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

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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-μV 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.

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 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\(_{i}\), \(j = 1, 2, 3, \ldots, N\). 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

\[
\text{ECG beat } A_i(i) = \text{ECG beat}_{2i-1}(i) \quad (1a)
\]

\[
\text{ECG beat } B_i(i) = \text{ECG beat}_{2i}(i) \quad (1b)
\]

where $i = 1, 2, 3, 4, \ldots, N$, $n = 1, 2, 3, 4 \ldots N/2$, 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

\[
\text{Computed beat } A_1(i) = \text{ECG beat } A_i(i) \quad (2a)
\]

\[
\text{Computed beat } B_1(i) = \text{ECG beat } B_i(i) \quad (2b)
\]

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. 3(a) and 3(b), 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

\[
\text{Computed beat } A_1(i) = \text{computed beat } A_{n-1}(i) + \Delta A
\]

\[
\Delta A = \begin{cases} -32 & \text{if } \eta \leq -32 \\ \eta & \text{if } -1 \leq \eta > -32 \\ -1 & \text{if } 0 > \eta > -1 \\ 0 & \text{if } \eta = 0 \\ 1 & \text{if } 1 \leq \eta > 0 \\ \eta & \text{if } 32 \geq \eta > 1 \\ 32 & \text{if } \eta \geq 32 \end{cases} \quad (3a)
\]

\[
\text{Computed beat } B_1(i) = \text{computed beat } B_{n-1}(i) + \Delta B
\]

\[
\Delta B = \begin{cases} -32 & \text{if } \beta \leq -32 \\ \beta & \text{if } -1 \leq \beta > -32 \\ -1 & \text{if } 0 \leq \beta > -1 \\ 0 & \text{if } \beta = 0 \\ 1 & \text{if } 1 \leq \beta > 0 \\ \beta & \text{if } 32 \geq \beta > 1 \\ 32 & \text{if } \beta \geq 32 \end{cases} \quad (3b)
\]

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 $A$

\[
\text{Computed beat } B_1(i) = \text{computed beat } B_{n-1}(i) + \Delta B
\]

\[
\Delta B = \begin{cases} -32 & \text{if } \beta \leq -32 \\ \beta & \text{if } -1 \leq \beta > -32 \\ -1 & \text{if } 0 \leq \beta > -1 \\ 0 & \text{if } \beta = 0 \\ 1 & \text{if } 1 \leq \beta > 0 \\ \beta & \text{if } 32 \geq \beta > 1 \\ 32 & \text{if } \beta \geq 32 \end{cases} \quad (3b)
\]

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 seg-

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**Fig. 1.** Flow chart of the major components of the modified moving average (MMA) method. The left ventricular (LV) electrocardiogram (ECG) was obtained from a representative experiment in which coronary artery occlusion subsequently resulted in ventricular fibrillation (VF). ECGs are filtered to reduce high-frequency noise and to remove baseline wander. Ventricular and supraventricular premature ECG beats, as well as ECG beats with a high-noise level, are removed. The even ECG beats in the sequence are then assigned to group $A$ and the odd ECG beats to group $B$. MMA computed beats of types $A$ and $B$ are computed continuously according to Eqs. 3(a) and 3(b). The $n$th MMA computed beat is developed from the $n - 1$th ECG beat and the $n - 1$th MMA computed beat. The amplitude of the effect of any one ECG beat on the MMA computed beat is also limited by the bounds on $\Delta A$ and $\Delta B$, where $\Delta$ is change, which are computed by Eqs. 3(a) and 3(b). The alternans estimate is determined as the maximum absolute difference between $A$ and $B$ MMA computed beats within the ST segment and T-wave region. The output period can be adjusted as desired.
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 ECG with the output alternans readings. A simulated ECG comparing known alternans input values in the simulated 15-s interval in the tests and study reported below. Maximum alternans magnitude was determined for each TWA is T-wave alternans and $n = 1, 2, 3, \ldots N/2$. Maximum alternans magnitude was determined for each

$$TWA_n = \max_{i=1,2 \ldots N} \left| B_n(i) - A_n(i) \right|$$

where TWA is T-wave alternans and $n = 1, 2, 3, \ldots N/2$. Maximum alternans magnitude was determined for each

15-s interval in the tests and study reported below.

Testing with simulated ECGs. The precision of the program during dynamically changing conditions was tested by comparing known alternans input values in the simulated ECG with the output alternans readings. A simulated ECG was generated by a C++ program. The R wave, T wave, P wave, and ST segment were approximated by geometric shapes whose relative timing and amplitude were similar to that of a surface ECG. A pulse with an amplitude of 10–1,000 $\mu V$ was added to alternate ECG beats of the simulated waveform and centered ~30 ms before the T-wave apex to simulate an ECG with T-wave alternans (Fig. 2). This location was chosen because the first one-half of the T wave is the period of enhanced dispersion of repolarization (20) when maximum alternans occurs (24, 26). Detection of T-wave alternans in this range of amplitudes has been sufficient for our experimental and clinical studies. We also assessed the algorithm’s capacity to measure alternans during abrupt increases in alternans level (Fig. 3), alternans phase reversals (Fig. 4), changing heart rates (Fig. 5), and stray single-beat spikes (Fig. 6), as these phenomena are typical of routine clinical and experimental ECGs.

Experimental studies. The program’s capacity to assess vulnerability to VF during experimental coronary artery occlusion was examined in 13 consecutive adult mongrel dogs of either sex weighing 23 ± 2 kg (Figs. 7, 8, and 9). The animals were premedicated with morphine sulfate (2 mg/kg sc) and anesthetized with $\alpha$-chloralose (150 mg/kg iv) with supplemental doses of $\alpha$-chloralose given as required. A left thoracotomy was performed at the fourth intercostal interspace. A Doppler flow probe was placed around the left anterior descending coronary artery, and a 2–0 silk snare was placed around the artery to allow occlusion of the vessel. Aortic blood pressure was measured with a Gould-Statham P50 pressure transducer. A left ventricular (LV) endocardial ECG was obtained using a 7-French USCI quadripolar catheter with an interelectrode distance of 10 mm and electrode width of 2 mm. The tip of the catheter was positioned in the 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 CO$_2$, and the partial pressure of O$_2$ 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 $\mu V$ in a staircase fashion, changing once every 10 min. Regression analysis yielded a slope of 0.996, an intercept of 4.33 $\mu V$, and correlation of $r^2 = 0.9999$. ECGs with 10-, 100-, and 1,000-$\mu V$ alternans are also shown. Alternans of 10 $\mu V$ is below the level that can readily be detected by the human eye, whereas 100-$\mu V$ alternans is visually detectable but small. Alternans of 1,000 $\mu V$ is large and is seen in only extreme cases and syndromes.

Fig. 3. Accuracy of MMA analysis in tracking a stepwise change in alternans level. For a 200-, 500-, or 1,000-$\mu V$ step, the MMA algorithm produces a result that is 87.97, 87.49, and 86.67% of the input step value respectively. For a 50- or 100-$\mu V$ step, the MMA algorithm produces a result that is 87.97, 87.49, and 86.67% of the input step value respectively. For a 10- $\mu V$ step, the MMA algorithm produces a result that is 87.97, 87.49, and 86.67% of the input step value respectively. Regression analysis yielded a slope of 0.996, an intercept of 4.33 $\mu V$, and correlation of $r^2 = 0.9999$. ECGs with 10-, 100-, and 1,000-$\mu V$ alternans are also shown. Alternans of 10 $\mu V$ is below the level that can readily be detected by the human eye, whereas 100-$\mu V$ alternans is visually detectable but small. Alternans of 1,000 $\mu V$ is large and is seen in only extreme cases and syndromes.
For the 200- or 500-V alternans signal, it recovers during the second 15-s interval to 100%
to handle surface ECGs with a range of 5 to 1,000-V (12-bit analog/digital).
Because the R-wave amplitude of the LV ECG is larger than the noise, we scaled down the LV ECG by a
constant bit resolution of 2.44 μV.

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 were verified by a trained operator and removed from analysis.

The first step in implementing the modified moving average algorithm was low-pass filtering to remove high-frequency noise. This was accomplished using an eighth-order digital Butterworth filter with a corner frequency of 50 Hz. Data in 15-s strips were buffered with 256 samples at the leading end and at the trailing end. Trailing and leading buffers were filled with a mirror image of the samples at the end and beginning of the 15-s strips. The buffered strips were run through the filter forward and backward to produce a zero-phase result and to confine the transients in the buffered ends. The filtered ECG strips, with the buffers deleted, were then recomposed into a continuous, filtered ECG strip. Baseline wander, a low-frequency artifact caused by changes in thoracic impedance during respiration, was estimated based on isoelectric points in each ECG beat by calculating a cubic spline and was subtracted from the ECG signal.

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 validity 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.

Fig. 4. Capacity of the MMA method 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.

Fig. 5. Minimum change in T-wave alternans level as a result of varying heart rates (HR) from 60 to 180 beats/min (bpm). An alternans pulse of constant amplitude (100 μV) was added to every other beat of the simulated ECG at 30 ms before the T-wave apex. The T-wave (TW) apex is described by the equation TW apex = 374 − 1.985·HR − 0.0036·HR², and the T-wave end follows the equation TW end = 455 − 1.878·HR − 0.0026·HR² (39). The T-wave width and alternans pulse width are approximated as T-W (TW end − TW apex). The width and timing of the pulse were allowed to vary with HR similar to a surface ECG. Whereas the alternans apex changes from 237.86 to 103.34 ms after the R wave as the HR varies from 60 to 180 beats/min, the measured alternans peak varied only from 96.65 to 104.61% of its true value of 100 μV.

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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
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 ($r^2 = 0.99$). Analysis of the LV blood pressure waveform revealed a progressive increase in alternans level on release reperfusion at 8 min after coronary artery occlusion. To provide data within the working range of the algorithm, the ECG signal was scaled down by a factor of 10. 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.

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.
or exercise and emotional stress in patients with the
which discloses heightened vulnerability such as may
scribed alternately above and below the isoelectric line,
measures bidirectional alternans, with the T-wave in-
latory monitoring (28, 38). The approach accurately
which are typical of motion or noise artifact and are
commonly encountered during exercise (27) and ambu-
atory monitoring (28, 38). The approach accurately
measures bidirectional alternans, with the T-wave in-
scribed 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 funda-
mental electrophysiological link between T-wave alter-
nans 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 re-
main 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 attribut-
able to a number of factors, including differences in the
extent of preformed collateral channels, baroreceptor
sensitivity, and the degree of sympathetic nerve acti-
vation in response to myocardial ischemia (32). Accu-
rate detection of alternans levels was probably opti-
mized 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 sus-
cceptibility to VF under diverse physiological and phar-
macological interventions (19, 24–26). The desirable
ROCs obtained with the modified moving average al-
gorithm in analyzing experimental laboratory ECGs
monitored with identical ECG recording systems indi-
cate 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 tread-
mill testing (27), modified moving average analysis is
likely to be preferable to complex demodulation, which
can be disrupted by motion and noise artifact (unpub-
lished observations).

Preliminary clinical studies. During routine symp-
tom-limited exercise treadmill testing, modified mov-
ing average analysis of T-wave alternans differenti-
ated patients with stable coronary artery disease from
age-matched normal volunteers (27). At exercise tread-
mill 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 special-
ized 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 In-
farction 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 throm-
bolysis. 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 av-
average analysis in standard exercise treadmill testing
and ambulatory monitoring without specialized elec-
trodes 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 pathophys-
iological factors on T-wave alternans. This method also
demonstrates the high predictive accuracy of T-wave
alternans for estimating risk for life-threatening ven-
tricular tachyarrhythmias. In addition, because effective
antiarrhythmic agents suppress T-wave alternans
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