivariate t -test was carried out on the most discriminant parameters.

The major finding of this prospective multicenter study is that the T-wave beat-to-beat variations (amplitude, shape, or duration) in ICD-stored EGM recordings were significantly greater immediately before spontaneous ventricular ar-

rhythmia than during reference signals from the same patients. Our results also reflect the highly variable beat-to-beat T-wave variations from one patient to another, since no reproducible T-wave behavior was observed in this population. Moreover, this study shows the interest of performing TWA/variations analysis using several parameters characterizing the T waves, while the previous studies^{15,17,18} focused only on variations in T-wave amplitude.

During the past years, several landmark studies clearly demonstrated the close mechanistic and temporal link between microvolt TWA and the propensity to malignant ventricular arrhythmias in various cardiac settings.¹⁻⁹ Thus, a method allowing detection of beat-to-beat repolarization alternans/variations would be very valuable for predicting the onset of ventricular arrhythmias.

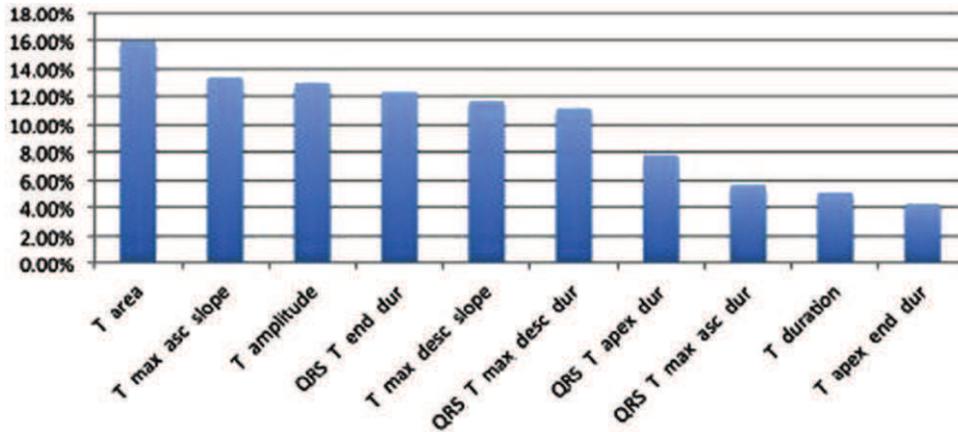


Figure 6. Mean Fisher score of each parameter computed on the 13 positive episodes. The Fisher score represents the percentage of information quantity of each parameter for discriminating between both the hypothesis.

Table II.

Averaged Beat-by-Beat Differences for the Most Discriminant Parameter for “Positive” Episodes and Magnitude of Increase in Beat-by-Beat Variations Compared to References from the Same Patients

Parameters	Mean Beat-by-Beat Difference	Magnitude of Increase versus References
QRS-T end	59 ms	5.4
T max descending slope	25 μ V/ms	2
QRS-T max asc slope duration	10 ms	3.2
QRS-T max desc slope duration	58 ms	6
QRS-T apex	59 ms	6.9
T max ascending slope	24 μ V/ms	2.6
T amplitude	150 μ V	2.6
T area	1,336 μ V. ms	3.6
T apex-T end	7 ms	1.6
T duration	56 ms	2.1

The concept of prediction of ventricular arrhythmias in a timely manner and enabling early interventions has attracted tremendous interest from both the basic science research and clinical investigators. For example, quick detection of repolarization instability by an ICD would possibly warn the patient about an imminent risk of syncope or shock, or enable future use of closed-loop control pacing algorithms aimed at perturb alternans dynamics and therefore preventing VT or VF occurrence.^{25–29} Closed controlled adapted ventricular pacing has been successfully used in humans for terminating sustained periods of alternans in atrioventricular conduction,²⁵ highlighting the clinical feasibility of nonlinear-dynamical control techniques. A similar pacing protocol may theoretically also lead to disappearance of ventricular alternans and

therefore to a lower risk of imminent arrhythmia occurrence. Thus, the beat-by-beat detection of repolarization instability by an ICD would possibly enable future use of closed-loop control pacing algorithms aimed at perturb alternans dynamics and therefore preventing VT or VF occurrence. For such a goal in real-time device, driven by the limited computation power in current ICDs, a computationally less expensive method such as beat-to-beat variation or periodic changes analysis in a short time window is probably more realistic than the established spectral analysis method used in noninvasive setting.

Endocardial repolarization alternans was shown to be detectable in animals^{9,10} and in humans.¹² There is a good concordance between TWA measured on surface ECG signals and on ICD-stored EGMs¹¹ or intracardiac standard

catheters^{13,14} with greater levels of TWA in EGM than in surface ECG.¹¹

The feasibility of detecting endocardial TWA in ICD-stored EGM signals before VT/VF in humans was recently evaluated in two retrospective clinical works.^{15,17} Both works demonstrated that TWA was significantly higher before VT than before inappropriate therapies or at baseline. This was further definitively demonstrated by the prospective study by Swerdlow et al., where amplitude of TWA was significantly greater immediately before spontaneous VT/VF in ICD patients than during various control recordings.¹⁸

To our knowledge, this study is the first to prospectively evaluate the feasibility of detection of beat-to-beat T-wave changes before arrhythmia onset in ICD-stored EGM using various T-wave parameters since only beat-to-beat changes in T-wave amplitude had been studied before.^{15,17,18} Although parameters including the T-wave apex amplitude were the more useful parameters for most episodes, other T-wave parameters were sometimes discriminant in selected cases. This implies that multivariate analysis of T-wave morphology may enhance the capability of TWA detection on top of a single feature method. Furthermore, the averaging technique used in this study allows detection of the degree of variation for beat-to-beat changes that were not in an alternating pattern, which could represent the complex T-wave oscillations, which have been shown to precede VF.^{6,8,9} More sophisticated spectral analyses adapted to the few available cardiac beats are necessary to better characterize these apparent nonperiodic patterns.

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Limitations

This study was performed on St. Jude Medical™ devices including specific hardware characteristics in amplification, filtering, and sample resolution. The device preprocessing of the signal may have some effects; however, the signal is probably not very different in other manufacturers and such differences do not have a significant impact on the applied averaging method and major findings.

Ventricular premature beats may induce transient repolarization alternans.³⁰ We exclude episodes or references including more than one premature beat. Since premature beats are common in ICD patients and particularly before VT/VF onset,³¹ this represents a technical limitation to the methods described here. However, averaging method is relatively insensitive to premature beats if excluded from analysis¹⁵ and a device-based automatic algorithm may potentially exclude premature beats by itself. However, we cannot exclude the possibility that some T-waves changes were caused by the deleted premature beats.

In this study, we only explored T-wave variations during very short periods of time. Results from short-term recordings may be limited because transient significant fluctuations of TWA levels in several minutes of unknown significance have been observed at fixed low heart rates in patients prone to ventricular arrhythmias.³²

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