Tracking cardiac electrical instability by computing interlead heterogeneity of T-wave morphology

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Nearing, Bruce D., and Richard L. Verrier. Tracking cardiac electrical instability by computing interlead heterogeneity of T-wave morphology. *J Appl Physiol* 95: 2265–2272, 2003. First published August 1, 2003; 10.1152/japplphysiol.00623.2003.—Oscillations in T-wave morphology, particularly T-wave alternans (TWA), have been fundamentally linked to increased susceptibility to ventricular fibrillation (VF). We investigated whether the escalation in complexity of T-wave oscillations before VF is attributable to increased spatial heterogeneity of repolarization. Peak interlead T-wave heterogeneity (TWH) was measured by second central moment analysis of T-wave morphology in epicardial electrograms in dogs during left anterior descending coronary artery occlusion. TWH differentiated cases in which myocardial ischemia provoked VF from those without VF (563 ± 56 vs. 139 ± 36 μV, P < 0.01). In the former group, progressive, significant increases in TWH above preclosure baseline (70 ± 8 μV) began at 2.25 min after the start of occlusion and were associated successively with TWA (at 155 ± 19 μV), T-wave multiplicity (at 386 ± 100 μV), complex oscillatory T-wave forms (at 560 ± 76 μV), discordant TWA (at 572 ± 98 μV), and VF at 4.36 ± 0.14 min. TWH in precordial ECGs in 12 pigs during angioplasty-balloon-induced myocardial ischemia also discriminated animals that experienced VF (from 90 ± 14 at baseline to 382 ± 39 μV, P < 0.05) from those without VF (from 96 ± 17 at baseline to 199 ± 61 μV, NS). Ischemia-induced changes in ST segment and T-wave amplitude did not predict VF. Heightened spatial heterogeneity of repolarization, as assessed by second central moment analysis of TWH, underlies TWA and increased risk for ischemia-induced VF. Monitoring spatial TWH from precordial leads could prove useful in stratifying risk for life-threatening arrhythmias.

sudden cardiac death; ventricular fibrillation; heterogeneity of repolarization

FLUCTUATIONS IN T-WAVE MORPHOLOGY, particularly in the form of T-wave alternans (TWA), have been linked to increased susceptibility to ventricular fibrillation (VF) (2, 20, 24, 31). Numerous experimental studies have demonstrated that the magnitude of TWA can gauge vulnerability to VF under diverse physiological and pharmacological interventions (2, 20–23, 31). Clinically, TWA has also proved promising in assessing risk for ventricular arrhythmias in patients with ischemic heart disease, heart failure, dilated cardiomyopathy, long QT syndrome, acute myocardial infarction, and other conditions (1, 4, 11, 13–15, 28, 30, 31, 38, 39). Heterogeneity of repolarization is an electrophysiological mechanism commonly linked to arrhythmogenesis (3, 9, 12, 18, 33, 35) and increasingly implicated in TWA (2, 16, 34, 37).

Recently, we demonstrated that just before onset of ischemia-induced VF, a progressive increase in the complexity of T-wave oscillations heralds the arrhythmia (24). The oscillations escalate from the ABAB pattern of TWA to tripling (ABCABC) or quadrupling (ABCD-ABCD) patterns that lead abruptly to more complex oscillatory T-wave forms and VF. Episodes of discordant TWA, with alternation out of phase in neighboring epicardial sites, frequently antecede VF (16, 24). Complex waveform behavior including quasi-periodicity has been implicated in cardiac fibrillation (10).

In the present study, we postulate that complex T-wave oscillations and discordant TWA before VF reflect states of heightened spatial heterogeneity of repolarization. To test this hypothesis, we developed a second-central-moment analysis technique to quantitate spatial heterogeneity of the entire morphology of the T wave simultaneously monitored from multiple epicardial or precordial leads. Second central moment is a concept from Newtonian mechanics that refers to a measure of splay of waveforms around the first moment, i.e., the average waveform (in this case a T wave), as its axis. This approach has the intrinsic advantages that heterogeneity throughout the entire T wave is assessed and that the measurement is not unduly weighted by protracted termination or inflections in the T wave, biphasic forms, ST segment changes, or the presence of U waves, features that limit measurement of dispersion of repolarization by conventional QT-interval analysis. The linkage between spatial TWH and the onset of VF was tested in both open- and closed-chest preparations using epicardial electrograms and precordial ECGs.

METHODS

Second central moment analysis of spatial heterogeneity of T-wave morphology. The square root of the second central moment of simultaneous T waves was computed to quantify...
the variability about the mean morphology (Figs. 1 and 2). Specifically, R waves are identified and an average waveform is computed on a point-by-point basis, where

$$e(t) = \frac{1}{4} \sum_{i=1}^{4} e_i(t)$$

where $e_i(t)$ is the ECG amplitude as a function of time ($t$) for electrode $E_i$ ($i = 1 \ldots 4$). Then, the simultaneous waveforms are superimposed and the second central moment ($\mu_2$) of the

$$\mu_2(t) = \frac{1}{4} \sum_{i=1}^{4} \left[ e_i(t) - e(t) \right]^2$$

T wave is calculated by taking the mean-square deviation, $\mu_2(t)$, of the waveforms about the average waveform

$$TWH = \frac{\mu_2(t)}{\sqrt{e_i(t)}}$$

The function $\mu_2(t)$ indicates taking the maximum value of the square root function for all values of $t$ between 60 and 29 ms after the R-wave. The results are averaged for each 15-s interval. Second central moment analysis of T-wave morphology differs from previous applications of root-mean-square calculations employed for identifying the end of the T wave (9).

The accuracy of the algorithm was examined by measuring TWH in simulated ECGs generated by a C++ program, having P waves, R waves, T waves, and ST segments approximated by geometric shapes whose relative timing and amplitude were similar to surface ECGs (Fig. 3). The resulting TWH readings were compared with input TWH of 0 to 800 $\mu$V depending on the desired amount of simulated TWH. Theoretical TWH, without noise, can be calculated as $\Delta V$ multiplied by $\sqrt{2.5}$.

Experimental studies. The experiments were conducted under a surgical plane of anesthesia according to protocols

Fig. 2. Superimposition of 4 simultaneous simulated ECG waveforms (A–D) illustrates heterogeneity of T-wave morphology, the parameter measured by second central moment analysis. ECGs A–D were simulated ECGs of identical morphology with the exception of the amplitude of the parabolic-shaped T wave. The peak T-wave amplitude of ECGs A–D were 500–2$\Delta$V, 500–$\Delta$V, 500+$\Delta$V, and 500+2$\Delta$V (in $\mu$V), where $\Delta V$ ranged from 10 to 500 $\mu$V depending on the desired amount of simulated TWH. Theoretical TWH, without noise, can be calculated as $\Delta V$ multiplied by $\sqrt{2.5}$. The function MAX of $t$ indicates taking the maximum value of the square root function for all values of $t$ between 60 and 29 ms after the R-wave. The results are averaged for each 15-s interval. Second central moment analysis of T-wave morphology differs from previous applications of root-mean-square calculations employed for identifying the end of the T wave (9).

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Experimental studies. The experiments were conducted under a surgical plane of anesthesia according to protocols
approved by the institutional animal care and use committee and standards set by the National Institutes of Health and described in American Physiological Society's 'Guiding Principles in the Care and Use of Animals'.

The epicardial electrograms from 12 mongrel dogs of either sex, weighing from 18 to 26 kg, were derived from a recent study in which the first demonstration of complex oscillatory T-wave forms leading to VF was reported (24). The focus of the present study was to provide a completely de novo analysis of spatial heterogeneity of T-wave morphology concurrent with the onset of complex T-wave oscillations. Canines of either sex were preanesthetized with xylazine (0.24 mg/kg sc) and anesthetized with 6-chloralose (150 mg/kg iv, with supplemental doses of 600 mg in 60 ml saline as required). After thoracotomy, the left anterior descending (LAD) coronary artery was occluded to induce myocardial ischemia. Spatial TWH was analyzed from ECGs obtained from 4 Ag-AgCl electrodes of 1-mm diameter spaced at 45, 135, 225, and 315° around a 5-mm circular Plexiglas plaque, which was placed on the epicardium in the expected zone of myocardial ischemia and sutured away from the electrodes to avoid current of injury. Bipolar ECGs were obtained with each of the four epicardial plaque electrodes as the negative poles and a needle electrode placed transcutaneously in the lower left hip region as the common positive reference pole. Heart rate was maintained constant by right atrial pacing at 150 beats/min. The effects of myocardial ischemia were evaluated by comparing baseline TWH at 4 min before occlusion with TWH levels monitored during an 8-min period of LAD coronary artery occlusion. T-wave multupling was quantified by complex demodulation by computing the area under the T wave from a series of samples from 60 to 220 ms after the R wave and analyzing the result with complex exponentials at the alternating, tripling, and quadrupling frequencies (24). Complex oscillatory T-wave forms were considered present when complex demodulation results decreased while repeating T-wave patterns remained visible. Episodes of discordant TWA in the epicardial four-electrode plaque were identified.
by multiplying the T-wave areas of all pairs of electrodes for each beat (24). When discordant TWA was present, the product was negative because the factors were positive and negative.

Spatial TWH in precordial ECGs (V2, V3, V4) was studied in 12 closed-chest Yorkshire pigs of either sex, weighing 32.9 ± 1.5 kg (range 22.9–39.5 kg) during right atrial pacing at 120 beats/min. The pigs were preanesthetized with telazol (4.7 mg/kg im) and xylazine (2.2 mg/kg im) and anesthetized with α-chloralose (bolus, 100 mg/kg iv, followed by continuous infusion, 40 mg·kg⁻¹·h⁻¹ iv). Myocardial ischemia was induced by intraluminal occlusion of the left anterior descending (LAD) coronary artery with an angioplasty balloon by using standard techniques and equipment. Specifically, under fluoroscopic guidance, the left main coronary artery was cannulated with an 8-Fr Judkins right guide catheter (JR4 with side holes, Boston Scientific, Natick, MA). An angioplasty guide wire (0.014-in. Wizdom guide wire, Cordis, Hialeah, FL) was threaded through the LAD coronary artery and past the second diagonal branch. An angioplasty balloon, 2.5 to 3.5 mm in diameter and 10–20 mm long (Boston Scientific), was passed over the guide wire to position the proximal end just beyond the first diagonal branch and was inflated to occlude the vessel completely, as verified by angiography. This closed-chest model of intracoronary artery occlusion yielded a high incidence of VF.

Preprocessing of experimental laboratory ECGs. Recording and analysis of data were performed with commercial equipment (GE Medical Systems Information Technologies, Milwaukee, WI) as previously described (23). Briefly, ECGs were low-pass filtered at 50 Hz, sampled at 500 Hz per channel, and stored on rewritable optical disks by Streamer software. The data were downsampled to 125 Hz for analysis on the MARS Workstation. Because the R-wave amplitude of the epicardial ECGs is larger than that of the surface ECG, we scaled down the epicardial ECGs by a factor of 10 for analysis. Ectopic beats, ventricular arrhythmias, or artifacts automatically identified by the MARS workstation were verified by a trained operator and removed from analysis.

Digitized ECGs were low-pass filtered to remove high-frequency noise by use of an eighth-order digital Butterworth filter with a corner frequency of 50 Hz. Baseline wander, a low-frequency artifact caused by changes in thoracic impedance during respiration, was estimated on the basis of iso-electric points in each ECG beat by calculating a cubic spline and was subtracted from the ECG signal.

Statistics. The statistical tests were carried out with an SAS statistical package (SAS Institute, Cary, NC). TWH levels were compared by one-way ANOVA with Tukey correction for multiple comparisons (Figs. 7–12). Values are means ± SE, P < 0.05.

RESULTS

Algorithm validation testing. The algorithm accurately tracked inhomogeneities in T-wave morphology, which are visible when the waveforms are superimposed (Figs. 1 and 2). We observed a linear relationship with a correlation coefficient of r² = 0.999 (P < 0.001) between the TWH value estimated by second central moment analysis and the input value in simulated ECGs (Fig. 3). The results were not affected by the introduction of ST-segment deviation, U waves, and T-wave inflections, which may obscure the terminal portion of the T wave (Figs. 4–6). The simulated ECGs contained a constant TWH of 99.6 μV, and the measured TWH differed <1% from the new waveforms.

Open-chest canine studies. TWH, as continuously measured by second central moment analysis, began to increase significantly at 2.25 min after the start of LAD occlusion and continued to increase in the six animals

![Fig. 7](image-url)  
**Fig. 7.** Second central moment analysis revealed increased TWH at 2.25 min after the start of occlusion in canines in which myocardial ischemia provoked VF at 4.36 ± 0.14 min vs. those without VF. TWH increased significantly from preocclusion baseline in the 6 cases with VF but did not increase in the 6 animals without VF.

![Fig. 8](image-url)  
**Fig. 8.** Pronounced TWH is evident in 4-electrode epicardial plaque electrograms at 4 min of occlusion in a representative canine in which myocardial ischemia provoked VF (right) but not in a representative case without VF (left). Superimposition (bottom) provides visual evidence of the significant differences in repolarization patterns.

![Fig. 9](image-url)  
**Fig. 9.** Progression of T-wave complexity in electrograms monitored from a 4-electrode plaque preceding VF is paralleled by the increasing magnitude of TWH.
in which myocardial ischemia-induced VF ensued at 4.36 ± 0.14 min (Fig. 7; representative examples, Fig. 8). TWH levels observed shortly before VF were markedly higher than in the six animals without VF at the same time point (563 ± 56 vs. 139 ± 36 μV, P < 0.01). The increase in TWH was not significant in the animals in which VF was not provoked (from 58 ± 6 at preocclusion baseline to 139 ± 36 μV, NS).

Successive, significant increases in TWH were observed as T-wave oscillations appeared and became more complex. Increasing levels of TWH were concomitant with increased TWA magnitude from preocclusion baseline of 70 ± 8 to 155 ± 19 μV at low levels of TWA (<1 mV) and to 272 ± 39 μV at higher levels of TWA (>1 mV). The greatest amount of spatial heterogeneity was observed during T-wave tripling and quadrupling (386 ± 100 μV), complex oscillatory T-wave forms (560 ± 76 μV), and episodes of discordant TWA (572 ± 98 μV), features that distinguished animals in which myocardial ischemia provoked VF (representative example, Fig. 9; summary data, Fig. 10; all comparisons P < 0.05).

**Closed-chest porcine studies.** Angioplasty-balloon-induced LAD occlusion provoked a significant increase in precordial TWH (from 90 ± 14 μV at preocclusion baseline to 382 ± 39 μV shortly before VF, P < 0.05) in 7 of 12 animals in which myocardial ischemia provoked VF (representative examples, Fig. 11; summary data, Fig. 12). Neither VF nor increased levels of TWH occurred in the other five pigs (from 96 ± 17 at preocclusion baseline to 199 ± 61 μV, NS, at the same time point). Likewise, in the seven pigs that experienced VF, there was a parallel significant rise in TWA in V2, the lead exhibiting the greatest TWA magnitude, from 18 ± 2 μV at baseline to 236 ± 34 μV (P < 0.05) at 3.5 min of occlusion, just before VF, but the rise in TWA was not significant in the animals that did not experience VF (from 14 ± 2 μV at baseline to 40 ± 13 μV, NS). T-wave multupling was not evident in the precordial leads, probably because their resolution is considerably less than that of local epicardial electrograms. Neither ST-segment level nor T-wave amplitude correlated with enhanced risk for ischemia-induced VF (Fig. 12).

**DISCUSSION**

The main objective of this study was to test the hypothesis that complex oscillations in T-wave morphology culminating in VF during acute myocardial ischemia reflect a state of increased spatial heterogeneity of repolarization. Therefore, we evaluated TWH by measuring the second central moment of simultaneous T waves recorded from several epicardial sites within the ischemic zone or from precordial leads. Increasing levels of TWH indicated the development of increased electrical instability and heralded the onset of myocardial ischemia-induced VF.

**Increased spatial heterogeneity of T-wave morphology, T-wave multupling, and TWA discordance.** Second central moment analysis indicated a significant, progressive increase in TWH in epicardial or precordial leads among animals vulnerable to myocardial ische-
mia-induced VF (Figs. 7–12), with a close correspondence to the crescendo in complex T-wave oscillations (Figs. 9 and 10). Specifically, heightened levels of TWH were temporally associated with augmented electrical instability as evidenced by increased TWA magnitude and the onset of T-wave multupling, complex oscillatory T-wave forms, discordant TWA episodes, and finally VF. In hearts in which fibrillation did not occur, no myocardial ischemia-induced increase in TWH was evident (Figs. 7, 8, 11, and 12) and neither T-wave multupling, complex oscillatory T-wave forms, nor discordant TWA ensued. Furthermore, TWH was determined to track the time course of the myocardial ischemia-induced increase in electrical instability established by VF threshold testing studies (2, 12, 36) and the incidence of myocardial ischemia-induced ventricular tachyarrhythmias (21, 36) during the first 4–5 min of occlusion of a coronary artery. Heart rate was not a factor in the rise in TWH because it was held constant by right atrial pacing.

The present findings represent the first measurement of TWH concurrent with T-wave multupling. The progressive increase in TWH concomitant with an increase in TWA magnitude and complexity of T-wave oscillations supports the proposition that heightened levels of spatial heterogeneity of repolarization underlie T-wave multupling during the development of VF.

The mechanisms responsible for the marked rise in spatial TWH in association with multupling remain unidentified. Several lines of evidence implicate the involvement of calcium both in heterogeneity of T-wave morphology and in myocardial ischemia-induced T-wave oscillations. Fluctuations in this ion have been observed in synchrony with repolarization alternans during myocardial ischemia (19, 27, 40). Particularly germane is the demonstration of marked spatial heterogeneity of intracellular calcium transients during the early phase of myocardial ischemia, which have been implicated as the basis for electrical instability and susceptibility to arrhythmias (27). Calcium channel blocking agents reduce heterogeneity of repolarization as assessed by VF threshold measurement (5) and suppress TWA (22). Conversely, intracoronary bolus injection of calcium chloride causes a significant increase in TWH (41). The facts that sarcoplasmic reticulum reuptake inhibitors reduce TWA (29) and that calcium ions oscillate during myocardial ischemia-induced overload of this ion in the cell (8, 25) are
consistent with disturbed calcium handling as an underlying mechanism of this marker of cardiac electrical instability. The substantial, well-documented changes in potassium during myocardial ischemia have also been implicated both in enhanced heterogeneity of repolarization (6) and in TWA (17).

Conclusions and implications. Heightened levels of spatial heterogeneity of repolarization as assessed by second central moment analysis appear to underlie the progression from elevated TWA levels to more complex mechanisms of VF. Detection of TWH could prove useful in elucidating mechanisms of VF. TWH monitored in precordial leads could contribute to stratifying risk for life-threatening arrhythmias.

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DISCLOSURES

This study was supported by National Heart, Lung, and Blood Institute Grant R01 HL-63968. The authors are inventors of licensed U.S. and foreign patents that protect the analytical approaches employed in this study to measure spatial T-wave heterogeneity and T-wave alternans.

REFERENCES


