A Novel Method for Determining the Phase of T-Wave Alternans
Diagnostic and Therapeutic Implications

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Background—T-wave alternans (TWA) has been implicated in the pathogenesis of ventricular arrhythmias and sudden cardiac death. However, to estimate and suppress TWA effectively, the phase of TWA must be accurately determined.

Methods and Results—We developed a method that computes the beat-by-beat integral of the T-wave morphology, over time points within the T-wave with positive alternans. Then, we estimated the signed derivative of the T-wave integral sequence, which allows the classification of each beat to a binary phase index. In animal studies, we found that this method was able to accurately identify the T-wave phase in artificially induced alternans (P<0.0001). The coherence of the phase increased consistently after acute ischemia induction in all body-surface and intracardiac leads (P<0.0001). Also, we developed a phase-resetting detection algorithm that enhances the diagnostic utility of TWA. We further established an algorithm that uses the phase of TWA to deliver appropriate polarity-pacing pulses (all interventions compared with baseline, P<0.0001 for alternans voltage; P<0.0001 for Kscore), to suppress TWA. Finally, we demonstrated that using the phase of TWA we can suppress spontaneous TWA during acute ischemia; 77.6% for alternans voltage (P<0.0001) and 92.5% for Kscore (P<0.0001).

Conclusions—We developed a method to quantify the temporal variability of the TWA phase. This method is expected to enhance the utility of TWA in predicting ventricular arrhythmias and sudden cardiac death and raises the possibility of using upstream therapies to abort a ventricular tachyarrhythmia before its onset. (Circ Arrhythm Electrophysiol. 2013;6:818-826.)

Key Words: alternans • arrhythmia (heart rhythm disorders) • defibrillators, implantable • intracardiac electrogram • pacing

T-wave alternans (TWA) testing has been associated with an increased risk for ventricular tachyarrhythmic events, such as ventricular tachycardia (VT), ventricular fibrillation (VF), and sudden cardiac death (SCD), during medium- and long-term follow-up.1,2

Clinical Perspective on p 826

However, beyond medium- and long-term risk prediction, several lines of preclinical and clinical evidence suggest that the presence of heightened TWA may play a more proximal role in creating the substrate necessary for malignant ventricular arrhythmias.3-6 Analysis of intracardiac electrograms from implantable cardioverter-defibrillator leads has demonstrated a sharp increase in TWA magnitude immediately before spontaneous ventricular arrhythmias,7-9 without a similar upsurge in TWA before induced ventricular arrhythmias or preceding inappropriate implantable cardioverter-defibrillator shocks.2 Simultaneous measurement of TWA from body-surface and intracardiac electrograms by our group10 and others11 has shown a high degree of correlation, suggesting that these measurements are detecting the same electric phenomenon. In aggregate, the clinical and experimental data suggest that the heart either passes through a state of heightened TWA on the way to VT and VF, or heightened TWA occurs in close conjunction with developing ventricular tachyarrhythmic events.12,13 In either scenario, these findings suggest that detecting significantly elevated levels of TWA may serve as an important short-term predictor of impending arrhythmias and also raise the possibility for a therapeutic role where TWA suppression therapies are delivered upstream to suppress the arrhythmogenic substrate and abort VT/VF prior to the arrhythmia onset.2,14

The clinical application of TWA, whether it serves a diagnostic role for medium- and long-term risk prediction or a therapeutic role for guiding short-term upstream antiarrhythmic therapy, requires the ability to estimate TWA accurately. It has been reported that abnormal beats with altered morphology or timing present inherent difficulties in the estimation of

Received December 28, 2012; accepted July 9, 2013.

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The online-only Data Supplement is available at http://circep.ahajournals.org/lookup/suppl/doi:10.1161/CIRCEP.113.000114/-/DC1.

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Circ Arrhythm Electrophysiol is available at http://circep.ahajournals.org

DOI: 10.1161/CIRCEP.113.000114

818
alternans, primarily by provoking changes in TWA phase. However, assessment of the alternans phase, a term that refers to the specific phase of an alternating sequence of long and short or large and small T-waves, has generally been underappreciated in clinical TWA testing. Current algorithms used to estimate TWA classify premature ventricular contractions (PVCs) and beats following transient prolongation or shortening of the cycle length as bad beats, but they do not estimate the phase of TWA either preceding or following such bad beats. However, a bad beat may cause phase resetting of TWA and therefore may either reduce the amplitude of alternans or potentiate the amplitude of alternans. In either case, PVCs may significantly hamper the TWA estimation by generating a false-positive or a false-negative result. Therefore, the development of methods to estimate the phase of TWA before and after a bad beat, and consequently account for changes in phase, may significantly improve the performance of TWA as a diagnostic test for predicting medium- and long-term arrhythmia risk.

Similarly, the ability to estimate the phase of TWA is also likely to have a critical impact on designing potential therapeutic strategies to suppress TWA and mitigate short-term arrhythmia risk. However, as has been demonstrated, lack of a priori knowledge of the phase of TWA (long and short or large and small T-waves) may increase the amplitude of alternans and potentiate, rather than suppress, the arrhythmogenic substrate. Therefore, developing methods to estimate the phase of alternans in real time is likely to play an important role in designing therapies to suppress TWA.

In this study, we aim to examine the hypothesis that algorithms to estimate the phase of TWA in intracardiac and body-surface signals can improve the diagnostic and therapeutic use of TWA.

Methods

Animal Preparation

Twenty-four male Yorkshire swine (40–45 kg) were anesthetized and acutely instrumented in the Animal Electrophysiology Laboratory of the Massachusetts General Hospital. The protocol was approved by the Animal Care and Use Committee of the Hospital. Anesthesia was induced with Telazol (4.4 mg/kg) IM and Xylazine (2.2 mg/kg) IM. Each subject was intubated and placed on a mechanical ventilator, and anesthesia was maintained with Isoflurane (1.5% to 5%).

Standard electrocardiographic electrodes were placed on the subject’s limbs and chest; the epidermis was excised at point of contact to maximize signal quality. An arterial line was used to monitor arterial blood pressure. Percutaneous intracardiac access was achieved in the jugular veins and femoral arteries and veins by using standard Seldinger techniques. Decapolar catheters were placed under fluoroscopic guidance (1) in the right ventricle (RV), (2) in the coronary sinus (CS), the distal lead being at the distal CS, and (3) in the left ventricle (LV), the proximal lead being at the LV apex. An inferior vena cava catheter was inserted as a reference electrode for unipolar signals.

Regional myocardial ischemia was induced in 11 subjects via balloon occlusion of the proximal left circumflex coronary artery by using standard percutaneous cardiac catheterization techniques.

Equipment and Data Collection Methods

Intracardiac and body-surface (leads II and V4) electrocardiographic signals as well as arterial blood pressure were recorded through a Prucka Cardiolab (General Electric) electrophysiology system that provided 16 high fidelity analog output signals, as previously described. We used a previously developed signal acquisition, analysis, and display system, consisting of custom software written in LabView 8.5 (National Instruments, Austin, TX) and MATLAB 7.6 (MathWorks Inc, Natick, MA).

Details of the alternans estimation algorithm are provided in the online-only Data Supplement. TWA estimates were obtained from 2 body-surface leads and 12 intracardiac unipolar leads (3 in each of the RV, LV, and CS catheters).

We have used a programmable stimulator that is capable of dynamically delivering pacing pulses on a beat-to-beat basis. Each pacing pulse is triggered upon detection of an ECG waveform (the R-wave).

TWA Phase Estimation

The algorithm we developed to estimate the phase of TWA is presented in Figure 1A, and is described below. To compute a phase index (PI) that differentiates between the 2 phases of TWA (Figure 1B), we devised a method that is based on the integral of the T-wave. The method relies on computing the beat-by-beat integral of the T-wave morphology (Figure 1C) between the onset and offset of the T-wave points (as determined by the wavelet transform).

To maximize the effect of T-wave samples with significant alternans on the integral value and at the same time to account for the...
temporal characteristics of the TWA, we estimated the alternans voltage and $K_a$ on a point-by-point basis throughout the T-wave, using a rolling 128-beat window that was shifted 1 beat at a time. Then, the integral was calculated at each time point within the T-wave with statistically significant TWA (ie, points with $K_a > 3$ and alternans voltage greater than a lead-dependent threshold) and normalized to the number of points used for the integral estimation. This improved integral provides a more accurate means of determining the phase of the alternating T-waves.

To overcome subtle changes in the beat-to-beat T-wave morphology that may affect the phase estimation, we introduced the signed derivative of the T-wave integral that allows the classification of each beat to a binary PI that takes 2 different values: +1 or −1 corresponding to large or small integral values, respectively (Figure 1D).

Finally, to minimize the sensitivity of the algorithm to an arbitrary ECG reference channel, we have devised an artificial alternating reference phase index sequence (+1, −1, +1, −1, …) against which the phase time series of each lead is compared.

To investigate the degree of synchronous alternation between 2 waveforms quantitatively, the coherence of 2 signals (estimated phase and reference phase) has been estimated using the Welch’s averaged periodogram method (for more information, please see the online-only Data Supplement).  

Statistical Methods
Aggregate variables were expressed as mean±SD. Box-plot representation including the median, 90% to 10%, and 95% to 5% percentiles was used to demonstrate statistical properties of the estimated coherence in data sequences with and without repolarization alternans. For each channel, coherence values were compared before and after R-wave–triggered pacing by using the Wilcoxon signed-rank test. The phase of TWA was compared across catheters by using the Kruskal–Wallis ANOVA. Comparisons between alternans voltage and $K_a$ across leads before and after R-wave–triggered pacing used 2-way ANOVA. The 95% confidence intervals for sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated based on binomial distribution. A $P<0.05$ was used to determine statistical significance. Statistical analysis was performed using MATLAB (MathWorks Inc, Natick, MA) and STATA (StataCorp LP, College Station, TX).

Results
Evaluation of the Estimation of the TWA Phase in the Normal Heart
We evaluated the ability of the algorithm to estimate the phase of TWA accurately by using R-wave–triggered pacing during the absolute refractory period. Pacing pulses of (1) amplitude: ±1 and ±5 mA, (2) width: 30 ms, and (3) coupling to the R-wave: 10 ms were delivered during the absolute refractory period on every-other-beat basis from 2 leads (RV12) of a decapolar catheter, at the apex of the RV, to modulate ventricular repolarization and induce TWA.

To investigate the ability of our algorithm to determine the phase of the T-wave, we estimated the PI at baseline and after R-wave–triggered pacing. We then evaluated the coherence at 0.5 cycles/beat between the artificial alternating reference sequence and the PI series for each of the leads at the body-surface and CS, LV, and RV catheters, before and after R-wave–triggered pacing. For each $K_a$ and alternans voltage, TWA was considered positive if $K_a > 3$ and alternans voltage were greater than the lead-specific thresholds (body-surface, 0.55 µV; CS, 1.98 µV; LV, 4.18 µV; RV, 4.235 µV).  

The box-plot representation of the phase coherence distributions for sequences of negative and positive alternans during all 4 pacing protocols is shown in Figure 2A for body-surface and intracardiac leads. The summary statistics demonstrate that the coherence is significantly higher for positive alternans than negative alternans across all leads on the body-surface and intracardiac leads ($P<0.0001$ for all paired comparisons; $n=36$ for each of the body-surface, CS, LV, and RV leads, where $n$ represents the overall sample size: 9 subjects for each of the ±1 and ±5 mA pacing interventions).
Then, to estimate the phase coherence thresholds for body-surface and intracardiac leads, we estimated the receiver-operating characteristic curve for coherence values ranging from 0 to 1 and computed the true and false detection rates for positive and negative alternans by using the coherence values, as follows. By using the TWA criteria described above (for $K_{core}$ and alternans voltage), the estimated coherence indicated a true-positive or false-negative outcome if it was greater or smaller than the corresponding threshold. Similarly, if alternans was negative, the coherence estimate was considered a false-positive or true-negative depending on whether its value was greater or smaller than the corresponding threshold.

In Figure 2B, we plot the sensitivity (Sn) and specificity (Sp) for body-surface and intracardiac leads as a function of coherence threshold. The corresponding receiver-operating characteristic curves are shown in Figure 2C. The area under the curve for body-surface leads and intracardiac CS, LV, and RV catheters was 0.99, 0.95, 0.98, and 0.99, respectively. For each lead configuration, the optimal phase coherence threshold was determined as the point that has the minimum distance to the point $(Sn,1−Sp)=(1,0)$, which is equal to minimizing $(1−Sn)^2+(1−Sp)^2)^{0.5}$ (Figure 2C). The estimated thresholds for body-surface, CS, LV, and RV leads were 0.419, 0.376, 0.406, and 0.647, respectively. These thresholds are shown by the horizontal lines in Figure 2A. The corresponding Sn and Sp pairs at the threshold were estimated to be (0.95,0.95), (0.89,0.89), (0.93,0.91), and (0.96,0.98) for body-surface, CS, LV, and RV leads, respectively.

**Evaluation of the Estimation of the TWA Phase in the Presence of Acute Ischemia**

To investigate the ability to estimate the phase of spontaneous TWA, we applied our algorithm on body-surface and intracardiac (CS, LV, and RV leads) electrograms recorded before (baseline) and during acute ischemia. The number of beats per subject recorded before and during coronary artery occlusion was 848±334 and 954±532, respectively ($P=0.69$; signed-rank=23; $n=10$). The mean heart rate at baseline and during coronary artery occlusion was 106.7±9.2 and 109.2±20.1 beats per minute, respectively ($P=1$; signed-rank=0; $n=10$).

The alternans voltage was significantly higher ($P<0.0001$ for all paired comparisons; $n=80$, where $n$ represents the total number of comparisons: 40 for baseline and 40 during ischemia, 10 each for the body-surface, CS, LV, and RV leads) during coronary artery occlusion compared with baseline: 0.12±0.17 versus 6.12±2.3 µV, 0.25±1.01 versus 10.39±9.42 µV, 0.60±1.69 versus 19.13±12.88 µV, and 0.51±1.70 versus 24.86±19.29 µV for body-surface, CS, LV, and RV leads, respectively. Similarly, the $K_{core}$ was significantly higher ($P<0.0001$ for all paired comparisons; $n=80$, where $n$ represents the total number of comparisons: 40 for baseline and 40 during ischemia, 10 each for the body-surface, CS, LV, and RV leads) during coronary artery occlusion compared with baseline: 0.87±1.61 versus 189.72±366.96, 0.14±0.51 versus 29.60±43.10, 0.27±0.76 versus 68.08±126.66, and 0.15±0.48 versus 90.44±176.76 for body-surface, CS, LV, and RV leads, respectively.

In Figure 3, we summarized the compiled results ($n=10$) of the coherence distributions for electrograms recorded before and during acute ischemia. The coherence is significantly higher for ischemia-induced TWA than baseline across all leads on the body-surface and intracardiac leads ($P<0.0001$ for all paired comparisons; $n=80$, where $n$ represents the total number of comparisons: 40 for baseline and 40 during ischemia, 10 each of the body-surface, CS, LV, and RV leads). No statistically significant difference was observed as a function of lead type, including between body-surface and any of the intracardiac catheter leads (baseline: Kruskal–Wallis test, $P=0.62$, $n=10$; post–balloon occlusion: Kruskal–Wallis test, $P=0.88$, $n=10$, where $n$ is the number of study subjects used in this comparison). For each lead, statistically significant comparisons (baseline vs ischemia) are marked by an asterisk.

**Detection of TWA Phase Resetting**

Having examined the ability of the proposed method to estimate the phase of TWA, we evaluated the use of the PI as a means to detect phase resetting (Figure 4). To detect potential TWA phase resetting, we estimated the cross-correlation of the...
estimated TWA phase with that of the reference PI sequence, which at the point of phase resetting is expected to result in a zero-crossing and a change in the polarity of the correlation coefficient (online-only Data Supplement).

In Figure 4A–4D, we demonstrate the performance of the proposed phase-resetting detection algorithm in 2 different study subjects in body-surface electrograms recorded during myocardial infarction. The first subject shows a reduction of the alternans voltage and Kscore caused by phase resetting from a PVC at beat numbers 628 and 831 (lead V4). The second subject shows an artificial increase of the alternans voltage and Kscore caused by a PVC at beat number 350 (lead V4). Each of these 2 PVCs results in an abrupt decrease or increase in the estimated correlation of the phase of the signal with that of the reference channel, manifested by a zero-crossing of the correlation coefficient and changes in the sign of the correlation coefficient before and after the zero-crossing point.

We applied the phase-resetting detection algorithm to all 10 subjects during acute ischemia and found a total of 67 incidents of phase resetting out of 224 QRS-complex morphology changes (ie, PVCs), yielding a 30% probability of experiencing phase resetting when a bad beat occurs. This signifies the relatively high incidence of artificial modulation of TWA estimation, which can now be determined by the proposed phase-resetting detection algorithm.

Utility of the TWA Phase to Trigger Appropriate Electrical Therapy

After evaluating the ability of the proposed method to estimate the phase of artificially induced and spontaneously occurring TWA, we evaluated its performance as a means to guide electrical therapy aimed to suppress TWA.

Specifically, we used R-wave–triggered pacing pulses during the absolute refractory period to induce and suppress TWA from 2 catheter leads in the RV (induction lead, RV12; suppression lead, RV34 or RV56; pulse amplitude, ±7 mA; pulse width, 30 ms; coupling to R-wave, 30 ms). In Figure 5, baseline (intervention A) corresponds to alternans induced during R-wave–triggered pacing from RV12 on an every-other-beat basis, whereas subsequent interventions refer to the effect of varying the R-wave–triggered stimulus polarity delivered from RV34 or RV56 with respect to the phase of alternans (induced from RV12). In interventions (B) to (E), R-wave–triggered pacing from RV12 continues on an every even beat

| Table. Performance Evaluation of Phase Estimation During Acute Ischemia |
|-------------------|-------------------|-------------------|-------------------|
|                   | Surface           | CS                | LV                | RV                |
| Sn                | 0.89 (0.88–0.90)  | 0.93 (0.92–0.94)  | 0.94 (0.93–0.94)  | 0.80 (0.79–0.81)  |
| Sp                | 0.93 (0.92–0.94)  | 0.95 (0.94–0.95)  | 0.92 (0.91–0.93)  | 1.00 (1.00–1.00)  |
| PV+               | 0.93 (0.92–0.93)  | 0.95 (0.94–0.95)  | 0.92 (0.91–0.93)  | 1.00 (1.00–1.00)  |
| PV−               | 0.90 (0.89–0.90)  | 0.93 (0.92–0.94)  | 0.93 (0.93–0.94)  | 0.83 (0.83–0.84)  |
| Accuracy          | 0.91 (0.90–0.92)  | 0.94 (0.94–0.94)  | 0.93 (0.92–0.94)  | 0.90 (0.90–0.90)  |

For each of the body-surface, coronary sinus (CS), left ventricle (LV), and right ventricle (RV) leads the receiver-operating characteristic–derived thresholds, determined in artificially induced T-wave alternans in control swine, have been applied to the coherence estimation results reported in Figure 3. The 95% confidence intervals are shown in parentheses. PV+ indicates positive predictive value; PV−, negative predictive value; Sn, sensitivity; and Sp, specificity.

Figure 4. Use of phase estimation to detect phase resetting. Effect of phase resetting on the alternans voltage (A and C) and Kscore (B and D) estimation on a body-surface lead in 2 different study subjects (subject 1: A and B; subject 2: C and D). Values of artificial decrease (A) or increase (C) of the alternans voltage with concomitant Kscore artificial decrease (B) or increase (D) are in each case associated with the presence of phase resetting caused by a premature ventricular contraction. Detection and removal of phase resetting (in black) results in the corrected alternans voltage and Kscore estimation (in gray). Dashed vertical lines indicate the index of the premature ventricular contraction.
basis; however, triggered stimuli are now delivered from RV34 or RV56 on every odd beat (B and C) or every even beat (D and E) with −7 mA (B and E) or +7 mA (C and D).

To establish a relationship between the outcome of the R-wave–triggered pacing with the pacing pulse polarity and the phase of TWA, we estimated the alternans voltage and K score using the protocol described above and reported the product of (pacing polarity)×(phase polarity). Phase polarity is defined as positive when the stimulus from RV34 or RV56 is triggered on beats with the opposite phase to the phase of alternans at baseline (out-of-phase pacing). In contrast, phase polarity is defined as negative when the RV34 or RV56 stimulus is triggered on beats with the same phase as the phase of alternans at baseline (in-phase pacing). The alternans voltage and K score for body-surface, CS, LV, and RV leads for each of the above interventions are shown in Figure 5 (n=8). We observe that in-phase pacing with negative pulse polarity, as well as out-of-phase pacing with positive pulse polarity, results in TWA increase, whereas in-phase pacing with positive pulse polarity or out-of-phase pacing with negative pulse polarity results in a reduction of TWA (comparison between baseline and each of the interventions used to suppress alternans for each lead type: \(P<0.0001\) for alternans voltage, \(P<0.0001\) for K score for the same paired interventions; \(n=8\)).

These results demonstrate that lack of a priori knowledge of the phase of TWA may result in an increase in the TWA amplitude (as shown in interventions C and E). Therefore, to effectively suppress TWA, one needs to know the phase of the estimated TWA. Based on these results, we propose that when the alternans phase and pacing pulse have opposite polarity, R-wave–triggered pacing will decrease TWA.

**Utility of the TWA Phase to Suppress Spontaneous TWA During Acute Ischemia**

We have further evaluated the use of the phase-dependent R-wave–triggered pacing during the absolute refractory period to suppress spontaneous TWA in sinus rhythm, in vivo.

In Figure 6, we plot the alternans voltage and K score of a triangular intracardiac bipolar lead configuration CS2CS8, CS2LV4, and CS2LV10 (an optimized intracardiac alternans detection lead system), after coronary artery balloon occlusion. In intervention A, one observes significant spontaneously occurring TWA. Upon detection of significant TWA, we estimated the phase of TWA and applied in-phase R-wave–triggered pacing with positive polarity from a catheter lead in the RV apex with the following parameters: amplitude: +4 mA; pulse width: 10 ms; pulse coupling: 10 ms, on every even beat (intervention B). The pacing polarity and phase polarity in intervention A, one observes significant spontaneous TWA. Upon detection of significant TWA, we estimated the phase of TWA and applied in-phase R-wave–triggered pacing with positive polarity from a catheter lead in the RV apex with the following parameters: amplitude: +4 mA; pulse width: 10 ms; pulse coupling: 10 ms, on every even beat (intervention B). We observe that R-wave–triggered pacing results in a significant reduction of spontaneous TWA during acute ischemia (77.59% average reduction across the 3 leads of the alternans voltage compared with baseline, \(P<0.0001\); 92.55% average reduction across the 3 leads of the K score compared with baseline, \(P<0.0001\)). In intervention C, RV12-triggered pacing is discontinued, leading to increase of the alternans voltage and K score (68.62% average increase across the 3 leads of the alternans voltage compared with TWA suppression, \(P<0.0001\); 87.06% average increase across the 3 leads of the K score compared with TWA suppression, \(P<0.0001\)).

Incidentally, pacing on an every beat basis does not decrease the level of alternans (data not shown). This finding is further supported by our recent observation that pacing during the absolute refractory period on every beat basis induces a consistent, lead-dependent modulation on ventricular repolarization. These data provide an important proof of concept that the phase of TWA is a critical parameter of TWA that can be estimated in real time and used to suppress spontaneously occurring TWA.

**Discussion**

In light of extensive preclinical and clinical data demonstrating an association between heightened TWA and the onset of malignant arrhythmias including VT and VF, the accurate detection and potential modulation of TWA may hold promise as a method to predict and preempt lethal heart rhythm disturbances. We have previously shown that a premature beat may alter the phase of alternans with significant implications on the estimation of TWA and its predictive use. The main aim of this study was to establish a robust method to quantify the temporal variability of TWA phase and to use
it to enhance the medium- and long-term SCD risk prediction of TWA as well as to guide short-term electrical therapy to suppress TWA.

This study is the first to provide a comprehensive and systematic approach to determine the phase of TWA in body-surface and intracardiac leads. Specifically, first we have shown that the method we have developed to estimate the phase of TWA is robust and sensitive to subtle changes of the T-wave morphology. Second, use of an artificial alternating reference PI sequence allows the real-time estimation of the temporal dynamics of the TWA phase. Third, during acute ischemia, the phase-derived coherence can discriminate between negative and positive TWA levels and provide highly accurate estimates of the TWA phase. Fourth, the phase-derived coherence can be used to determine phase-induced variability of TWA that results in significant improvement in the TWA estimation. Fifth, the phase of TWA and the polarity of a pacing pulse are sufficient to define a pacing strategy to suppress TWA in vivo. Sixth, we have been able to demonstrate that the TWA phase can be used to suppress spontaneously occurring TWA following acute myocardial infarction, in vivo.

Our results may have important clinical applications for diagnostic and therapeutic procedures that are based on TWA estimation. From a diagnostic point of view, microvolt TWA testing has emerged as an important predictor of SCD during medium- and long-term follow-up. However, although the negative predictive value of TWA testing has generally been good, the positive predictive value has been much less robust. Our data suggest that methods to improve the positive and negative predictive value of TWA testing may significantly improve its predictive use. It has previously been shown that the presence of PVCs or other bad beats (with altered morphology and timing) may have a profound detrimental effect on TWA testing by either underestimating or overestimating the level of TWA. Our study extends these previous findings by demonstrating that PVCs frequently lead to modulation of TWA in a swine model of acute coronary ischemia. The presence of PVCs is very common during clinical TWA testing, and the presence of frequent PVCs is the most common reason for indeterminate test results. Additionally, the likelihood of indeterminacy increases with progressively more impaired left ventricular systolic function, suggesting that patients at highest risk of SCD may be particularly susceptible to false-positive or false-negative TWA results attributable to PVC-induced phase resetting. The algorithm developed and validated in this study may provide a robust method for detecting scenarios where phase reversals are likely to lead to false-positive or false-negative TWA estimates and thus may significantly improve the sensitivity and the positive and negative predictive values of TWA testing.

Furthermore, studies in humans in which TWA was measured during ventricular pacing have demonstrated that the
presence of alternans phase reversal after PVCs carries important prognostic information and predicts a significantly lower arrhythmia-free survival when compared with patients without post-PVC phase reversal.28 However, extension of these findings has been limited by the lack of a validated method to measure the alternans phase in an efficient manner. Our data suggest that in addition to improving positive and negative predictive values, incorporating information about phase reversal into clinical TWA testing algorithms may independently improve the use of noninvasive TWA testing for medium- and long-term SCD risk prediction.

From a therapeutic perspective, several lines of preclinical and clinical evidence suggest that the presence of heightened TWA may play a causative or permissive role in creating an arrhythmogenic substrate and setting the stage for impending ventricular arrhythmias.29 It has been suggested that appropriately timed pacing therapy, potentially delivered from an implantable device (eg, implantable cardioverter-defibrillator), may be capable of suppressing the amplitude of TWA and potentially pre-empting the onset of VT and VF.2,14 In order for such upstream therapies to be viable, several conditions must be met. First, TWA must be detectable from an implantable device in real time with a high degree of sensitivity and fidelity. In this regard, we have developed and validated a novel intracardiac lead configuration system which has been shown to be highly sensitive in capturing the spatiotemporal nature of intracardiac alternans.10 Second, once a state of heightened TWA is detected, device-delivered therapy must be administered with the goal of rapidly suppressing the alternans magnitude and quelling the arrhythmogenic substrate. We have recently demonstrated that R-wave–triggered pacing pulses delivered during the absolute refractory period are capable of suppressing TWA.2,14 However, the outcome of R-wave–triggered pacing therapy is critically dependent on the alternans phase and if pacing therapy does not consider the TWA phase, the amplitude of TWA may be potentiated rather than suppressed. Therefore, being able to measure the TWA phase in real time and then to deliver customized therapy is a critical step in being able to suppress TWA reproducibly. In this study, we have demonstrated the importance of phase and pacing pulse polarity in determining the response to pacing therapy. Specifically, in-phase pacing with positive polarity pulses or out-of-phase pacing with negative polarity pulses provides a consistent suppression effect on TWA. It is likely that TWA suppression helps reduce repolarization gradients and thus reduce arrhythmia susceptibility. The important relationships established in this article between phase polarity and response to R-wave–triggered therapy are likely to become a crucial step in designing future studies that specifically assess the effect of alternans suppression algorithms on arrhythmia inducibility with the aim of validating the concept of upstream therapy. However, it should be noted that acute ischemia–induced alternans and SCD may have a different physiology than chronic ischemic–related alternans and SCD.

Conclusions

Our findings support the idea that the temporal variability of the phase of TWA can be effectively estimated by analysis of subtle changes of the T-wave amplitude that occur on a beat-to-beat basis. The algorithm presented in this study aims to enhance both the diagnostic and therapeutic clinical utility of TWA estimation.

Sources of Funding

The work was supported by a Scientist Development Grant (#0635127 N) and a Founders Affiliate Post-doctoral Fellowship (#12POST9310001) from the American Heart Association, and by National Institutes of Health (NIH) grant 1R21AG035128. This work was also supported by a Fellowship and a Science Award from the Center for Integration of Medicine and Innovative Technology (CIMIT), the Deane Institute for Integrative Research in Atrial Fibrillation and Stroke, and the Cardiovascular Research Society. This work was performed with support from Harvard Catalyst, The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, NIH Award 8UL1TR000170-05, and financial contributions from Harvard University and its affiliated academic healthcare centers). The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic healthcare centers, or the NIH.

Disclosures

T. Mela, MD, received honoraria of <$10K each from Medtronic, Biotronik, and St Jude. J.P. Singh, MD, PhD, received research grants from St. Jude Medical, Medtronic Inc, Boston Scientific Corp, and Biotronik; is an advisory board/steering committee/consultant in Boston Scientific Corp, Biotronik, St. Jude Medical, Medtronic, CardiOInsight Inc, Thoratec Inc, and Biosense Webster; and received honoraria/speaker fees from Medtronic Inc, Biotronik, Guidant Corp, St. Jude Medical, and Sorin Group. E.K. Heist, MD, PhD, received a modest amount of honoraria from Biotronik, Boston Scientific, Medtronic, Sorin, and St. Jude Medical; received a modest amount of research grants from Biotronik, Boston Scientific, and St. Jude Medical; and is a consultant for a modest amount in Boston Scientific, Sanofi, Sorin, and St. Jude Medical. The other authors report no conflict.

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CLINICAL PERSPECTIVE

T-wave alternans (TWA) reflects an oscillation pattern in cardiac repolarization that occurs on an every-other-beat basis. TWA has been mechanistically linked to reentrant arrhythmias and associated with an increased risk for sudden cardiac death. Although implantable cardioverter-defibrillators have demonstrated efficacy in prevention of sudden cardiac death, a major drawback of implantable cardioverter-defibrillator therapy is that it attempts to terminate an arrhythmia only after the arrhythmia has started, thereby exposing patients to hemodynamic consequences such as loss of consciousness and uncomfortable implantable cardioverter-defibrillator shocks. Therefore, although unproven, the ability to detect a potentially unstable arrhythmic substrate could result in therapy delivery before the onset of the arrhythmia, which could potentially be an attractive way to improve current implantable cardioverter-defibrillator technology. This study investigated the hypothesis that algorithms to estimate the phase of TWA in intracardiac and body-surface signals can improve the diagnostic and therapeutic utility of TWA. We sought this hypothesis in a swine acute ischemia model in which intracardiac TWA and body-surface TWA were estimated from electrograms obtained from catheters placed in the right ventricle, coronary sinus, and left ventricle. To develop an algorithm to estimate the phase of TWA that enhances the diagnostic utility of TWA. Additionally, we used that algorithm to deliver appropriate polarity-pacing pulses to suppress spontaneously occurring TWA successfully. This research is expected to enhance the use of TWA in predicting ventricular arrhythmias and sudden cardiac death and raises the possibility of using upstream therapies to abort a ventricular tachyarrhythmia before its onset.
A Novel Method for Determining the Phase of T-Wave Alternans: Diagnostic and Therapeutic Implications

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*Circ Arrhythm Electrophysiol.* 2013;6:818-826; originally published online July 24, 2013; doi: 10.1161/CIRCEP.113.000114

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Supplemental Material

Body Surface and Intracardiac Electrograms

T-wave alternans (TWA) estimates were obtained from the two body surface leads, 12 intracardiac unipolar leads (three in each of the right-ventricular, left-ventricular, and coronary sinus catheters) seen in Figure OS1.

Figure OS2 shows representative examples of body surface and intracardiac electrograms obtained prior to R-wave triggered pacing. These electrograms demonstrate that all catheter leads provide artifact-free and high-fidelity signals with high signal to noise ratio, appropriate for the TWA analysis.

Delineation of the T-wave Boundaries Using the Wavelet Transform

The first step in the phase analysis involves the robust estimation of the T-wave boundaries. Considering the variability in the morphology as well as the timing of the T-wave among different leads, the T-wave boundaries were independently determined on a beat-by-beat basis for each of the body-surface and intracardiac leads. Therefore, we developed a software-based T-wave delineation algorithm. This method is an updated version of the previously developed technique for surface ECG delineation based on the wavelet transform (WT) \(^1\).

The wavelet transform provides a multi-resolution decomposition of the signal as a combination of a set of basis functions, obtained by means of dilation and translation of a single prototype function, namely the mother wavelet \(^2\). It is possible to identify the significant points of the ECG signal using the information of local maxima, minima and zero crossings of the WT coefficients at different scales.

Briefly, for each beat, the dyadic wavelet transform of the signal was estimated using a quadratic spline wavelet for the first five scales, wherein most of the energy of the signal lies. We obtained QRS complex annotations (QRS onset, Q, S and QRS offset) by the zero crossing detection of the wavelet coefficients between a positive maximum-negative minimum pair at the first scale, which corresponds to the highest frequency component of the ECG beat. Afterwards, a search window relative to the R position and depending on the RR interval was defined. Within this window, the maximum modulus of WT in scale \(2^4\) was computed, based on which we
assigned one out of six possible morphologies to the T-wave as positive, negative, positive-negative biphasic, negative-positive biphasic, ascending and descending.

It is noteworthy that the presented WT algorithm can be applied directly over the raw ECG signal without any pre-processing. In fact, the frequency domain filtering is implicitly performed when computing the WT, eliminating the need to pre-filtering the digitized signal and allowing the direct application over the raw data.

**T-wave Alternans Estimation Algorithm**

We employed a previously described alternans analysis algorithm\(^3,4\) for the estimation of intracardiac TWA.

Preliminary R-wave time points were obtained by applying a software-based QRS detection algorithm to surface electrogram lead V4. Then, QRS detections were refined and abnormal beats, for example, premature ventricular complexes (PVCs) and aberrantly conducted beats were identified using a template-matching QRS algorithm\(^3\). Briefly, for each new beat, an 80-ms window centered at the peak of the QRS complex was formed from the preliminary beat detection; an isoelectric PR segment was automatically subtracted as a zero amplitude reference point (by estimating the mean voltage in a 10-ms window preceding the start of each QRS complex). A median QRS template was generated from all “normal” QRS complexes across the previous 127 beats, and the beat was aligned to the QRS template using cross-correlation. Cross-correlation was repeated twice for each new QRS complex to ensure proper QRS alignment. A beat was considered “abnormal” if its correlation coefficient was less than a threshold value of 0.95 or if the preceding R-to-R (R-R) interval was at least 10% shorter than the mean R-R interval of the previous 7 beats. Once all abnormal beats were identified in a 128-beat sequence, each abnormal beat was substituted with a median odd or even template beat on a lead-by-lead basis (derived from the odd or even “normal” beats respectively in the 128-beat sequence), depending on whether the abnormal beat was an even or odd beat.

Then, delineation of the T-wave boundaries (T\(_{onset}\), T\(_{offset}\)) was performed using the wavelet transform, as described above. Spectral alternans analysis was performed on a beat-by-beat basis for each 128-beat data sequence using a 512-point power spectrum to improve the frequency-domain resolution. To account for the spatial variability of TWA, spectral analysis was independently performed for each lead. Repolarization alternans indices were estimated as follows:
alternans voltage \((\mu V) = \sqrt{\text{alternans peak} - \mu_{\text{noise}}}\)

\[ K_{\text{score}} = \frac{\text{alternans peak} - \mu_{\text{noise}}}{\sigma_{\text{noise}}} \]

where, the alternans peak is the peak in the aggregate power spectrum corresponding to 0.5 cycles/beat and the mean \((\mu_{\text{noise}})\) and the standard deviation \((\sigma_{\text{noise}})\) of spectral noise are estimated from a predefined aggregate power spectrum noise window (0.40-0.46 cycles/beat). The alternans voltage is a direct measure of the presence of alternans while the alternans \(K_{\text{score}}\) is a measure of the statistical significance of the alternans voltage. For each lead, alternans was estimated on a beat-by-beat basis using a rolling 128-beat window that was shifted one beat at a time.

**Signal Processing Methods**

To quantitatively investigate the degree of synchronous alternation between two waveforms, the coherence of two signals \((x[n] \text{ and } y[n])\) has been estimated using the Welch's averaged periodogram method. The magnitude squared coherence is defined as the ratio of the power spectral densities of signals \(x[n]\) and \(y[n]\) to the cross power spectral density of \(x[n]\) and \(y[n]\). The cross-spectral density indicates the part of \(y[n]\) that is linearly related to \(x[n]\) as a function of frequency, or alternatively it can be interpreted like the cross-correlation function except it provides the expected results as a function of frequency. The coherence estimate is a function of frequency with values between 0 and 1 that indicates how well \(y[n]\) corresponds to \(x[n]\) at each frequency (0/1 indicating the lowest/highest coherence); in the case of T-wave alternans, we focus on the coherence values at 0.5 cycles/beat.

In order to detect TWA phase resetting, we estimated the cross-correlation of the estimated phase of TWA with the reference phase-index sequence which at the point of phase resetting, results in a zero-crossing of the correlation coefficient and a change in the polarity of the correlation coefficient in the vicinity of the zero crossings.

**Triggered Pacing Induced TWA in the Normal Heart**

R-wave triggered pacing during the absolute refractory period was used to induce alternans in the normal heart.
Pacing pulses were delivered on every other beat basis from two leads (RV12) of a decapolar catheter at the apex of the RV. We used pacing pulses of (i) amplitude: ±1 mA and ±5 mA, (ii) width: 30 ms and (iii) coupling to the R-wave: 10 ms. Figure OS3 demonstrates the $K_{\text{score}}$ for a single subject before and after R-wave triggered pacing (initiated at beat #177), for body-surface, CS, LV and RV leads. The increase in $K_{\text{score}}$ suggests the ability to modulate ventricular repolarization and induce TWA.

Detection of TWA Phase Resetting

Having examined the ability of the proposed method to estimate the phase of TWA, we evaluated the use of the PI as a means to detect phase resetting (Figure OS4). In order to detect potential TWA phase resetting, we estimated the cross-correlation of the estimated TWA phase with that of the reference phase-index sequence, which at the point of phase resetting is expected to result in a zero-crossing and a change in the polarity of the correlation coefficient.

We generated an N point time series of an ideal alternating phase-index. Two phase resetting points were introduced into this sequence by reverting the PI at two different pre-specified points, i=70 and j=130. An M-point (M=36) running window was used to estimate the cross correlation with the reference alternating time series. In computer simulated data (Figures OS4, panels A and B), we demonstrate that in the presence of phase resetting, the cross correlation of the phase index changes from 1 to -1 (or vice versa), crossing the zero point at the phase resetting point. The transient decrease/increase starts M/2 points before the phase resetting point and lasts for M/2 points after the phase resetting point. The change in the polarity of the estimated cross correlation in the M-point window is used to determine the phase resetting location at the zero crossing point.

Phase-Dependent Coherence Estimation During R-wave Triggered Pacing

In Figure OS5, we show the phase coherence variation as a result of applying R-wave triggered pacing pulses to induce and suppress TWA from two catheter leads in the RV (induction lead: RV12; suppression lead: RV34; pulse amplitude: -7mA; pulse width: 30ms; coupling to R-wave: 30ms).

Intervention A shows that the level of coherence in the presence of atrial pacing (100 bpm), is low. Intervention B demonstrates a significant rise in the coherence (due to an increase in the alternans voltage and $K_{\text{score}}$) resulting from R-wave triggered pacing from RV12 on an every even beat basis. In intervention C, triggered pacing continues from RV12 on even beats, however, triggered stimuli are now delivered from RV34 on every odd beat, and the
coherence substantially decreases (due to a decrease in the alternans voltage and $K_{\text{score}}$) because the distinction between odd and even beats is essentially lost by delivering R-wave triggered pacing pulses during each beat. In intervention D, R-wave triggered pacing continues from RV12 on every even (-7 mA) and from RV34 on every odd beat; however, the polarity of the pacing stimulus delivered on each odd beat from RV34 is reversed (+7 mA). Reversing the polarity of RV34 results in a significant increase in the coherence (due to an increase in the alternans voltage and $K_{\text{score}}$) because the opposite polarity pacing pulses accentuate the distinction between odd and even beats. In the following intervention (E), R-wave triggered pacing from RV12 continues on every even beat (-7 mA) but triggered pacing is now delivered from RV34 also on every even beat but with an opposite polarity pulse (+7 mA). Finally, in intervention G, the coherence again decreases (due to a decrease in the alternans voltage and $K_{\text{score}}$) during triggered pacing from RV12 on every even beat because the distinction between odd and even beats is eliminated. Thus, lack of a priori knowledge of the phase of TWA may result in an increase in the TWA amplitude (as shown in interventions B, D and F). Therefore, in order to effectively suppress TWA, one needs to know the phase of the estimated TWA.

**ECG Morphology Changes During TWA Suppression in the Presence of Acute Ischemia**

In Figure 6 of the manuscript we present the utility of phase-dependent R-wave triggered pacing during the absolute refractory period to suppress spontaneous TWA.

In Figure OS6, we present the change of ECG morphology from baseline in sinus rhythm (when significant TWA is present), to TWA suppression by pacing during the absolute refractory period (one may see the pacing pulse and appreciate that the discrimination of even/odd beats is lost) and back to baseline (when significant TWA is manifested again). In Figure OS6, the median odd/even beats (in a 128-beat sequence) of the triangular intra-cardiac bipolar lead configuration CS2CS8, CS2LV4 and CS2LV10 are shown during spontaneous TWA (intervention A), in-phase R-wave triggered pacing with positive pulse polarity (intervention B) and baseline TWA (intervention C). While we observe visible TWA in both baselines (interventions A and C), intervention B demonstrates a significant reduction in the alternans level, to the extent that TWA is no longer visible.
Online Supplement Figure Captions

**Figure OS1** Typical catheter position in the right ventricle (RV), left ventricle (LV), coronary sinus (CS) and right atrium (RA).

**Figure OS2** Representative electrograms from surface lead V4 and unipolar intracardiac leads from Coronary Sinus (CS), Left Ventricular (LV) and Right Ventricular (RV) catheters with reference to an electrode in the inferior vena cava. The amplitudes of signals have been normalized.

**Figure OS3** Repolarization alternans induction following R-wave triggered pacing on every other beat during absolute refractory period in the normal heart. $K_{score}$ is plotted for a body-surface lead (ECGII), one CS lead (CS1U), one LV lead (LV9U) and one RV lead (RV3U) from a single study subject. There is a significant increase in $K_{score}$ after the onset of R-wave triggered pacing during the absolute refractory period (initiated at beat no 177). The TWA increase in RV lead is more profound due to its proximity to the pacing site.

**Figure OS4** Use of phase estimation to detect phase resetting. (A) Computer simulated data indicate two examples of phase resetting, at points $i=70$ and $j=130$. (B) Detection of the phase resetting points using the cross-correlation of the simulated data shown in (A) with the reference phase using an M-point ($M=36$) running window.

**Figure OS5** Phase-dependant average coherence in body-surface leads, and intracardiac CS, LV and RV leads resulting from RV12 and RV34 ventricular triggered pacing (amplitude: -7 mA; pulse width: 30 msec; coupling to R-wave: 30 msec) in the presence of atrial pacing at 100 bpm. The following pacing interventions were performed from the pacing leads: **A**: baseline, atrial pacing only, **B**: RV12 every even beat, **C**: RV12 every even & RV34 every odd beat, **D**: RV12 every even beat (-7 mA) & RV34 every odd beat but with the opposite polarity current pulse (7 mA), **E**: RV12 every even (-7 mA) & RV34 every even beat but with the opposite polarity current pulse (7 mA), **F**: RV12 every even beat & RV34 every even beat, **G**: RV12 every beat.

**Figure OS6** ECG morphology changes during spontaneous TWA suppression in the presence of acute ischemia. Intervention A: visible TWA in sinus rhythm following coronary artery balloon occlusion; Intervention B: in-phase triggered pacing with positive pulse polarity delivered from
RV12 on every even beat decreases alternans level; Intervention C: R-wave triggered pacing is discontinued and TWA becomes visible during sinus rhythm. Panels show the median odd(red)/even(blue) beats in a 128-beat sequence of the triangular intra-cardiac bipolar lead configuration CS2CS8, CS2LV4 and CS2LV10 during each intervention.
References


Online Supplement Figure 1

RA
CS
LV
RV
2 mm
Online Supplement Figure 4
Online Supplement Figure 6

A

B

C

CS2CS8

CS2LV4

CS2LV10