Modified moving average analysis of T-wave alternans to predict ventricular fibrillation with high accuracy

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Received 8 June 2001; accepted in final form 17 September 2001

Nearing, Bruce D., and Richard L. Verrier. Modified moving average analysis of T-wave alternans to predict ventricular fibrillation with high accuracy. J Appl Physiol 92: 541–549, 2002; 10.1152/japplphysiol.00592.2001.—T-wave alternans is a marker of cardiac electrical instability with the potential for arrhythmia risk stratification. The modified moving average method was developed to measure alternans in settings with artifacts, noise, and nonstationary data. Algorithms were developed and performance characteristics were validated with simulated electrocardiograms (ECGs). Experimental laboratory ECGs with dynamically changing alternans values were analyzed. Alternans values estimated by modified moving average analysis correlated strongly with input alternans values ($r^2 = 0.9999$). Rapidly changing alternans levels and phase reversals did not perturb the measurement. When heart rate was increased from 60 to 180 beats/min, with T-wave alternans apex moving from 237 to 103 ms after the R wave, the measured alternans peak varied <5% from input value. Simulated 50- to 1,000-$\mu$V motion artifact spikes typical of treadmill ECGs produced inaccuracies <2%. Alternans values in experimental laboratory study using standard electrodes tracked vulnerability to myocardial ischemia-induced ventricular fibrillation with 100% sensitivity and specificity at a cut point of 0.75 mV. Modified moving average analysis is a robust method that precisely measures T-wave alternans in settings with artifacts, noise, and nonstationary data typical of clinical ECGs and yields an accurate estimate of risk for ventricular fibrillation.

risk assessment; sudden cardiac death; ventricular arrhythmias; ambulatory electrocardiogram; exercise treadmill testing

A SUBSTANTIAL BODY OF CLINICAL and experimental evidence indicates that T-wave alternans, a beat-to-beat fluctuation in the amplitude of that waveform, is fundamentally linked to vulnerability to ventricular fibrillation (VF) (2, 19, 24, 25, 26, 34, 37). In the experimental laboratory, it has been shown that T-wave alternans magnitude tracks vulnerability to ventricular tachyarrhythmias under diverse physiological and pharmacological interventions (2, 19, 24, 25, 26, 34). Available clinical data indicate that this parameter is equivalent to electrophysiological testing in assessing risk for arrhythmic events in a number of patient groups at moderate-to-high risk for cardiac events, including those with coronary artery disease, ventricular arrhythmia, myocardial infarction, cardiomyopathy, or congestive heart failure (1, 6–8, 11, 14–17, 22, 30, 36).

However, broader application of T-wave alternans analysis in the standard clinical applications of exercise treadmill testing and ambulatory electrocardiogram (ECG) has been limited. This constraint has been, in part, attributable to the intrinsic properties of spectral analytic methods that have been employed. Spectral analysis is relatively intolerant of changes in data stationarity and motion artifact and generally requires stabilizing heart rate for ~2 min (12, 29). The stationarity requirement is also problematic because major arrhythmias are often precipitated by transient physiological events, such as heightened sympathetic nerve activity, acute myocardial ischemia and reperfusion, and episodes of intense physiological or mental stress (5, 21, 23).

The goal of the present study was to develop a robust means to assess T-wave alternans that would be compatible with routine clinical monitoring and experimental laboratory studies. To optimize the extent of use, the method would need to provide interpretable results without controlling heart rate and would handle artifacts and noise. We also required that the method be dynamic, i.e., be sensitive to transient changes in cardiac electrical instability. To achieve these objectives, we developed a new technique, which we termed modified moving average analysis, formerly named “median beat” analysis (27, 38). The approach and algorithms are described together with validation studies. In addition, experimental laboratory data are provided that demonstrate the capability of the method to predict the occurrence of VF during acute coronary artery occlusion.

METHODS

Modified moving average computed beat construction and analysis of T-wave alternans. The underlying assumption in our development of modified moving average analysis was that the most robust means of quantifying T-wave alternans...
would disclose its predictive power most fully. Accurate measurement is difficult, as alternans magnitude can range from $<20 \mu V$ to several hundred microvolts on a surface ECG. The approach involves constructing modified moving average computed beats by averaging alternate ECG beats. A weighted moving average is applied to limit the contribution of any one beat. The alternans estimate for any ECG segment is then determined as the maximum difference between $A$ and $B$ modified moving average computed beats within the ST segment and T-wave region. These strategies allow the algorithm to discriminate surges in alternans attributable to physiological and pathophysiological triggers. The accuracy of the algorithm in quantifying T-wave alternans was verified with simulated ECGs, and its predictive accuracy was established in an experimental study.

The algorithm (Fig. 1) is streamlined and employs a minimum of signal averaging to avoid requiring data stationarity. After arrhythmias and noisy ECG beats have been removed, the data consist of a series of ECG beats: ECG beat$_{i,j}$, $j = 1, 2, 3 \ldots N$. The first step is to classify alternate ECG beats in a stream of ECG beats as $A$ for even ECG beats and $B$ for odd ECG beats.

\begin{align}
\text{ECG beat } A_{n(i)} &= \text{ECG beat}_{2i-1}(i) \\
\text{ECG beat } B_{n(i)} &= \text{ECG beat}_{2i}(i)
\end{align}

where $i = 1 \ldots n$ is the number of samples per beat, $n = 1, 2, 3, 4 \ldots N/2$, and $N$ is the total number of beats in the data. Then, modified moving average complex $A$ is initialized with the first even ECG beat, and modified moving average complex $B$ is initialized with the first odd ECG beat.

\begin{align}
\text{Computed beat } A_{1(i)} &= \text{ECG beat } A_{1(i)} \\
\text{Computed beat } B_{1(i)} &= \text{ECG beat } B_{1(i)}
\end{align}

The next modified moving average computed beat is formed using the present modified moving average computed beat and the next ECG beat in the series. If the next ECG beat is larger than the present modified moving average computed beat, then the next modified moving average computed beat’s value will be increased above the present modified moving average computed beat. If the next ECG beat is smaller than the present modified moving average computed beat, then the next modified moving average computed beat’s value will be decreased below the present modified moving average computed beat. As described in Eqs. 3a and 3b, this increase or decrease, $\Delta_A$ and $\Delta_B$, is a fraction of the difference between the next ECG beat and the present modified moving average computed beat and is thus bounded from being too large.

\begin{align}
\Delta_A &= -32 \text{ if } \eta \leq -32 \\
\Delta_A &= \eta \text{ if } -1 \leq \eta > -32 \\
\Delta_A &= -1 \text{ if } 0 > \eta > -1 \\
\Delta_A &= 0 \text{ if } \eta = 0 \\
\Delta_A &= 1 \text{ if } 1 \leq \eta > 0 \\
\Delta_A &= \eta \text{ if } 32 \leq \eta > 1 \\
\Delta_A &= 32 \text{ if } \eta \geq 32
\end{align}

\begin{align}
\Delta_B &= -32 \text{ if } \beta \leq -32 \\
\Delta_B &= \beta \text{ if } -1 \leq \beta > -32 \\
\Delta_B &= -1 \text{ if } 0 > \beta > -1 \\
\Delta_B &= 0 \text{ if } \beta = 0 \\
\Delta_B &= 1 \text{ if } 1 \leq \beta > 0 \\
\Delta_B &= \beta \text{ if } 32 \geq \beta > 1 \\
\Delta_B &= 32 \text{ if } \beta \geq 32
\end{align}

where $\eta = |\text{ECG beat } A_{n-1}(i) - \text{computed beat } A_{n-1}(i)|/8$, and $n$ is the $n$th beat in the beats of type $A$.

\begin{align}
\text{Computed beat } B_{n(1)} &= \text{computed beat } B_{n-1}(i) + \Delta_B
\end{align}

The modified moving average beats are continuously calculated. To measure T-wave alternans, the maximum absolute value of the difference between the $A$ and $B$ modified moving average computed beats is determined within the ST segment and T-wave region. The output period can be adjusted as desired.

\[ J \text{ Appl Physiol} \bullet \text{VOL 92} \bullet \text{FEBRUARY 2002} \bullet \text{www.jap.org} \]
waveform and centered /H9262 V was added to alternate ECG beats of the simulated that of a surface ECG. A pulse with an amplitude of 10 shapes whose relative timing and amplitude were similar to wave, and ST segment were approximated by geometric was generated by a C/H11001/H11001 ECG with the output alternans readings. A simulated ECG comparing known alternans input values in the simulated gram during dynamically changing conditions was tested by 15-s interval in the tests and study reported below. Maximum alternans magnitude was determined for each n where TWA is T-wave alternans and T-wave region, from the J point to the end of the T apex of the LV through a carotid artery. A pigtail pressure catheter was positioned to monitor LV blood pressure. Arterial blood pH, the partial pressure of CO2, and the partial pressure of O2 were monitored with an Instrumentation Laboratory 1304 blood-gas analyzer. Values were maintained within physiological ranges by adjusting the ventilation of the Harvard respirator.

Two occlusion-release sequences separated by 30 min were performed during atrial pacing at 150 beats/min. Data from the first sequence, which was for preconditioning, were discarded according to standard practice because of the variabil-

![Fig. 2. Calibration curve demonstrating a linear relationship between the alternans value estimated by MMA analysis and the alternans input signal in a simulated waveform. The alternans level measured by the MMA method is plotted against the input alternans level in a simulated waveform, which was elevated from 10 to 1,000 μV in a staircase fashion, changing once every 10 min. Regression analysis yielded a slope of 0.996, an intercept of 4.33 μV, and correlation of r² = 0.9999. ECGs with 10-, 100-, and 1,000-μV alternans are also shown. Alternans of 10 μV is below the level that can readily be detected by the human eye, whereas 100-μV alternans is visually detectable but small. Alternans of 1,000 μV is large and is seen in only extreme cases and syndromes.](image)

![Fig. 3. Accuracy of MMA analysis in tracking a stepwise change in alternans level. For a 50- or 100-μV step, the MMA algorithm produces 100% of the input step during the first 15 s and 100, 100, and 99.01% of the input step value shown. Alternans of 10-, 100-, and 1,000-μV alternans are also shown. Alternans of 10 μV is below the level that can readily be detected by the human eye, whereas 100-μV alternans is visually detectable but small. Alternans of 1,000 μV is large and is seen in only extreme cases and syndromes.](image)
of results. Each occlusion-release sequence consisted of a 4-min baseline period, 8-min occlusion period, and 4-min release period. Alternans values were measured during the second, or control, occlusion at 3.6 ± 0.2 min after the start of occlusion.

Preparation of experimental laboratory tracings. Recording and analysis of data were performed with commercial equipment (GE Medical Systems Information Technologies, Milwaukee, WI). Experimental laboratory ECG data recorded with standard electrodes were low-pass filtered at 50 Hz before sampling at 500 Hz per channel and stored on rewritable optical disks by Streamer software. These ECG data were down-sampled to 125 Hz for loading on the MARS workstation designed to handle phase reversals in the alternans pattern. Arrhythmias can sometimes trigger a phase reversal so that the alternans pattern changes from ABABAB to BABABA. An uncorrected phase reversal that occurs in the center of the data in Fourier transform analysis of alternans can mistakenly reduce the alternans estimate to zero. By contrast, the MMA method recovers completely in one or two 15-s measurement intervals. For a 50- or 100-μV alternans signal, the accuracy of the reading for the first 15-s interval after the phase reversal remains at 100%. Whereas, during the initial 15-s interval, the accuracy drops to 75% for a 200- or 500-μV alternans signal and to 73% for 1,000-μV alternans signal, it recovers during the second 15-s interval to 100% for the 200- or 500-μV alternans signal and to 98% for the 1,000-μV signal. During the third 15-s interval, all readings exhibited 100% accuracy.

ECG beats with TP segments that were not relatively isoelectric were marked for elimination, as TP segments that are not flat indicate corruption by electronic noise. The TP segment occurs approximately between 55 and 70% of the R-wave-R-wave interval. To determine whether a particular ECG beat was too noisy to be used, the mean value and the standard deviation of the ECG amplitude within this TP interval were calculated. If the standard deviation was above a predefined threshold (typically 50 μV), then the ECG beat was excluded from analysis. Segments identified as displaying elevated alternans magnitudes were visually reviewed for artifact.

Statistical methods. The statistical tests were carried out with a STATA statistical package (Santa Monica, CA). Results are expressed as means ± SE. A linear regression analysis was performed (Fig. 2). An ANOVA was performed to calculate the differences between the two groups of experimental laboratory data (Figs. 8 and 9). Specificity and sensitivity were calculated with standard formulas (Fig. 9). The
cut point was determined from the receiver-operator characteristic (ROC) curve, where both specificity and sensitivity were 100%, to be 0.75 mV.

RESULTS

Simulation studies. Validation testing with the simulated alternans signal, added to increase alternans in a stepwise fashion from 10 to 1,000 μV, determined that this relatively simple algorithm measured T-wave alternans as the maximum difference in T-wave amplitude of successive ECG beats with a high degree of accuracy across this range of values. We observed a correlation coefficient of 0.9999, indicating a significant level of precision (Fig. 2). The algorithm performed accurately from 1,000 to 10 μV, which has been an adequate lower limit in our studies. Alternans levels <10 μV were not tested because the current least significant bit resolution of the MARS workstation is 2.44 μV. However, lower levels of T-wave alternans could be detected with equipment using analog-to-digital converters with higher resolution. The program assessed abrupt increases in alternans level of 50–1,000 μV, demonstrating its capacity to track changes in alternans level, such as those that occur in response to physiological triggers (Fig. 3). The algorithm also accurately handled sudden phase reversals or resetting that can result from arrhythmias (Fig. 4). This capability was demonstrated by adding an abrupt
Fig. 8. Pronounced T-wave alternans in LV endocardial tracings at ~3.5 min after the start of occlusion in a representative animal in which VF occurred (top). The amplitude of the LV blood pressure (LVBP) waveform (middle) decreased by ~10% during occlusion but did not alternate, indicating that mechanical alternans did not contribute to the appearance of T-wave alternans. Alternans was minimum in the ECG obtained at the same time point during occlusion from an animal in which VF did not occur (bottom). T-wave alternans was not visible at preocclusion baseline in any animal. To exclude a contribution to alternans levels by HR, all animals were paced at 150 beats/min.

phase reversal in the alternans pattern from ABABAB to BABABA. The magnitude of alternans varied <5% from its input value as heart rate was raised from 60 to 180 beats/min, and the width and timing of the simulated alternans pulse were allowed to change realistically with heart rate (Fig. 5). The method discriminated between an isolated ECG beat spike, such as that which is commonly due to motion artifact, and an alternans signal; this capacity was tested by adding an alternans pulse to a single ECG beat in a stream of otherwise constant-amplitude beats (Fig. 6).

Experimental laboratory study. Modified moving average analysis revealed a progressive increase in T-wave alternans magnitude at 3–4 min and a subsequent abrupt rise in alternans level on release reperfusion at 8 min after coronary artery occlusion (Fig. 7). This pattern coincides with previous reports of the time course of cardiac vulnerability in response to ischemia and reperfusion, as tracked by programmed electrical stimulation (20) and spontaneous occurrence of ventricular tachyarrhythmias (20, 26). Modified moving average algorithm demonstrated that T-wave alternans was capable of differentiating the animals that subsequently experienced VF from those that did not fibrillate during coronary artery occlusion (Figs. 8 and 9). Alternans levels were measured at 3.6 ± 0.2 min, and fibrillation ensued at 4.37 ± 0.15 min after the start of the occlusion in susceptible animals. This predictive ability is independent of heart rate, which was held constant at 150 beats/min by atrial pacing. Analysis of the LV blood pressure waveform revealed no evidence of mechanical alternans. The predictive capability was exceptionally high, as the sensitivity and specificity for indicating susceptibility to ischemia-induced VF were both 100% at the cut point of 0.75 mV (Fig. 9).

DISCUSSION

The main goal of the present study was to develop a robust method for T-wave alternans analysis to optimize its predictive accuracy for life-threatening arrhythmias. The critical performance characteristics required were reliability of measurement during abrupt changes in alternans magnitude and phase reversals and insensitivity to changes in data stationarity, including heart rate fluctuations and ECG beat spikes. These ECG phenomena are commonly encountered during acute myocardial ischemia and reperfusion, as well as altered autonomic nervous system activity. Modified moving average analysis is a nonspectral method that builds on the powerful noise-reduction principle of signal averaging by estimating moving average computed beats (Fig. 1). Experimental laboratory data are provided that document the high predictive capacity of the method in measuring T-wave alternans to assess risk for VF during acute coronary artery occlusion.

ECG simulation studies. The calibration curve (Fig. 2) demonstrated a strong linear relationship ($r^2 = 0.96$) between alternans magnitude at 3.6 min and VF occurrence (Fig. 9).

Alternans
Threshold(mV): 3.0 2.0 1.0 0.75 0.5 0.25 0.0

Sensitivity
0 50 75 100

Specificity
0 25 50 75 100

VF Group

Baseline

Occlusion

LV ECG

LVBP (mmHg)

No VF Group

Fig. 9. Ischemia-induced T-wave alternans (TWA) in LV endocardial lead was significantly higher in the 6 animals in which VF occurred than in the 7 animals without VF during coronary artery occlusion (1.84 ± 0.29 vs. 0.38 ± 0.09 mV; $P < 0.001$) but not at baseline (0.31 ± 0.08 vs. 0.20 ± 0.02 mV; not significant). Ischemia induced an increase in alternans in the animals in which VF occurred (1.84 ± 0.29 vs. 0.31 ± 0.08 mV at baseline) but not in the animals in which VF did not occur (0.38 ± 0.09 vs. 0.20 ± 0.02 mV at baseline; not significant). Alternans was measured at 3.6 ± 0.2 min, and VF occurred 4.37 ± 0.15 min after the start of left anterior descending coronary artery occlusion. To provide data within the working range of the algorithm, the ECG signal was scaled down by a factor of 10 to the size of alternans in a surface ECG. The actual intracavitary alternans values were determined by restoring the factor of 10. Ischemia-induced alternans in LV endocardial lead was >0.75 mV in all 6 animals in which VF occurred, whereas, in 7 animals in which VF did not occur, alternans remained <0.75 mV. The cut point was determined from the receiver-operator characteristic curve to be 0.75 mV, where both specificity and sensitivity were 100%.

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0.9999) between the T-wave alternans value estimated by modified moving average analysis and the input signal of a simulated ECG waveform with increasing alternans magnitudes. The algorithms also performed well in tracking stepwise changes in alternans level (Fig. 3) and handling phase reversals in alternans patterns (Fig. 4). Importantly, we observed minimum effects on alternans measurements from increases in heart rate (Fig. 5) or from single-beat spikes (Fig. 6), which are typical of motion or noise artifact and are commonly encountered during exercise (27) and ambulatory monitoring (28, 38). The approach accurately measures bidirectional alternans, with the T-wave inscribed alternately above and below the isoelectric line, which discloses heightened vulnerability such as may occur on reperfusion of ischemic myocardium (24, 26) or exercise and emotional stress in patients with the Long QT Syndrome (4, 33).

**Electrophysiological considerations.** In the present study, modified moving average analysis of T-wave alternans was demonstrated to be capable of tracking vulnerability to VF during myocardial ischemia with a high degree of sensitivity and specificity (Figs. 7–9). This desirable result probably reflects both the fundamental electrophysiological link between T-wave alternans and vulnerability to VF (24, 26, 36, 37) and the capacity of the present method to assess the level of T-wave alternans accurately. Although the precise mechanisms of ischemia-induced T-wave alternans remain to be determined, the phenomenon appears to reflect the degree of heterogeneity of repolarization, an electrophysiological property that has been extensively implicated in the genesis of VF (9, 36, 37). The close coupling between T-wave alternans and vulnerability to VF is also supported by the characteristic crescendo in alternans magnitude observed during transition from normal rhythm to VF in both the present (Fig. 8) and previous studies (19, 24, 26). In animals that did not fibrillate during coronary artery occlusion, a low level of alternans was registered (Figs. 7–9), but its magnitude remained below the level found in their vulnerable counterparts. The lower level of alternans in the animals that did not fibrillate may be attributable to a number of factors, including differences in the extent of preformed collateral channels, baroreceptor sensitivity, and the degree of sympathetic nerve activation in response to myocardial ischemia (32). Accurate detection of alternans levels was probably optimized by the use of electrodes positioned in the LV near the site of ischemia, because ischemia-induced T-wave alternans is a regionally specific phenomenon (18, 26, 35). In humans and animals, even during severe myocardial ischemia, local electrograms from outside the zone of ischemia reveal little or no T-wave alternans. It remains unknown, however, whether the ideal sensitivity and specificity observed in the present study, with data obtained with LV electrograms, will be matched using body surface electrodes, which yield a lower signal-to-noise ratio.

**Performance of modified moving average analysis compared with complex demodulation.** In previous studies using complex demodulation, we demonstrated that T-wave alternans magnitude correlates with susceptibility to VF under diverse physiological and pharmacological interventions (19, 24–26). The desirable ROCs obtained with the modified moving average algorithm in analyzing experimental laboratory ECGs monitored with identical ECG recording systems indicate that its signal processing features are superior to those of complex demodulation (26) (Fig. 9). The ROC curve for predicting VF using surface ECGs, which yield a less favorable signal-to-noise ratio than LV ECGs, remains to be determined. However, based on our experience with ambulatory ECGs (38) and treadmill testing (27), modified moving average analysis is likely to be preferable to complex demodulation, which can be disrupted by motion and noise artifact (unpublished observations).

**Preliminary clinical studies.** During routine symptom-limited exercise treadmill testing, modified moving average analysis of T-wave alternans differentiated patients with stable coronary artery disease from age-matched normal volunteers (27). At exercise treadmill testing heart rates of 120 beats/min, alternans was higher in patients than in normal subjects (55.7 ± 5.5 vs. 37.4 ± 4.7 μV; P < 0.05; n = 7 for both groups), although there was no difference in alternans levels between the groups at preexercise baseline (11.9 ± 1.4 μV for patients vs. 15.5 ± 2.3 μV for normal subjects; not significant). Interpretable values were obtained in all cases during both rest and activity without specialized ECG electrodes or protocols to maintain heart rate constant. Modified moving average analysis of T-wave alternans is also promising in terms of predicting a significant increase in the risk of arrhythmic death (38). These results were obtained from routine 24-h ambulatory ECG tapes from a moderate-risk group of 1,284 postmyocardial infarction patients enrolled in the Autonomic Tone and Reflexes After Myocardial Infarction multicenter study. Using a nested-case control study design, we analyzed, in a blinded fashion, 14 cases and 25 controls matched for gender, age, site of myocardial infarction, LV ejection fraction, and thrombolysis. A statistically significant increase in risk of arrhythmic death was predicted by T-wave alternans level (P < 0.05). Thus results of the predictive power T-wave alternans obtained using modified moving average analysis in standard exercise treadmill testing and ambulatory monitoring without specialized electrodes are encouraging, although preliminary.

**Conclusions and implications.** Laboratory testing of simulated ECG signals and experimental laboratory data indicate that modified moving average analysis possesses suitable performance characteristics for evaluating the impact of physiological and pathophysiological factors on T-wave alternans. This method also demonstrates the high predictive accuracy of T-wave alternans for estimating risk for life-threatening ventricular tachyarrhythmias. In addition, because effective antiarrhythmic agents suppress T-wave alternans...
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