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Interpretation and Classification of Microvolt T Wave Alternans Tests

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Interpretation of T Wave Alternans Tests. Measurement of microvolt-level T wave alternans (TWA) during routine exercise stress testing now is possible as a result of sophisticated noise reduction techniques and analytic methods that have become commercially available. Even though this technology is new, the available data suggest that microvolt TWA is a potent predictor of arrhythmia risk in diverse disease states. As this technology becomes more widely available, physicians will be called upon to interpret microvolt TWA tracings. This review seeks to establish uniform standards for the clinical interpretation of microvolt TWA tracings. *(J Cardiovasc Electrophysiol, Vol. 13, pp. 502-512, May 2002)*

repolarization, T wave alternans, sudden cardiac death, exercise testing, signal processing

Introduction

T wave alternans (TWA) is a beat-to-beat fluctuation in the amplitude or shape of T wave. Macroscopic TWA has been recognized as a harbinger of malignant ventricular arrhythmias[1] and is commonly associated with long QT syndrome[2,3] and electrolyte abnormalities.[4,5] Over the past 10 years, an association between microvolt TWA (not detectable upon visual inspection of the ECG) and the genesis of ventricular arrhythmias has been demonstrated in animal models and human studies.[6,7] In these studies, the vulnerability of the myocardium to ventricular arrhythmias was strongly related to the presence and magnitude of microvolt TWA. These studies also demonstrated that the development of microvolt TWA is highly dependent on heart rate. Microvolt TWA often was not present at rest, but only after the heart rate was increased above ~90 beats/min.

The initial human studies of microvolt TWA utilized atrial pacing to enable the measurement of microvolt TWA at increased heart rates with relatively low noise levels. In 1994, Rosenbaum et al.[8] published the first prospective human study demonstrating a strong relationship between the presence of microvolt TWA and the inducibility of ventricular arrhythmias during electrophysiology testing as well as during 20-month arrhythmia-free survival. Over the next few years, a number of elegant advances in signal processing and noise reduction made it possible to measure microvolt TWA during exercise (summarized in reference 9). Hohnloser et al.[10] demonstrated the equivalence of microvolt TWA measured during bicycle exercise or during atrial pacing.

Recently, Gold et al.[11] reported results from a multicenter trial of microvolt TWA measured during bicycle exercise in patients undergoing electrophysiologic study. In this study, microvolt TWA measured during bicycle exercise was associated with a markedly increased risk of having inducible ventricular tachycardia during an electrophysiologic study as well as the spontaneous occurrence of ventricular arrhythmias during 1-year follow-up. A number of smaller studies demonstrated prospectively the relationship between microvolt TWA and an increased risk of developing ventricular arrhythmias in different patient groups. Ikeda et al.[12,13] demonstrated that microvolt TWA predicts arrhythmic events in patients after myocardial infarction (MI). In patients with implantable cardioverter defibrillators (ICDs), the presence of microvolt TWA was associated with an increased risk of subsequent appropriate ICD firings.[14] Microvolt TWA also was associated prospectively with an increased risk of subsequent arrhythmic events in patients with congestive heart failure.[15-17] Preliminary evidence has linked microvolt TWA and arrhythmic risk in patients with the long QT syndrome[18] as well as with hypertrophic cardiomyopathy.[19] It is important to note, however, that those studies are natural history studies indicating the ability of TWA to identify patients at increased risk of future arrhythmic events. To date, no TWA-based treatment study has been reported.

As additional data are collected evaluating the ability of microvolt TWA to predict arrhythmic events, the interpretation and classification of microvolt TWA tracings needs to be standardized. At present, the majority of research studies on microvolt TWA had microvolt TWA tracings read by a small group of physicians who developed the principles and standards for interpretation of these tracings. These techniques have been applied prospectively in a number of published clinical studies.[11-14] This review outlines these methods and reviews our present approach for interpreting and classifying microvolt TWA tracings.

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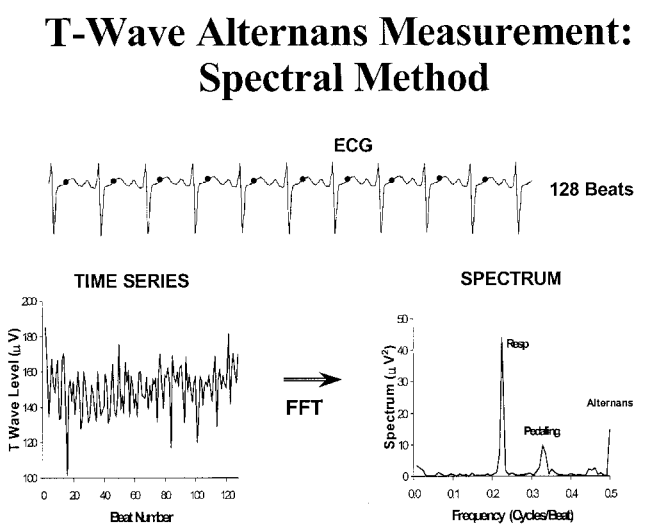

Figure 1. *Spectral method for assessing T wave alternans (TWA). The amplitudes of the corresponding points on the T wave are measured for 128 beats. A time series consisting of these 128 amplitudes is created. The power spectrum of this time series is computed using fast Fourier transform methods. In the power spectrum obtained from recordings during bicycle exercise, peaks corresponding to frequencies of respiration, pedaling, and alternans are illustrated. Microvolt TWA appears as a peak at exactly one half of the beat frequency (0.5 cycles per beat). The amplitude of this peak is compared to the mean and standard deviation of the spectrum in a reference "noise band." (Reproduced with permission from Cohen RJ: TWA and Laplacian imaging. In Zipes DP, Jalife J, eds:* Cardiac Electrophysiology: From Cell to Bedside. *WB Saunders, Philadelphia, 2000, pp. 781-789.)*

Spectral Method of Measuring Microvolt TWA

The spectral method of measuring microvolt TWA uses 128 measurements taken on corresponding points of 128 consecutive T waves to compute a spectrum. Each T wave is measured at the same time relative to the QRS complex. Because this spectrum is created by measurements taken once per beat, its frequencies are in the units of cycles per beat (instead of cycles per second). The point on the spectrum corresponding to exactly 0.5 cycles per beat indicates the level of alternation of the T wave waveform (Fig. 1). In fact, multiple spectra are generated, each corresponding to a different time on the T wave. These spectra then are averaged to produce a composite spectrum. This composite spectrum has the characteristic that it is sensitive to any change in the morphology of the T wave even if the peak amplitude does not change.

The alternans power (μV^2) is defined as the difference between the power at the alternans frequency (0.5 cycles per beat) and the power at the noise frequency band (calculated over the reference frequency band between 0.44 and 0.49 cycles per beat). This is a measure of the true physiologic alternans level. The alternans voltage (V_{alt} measured in μV) is simply the square root of alternans power and corresponds to the root mean square difference in the voltage (averaged over the T wave) between the overall mean beat and either the even-numbered or odd-numbered mean beats (i.e., is half the difference between the even mean and the odd mean). A measure of the statistical significance of the alternans is defined as the alternans ratio (K score) calculated as the ratio of the alternans power divided by the standard deviation of the noise in the reference frequency band. Alternans is considered significant if the K score is ≥ 3.

The spectral method has a number of features that provide a robust measurement of microvolt TWA. Use of a 128-beat spectrum provides for a very accurate measurement of frequency in the beat-frequency domain. This allows for differentiation of true physiologic alternans, which occurs at exactly one half of the beat frequency, from movement or other repetitive artifact that may cause peaks at close to half the beat frequency. The use of a reference noise band (close to the alternans frequency 0.44 to 0.49 cycles per beat) and the subtraction of the mean noise level from the alternans power makes the alternans level relatively independent of mean noise levels. An increase in white noise raises the noise levels of the entire spectrum; this is corrected by subtracting the mean noise level from the power at the alternans frequency (0.5 cycles per beat). In addition, use of the alternans ratio takes into account the variation of noise in the spectrum and requires that the magnitude of alternans power is >3 SD above the noise levels, indicating that alternans is statistically unlikely to be an artifact. Finally, measurements of many points over the T wave makes the alternans measurement sensitive to all T wave morphology changes.

The success of the spectral method in identifying microvolt TWA requires profound noise reduction. In most patients with microvolt TWA, the magnitude of alternans is on the order of several microvolts (roughly 1/50th of a millimeter in standard ECG printouts). Careful skin preparation is important to reduce the impedance of each lead. In addition, specialized electrodes have been developed (Micro-V Alternans Sensors™, Cambridge Heart Inc., Bedford, MA, USA), which record and process ECG signals, as well as a measurement of impedance, from multiple segments of an electrode. Respiratory activity is also measured. This allows a noise reduction process through an adaptive averaging method that cancels the noise. The electrode enhancement method forms a linear combination of the impedance signal, respiratory activity, and electrode segments.[20] This produces a composite ECG signal that has the same morphology but lower noise than an ECG signal taken from the center segment of the electrode alone.

Interpretation and classification of a microvolt TWA tracing depend heavily on the quality of the data collected. Microvolt TWA is a low-amplitude and relatively low-frequency phenomenon that can be obscured by artifacts that include baseline wander and muscle artifact (noise). Measurement of microvolt TWA therefore requires careful preparation of the skin (including shaving hair and moderate skin abrasion) to minimize electrode-to-skin impedance. The electrode-to-skin impedance should be measured prior to exercise to ensure proper lead placement and preparation. Placing the right and left arm electrodes away from the pectoral muscles can reduce muscle artifact. During exercise, patients should be instructed to loosely rest their arms on the handlebars of the bicycle ergometer or safety bar of the treadmill.

Interpretation of Microvolt TWA

Ultimately, the interpretation of a microvolt TWA study will require answers to two fundamental sets of questions.

TABLE 1
Classification of Microvolt T Wave Alternans Recordings

Definitions

Sustained alternans is defined as alternans that is consistently present at heart rates above a patient-specific onset heart rate (except for gaps believed to be caused by obscuring factors such as ectopics, noise or heart rate dips)

- With at least 1 minute with $V_{alt} \geq 1.9$ μV and alternans ratio ≥3
- In any of the vector leads *X*, *Y*, *Z*, or VM (vector magnitude), or in a precordial lead and confirmed (with $V_{alt} \geq 1.9$ μV) in an adjacent precordial lead
- With some period of artifact-free data (defined below)

Alternans can be considered sustained even if the magnitude declines or disappears at heart rates >120 beats/min.

Interval heart rate: Lowest smoothed heart rate in a 1-minute interval

Maximum negative heart rate: Highest interval heart rate associated with an interval without significant alternans, with noise level in the vector magnitude lead ≤ 1.8 μV (or when the sum of the noise level plus the magnitude of alternans is ≤ 2.5 μV), with ≤10% ectopic beats, and without lead malfunction.

Onset heart rate: Alternans onset heart rate is the smoothed heart rate above which sustained alternans is consistently present. In determining the onset heart rate, one should be prepared to read across short gaps that can be attributed to noise, ectopics, or heart rate dips.

Maximum heart rate: Highest interval heart rate

Artifact-free data: Data are considered artifact-free if they meet the following conditions:

- Ectopic or premature beats ≤10% of all beats
- Respiratory activity is not at 0.25 cycles per beat
- Variation in instantaneous heart rate is <30 beats/min over a 128-beat segment
- R-R interval alternans level is not present (≥2 msec with alternans ratio ≥3)

Classification Criteria

Positive: Test is positive if it has sustained alternans with an onset heart rate ≤110 beats/min or has sustained alternans at the resting heart rate, even if that is >110 beats/min.

Negative: Test is negative if (1) it does not meet the criteria for being positive and (2) maximum negative heart rate ≥105 beats/min (A rules). According to B rules (see text), a test also is classified as negative if during a *maximal* exercise test the maximum heart rate ≥80 beats/min and if the maximum negative heart rate ≥(maximum heart rate − 5 beats/min).

Indeterminate: Test is indeterminate if it cannot be definitively classified as either positive or negative.

(1) Is alternans present? If it is present, is the alternans real or potentially artifactual? (2) If alternans is not present, are there artifacts present that could potentially obscure or mask true alternans? An approach to answering these questions follows in the discussion following and is summarized in Table 1.

Presence of Microvolt TWA

The presence of microvolt TWA is defined by its magnitude, the alternans ratio (K score), the relationship between microvolt TWA and heart rate, and the assessment of the presence of artifacts that can cause alternans. *Significant microvolt TWA* is defined as alternans having $V_{alt} \geq 1.9$ μV with a K score ≥3. When alternans is present in a single orthogonal lead, it can be considered significant. However, because the precordial leads tend to have higher noise levels than the orthogonal leads, alternans meeting the V_{alt} and K score criteria in one precordial lead must be confirmed by alternans meeting the V_{alt} criteria in an adjacent lead, in order for the alternans to be considered significant. In rare cases, alternans can be considered significant in a single precordial lead if that lead has a substantial amount of alternans that increases in magnitude with increasing heart rate and if the noise levels are low in that lead.

Sustained alternans is defined as significant alternans that is at least 1 minute in duration and is consistently present above a patient specific threshold heart rate (referred to as the onset heart rate). The onset heart rate is measured from the smoothed heart rate trace. The smoothed heart rate trace displays the heart rate smoothed over a 128-beat window centered at the indicated time-point. Typically, patients will not have alternans below the onset heart rate. Once the onset heart rate is achieved, they consistently have alternans until their heart rate falls below that threshold. The amplitude of the alternans generally increases with increasing heart rate. Once the heart rate reaches 120 beats/min, however, the magnitude of alternans may at times decline or even disappear. The cause of this loss of alternans at high heart rates is not known.

The onset heart rate is optimally determined by evaluating the smoothed heart rate at which the magnitude of alternans exceeds 1.9 μV as the heart rate increases during exercise. There are circumstances, however, where it is difficult to identify the onset heart rate as the heart rate is rising during exercise because of ectopic beats or high noise levels, or because the heart rate rise during exercise is too rapid to permit accurate determination of the onset heart rate. In these circumstances, the onset heart rate can be determined as the smoothed heart rate at which alternans magnitude drops below 1.9 μV as the heart rate is falling during recovery (essentially the offset heart rate).

An example of sustained alternans is shown in Figure 2. In this example, the alternans voltage exceeds 1.9 μV at a threshold onset heart rate of 95 beats/min. The alternans is considered sustained alternans because it is consistently present above the onset heart rate of 95 beats/min. As the heart rate increases, the magnitude of the alternans increases. Note that at the end of the tracing, alternans is still present because the heart rate is 100 beats/min, which is above the onset threshold heart rate of 95 beats/min. The alternans shaded in gray indicates that the alternans ratio is ≥3.

If microvolt TWA is present, it is important to assess for the presence of artifacts that can cause alternans. Artifactual alternans can result from a number of sources: ectopic beats, excessive muscle noise, respiration, rapidly varying heart rate, and R-R interval alternans. These sources of artifactual alternans can produce sustained alternans if the artifact persists. For this reason, each of these other sources of artifactual alternans are displayed on the trend report (Fig. 3), which allows the physician to interpret the presence of alternans and determine if the alternans may be artifactual rather than real. In the trend report, each of the plots of potential artifact is shaded in gray if the artifact is present at a frequency that could result in artifactual alternans.

Bad beats are defined as being >10% premature or beats that have a morphology that is significantly different from the morphology of a template beat (correlation coefficient with a template beat <0.9). Bad beats are most commonly ectopic beats, although falsely detected beats also will generally register as *bad*. Ectopic beats can cause artifactual alternans, although the alternans that results from an ectopic beat is usually brief and is not sustained.

High noise levels can cause short bursts of artifactual

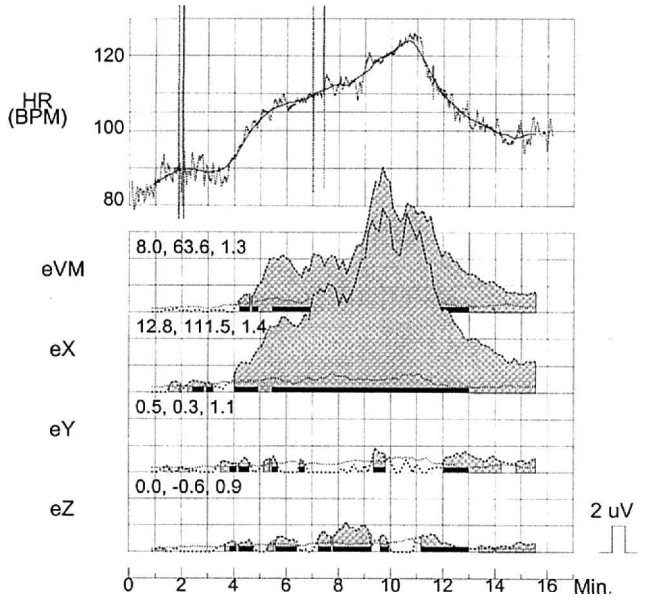

Figure 2. *Example of sustained microvolt T wave alternans (TWA). Top panel represents heart rate. Dotted line represents the instantaneous beat-to-beat heart rate, and darker solid line represents a smoothed heart rate (heart rate averaged over a 128-beat segment centered at the indicated time-point). The lower two panels represent microvolt TWA from the vector magnitude lead and from the orthogonal lead eX. Each box is 2 μV. Darker line indicates the alternans voltage, and lighter dotted line represents noise levels from that lead. The alternans is shaded in gray when the alternans ratio (K score) is ≥3. See text for details of the interpretation of this tracing.*

alternans. Most often, the alternans that results from high noise levels occurs predominantly in the precordial leads and has an extremely short duration, with high amplitude giving it a "spiky" appearance on the tracing.

Respiration can affect the alternans power spectrum. During exercise, the respiratory frequency usually is between 0.2 and 0.33 cycles per beat. However, if respiration occurs at exactly one fourth of the heart rate (0.25 cycles per beat), it is possible for a harmonic of respiration to cause a peak at the alternans frequency (0.5 cycles per beat). If this occurs, the respiration indicator will be shaded in gray.

Rapidly changing heart rate can cause artifactual alternans, although the alternans caused by this artifact is rarely sustained. If the instantaneous heart rate changes by >30 beats/min over a 128-beat segment, the heart rate delta indicator will be shaded in gray.

R-R interval alternans can result in microvolt TWA. If the amplitude of R-R interval alternans is >2 msec and if the R-R interval ratio is >3, then the R-R interval alternans indicator will be shaded in gray. R-R interval alternans is extremely uncommon. When present, it is almost exclusively present at rest and disappears during exercise. An example of R-R interval alternans resulting in microvolt TWA is shown in Figure 3.

Despite the potential for these factors to produce artifactual alternans, it is uncommon for these factors to produce sustained alternans. Most often, if present, these artifacts will only produce brief periods of alternans that will not be sustained above a threshold heart rate. For example, it would be unlikely that a subject would pedal at exactly one half of their heart rate or breathe at one fourth of their heart rate for a prolonged period of time. Even if this were possible, the magnitude of the artifactual alternans is unlikely to increase as the heart rate increased. With this in mind, these artifacts rarely interfere with the interpretation of a microvolt TWA study. For alternans to be considered sustained, there must be at least one point in time during the period of alternans that is *artifact free,* which is defined as a period during which the bad beat, respiration, heart rate delta, and R-R interval indicators are not flagged (shaded in). A heavy line underneath the alternans trace indicates a period that is artifact free (Fig. 2 or 3). If the increase in alternans magnitude closely parallels the heart rate pattern, the requirement for an artifact-free point may be waived.

Absence of Microvolt TWA

If microvolt TWA is not present, then interpretation of a microvolt TWA tracing requires assessment of whether there are artifacts present that may obscure alternans. There are four factors that can mask true microvolt TWA: high noise levels, ectopic beats, rapid changes in heart rate, and lead malfunction (*leads off*). If these artifacts or factors are present at sufficiently high levels, each of the artifact indicators will be shaded in gray, indicating that it is difficult to exclude the possibility that true alternans is not present and is being masked by these artifacts.

High noise levels usually result from excessive muscle noise and baseline wander. As the level of artifact in the ECG increases, noise levels may mask true alternans. If the mean noise level on the vector magnitude lead is >1.8 μV,

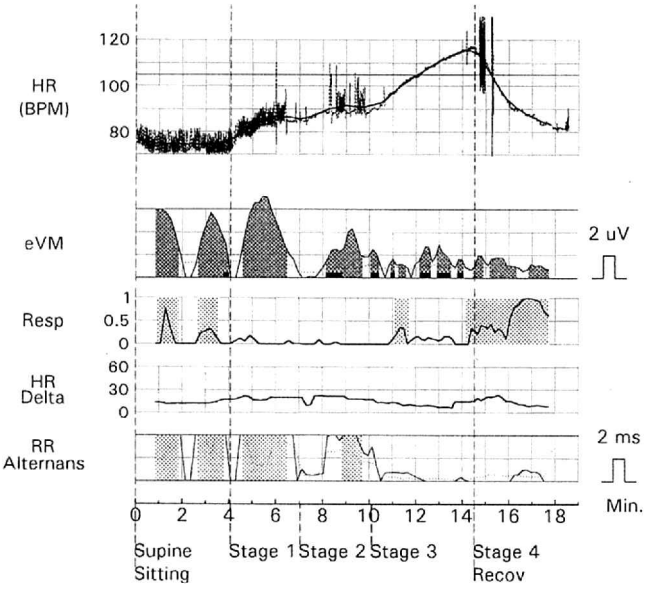

Figure 3. *Example of RR interval alternans causing microvolt T wave alternans (TWA). Microvolt TWA is present at the beginning of this tracing at a heart rate of 76 beats/min. RR interval alternans also is present at the beginning of this tracing. In fact, microvolt TWA and RR interval alternans are occurring simultaneously. RR interval alternans also is reflected in the large amount of variability in the instantaneous heart rate trend. RR interval alternans probably is mediated by vagal modulation of the sinus node and disappears during exercise when the vagus withdraws. As the heart rate increases during exercise, microvolt TWA is present at low levels but not consistently present with a magnitude >2 μV and thus is not considered significant or sustained.*

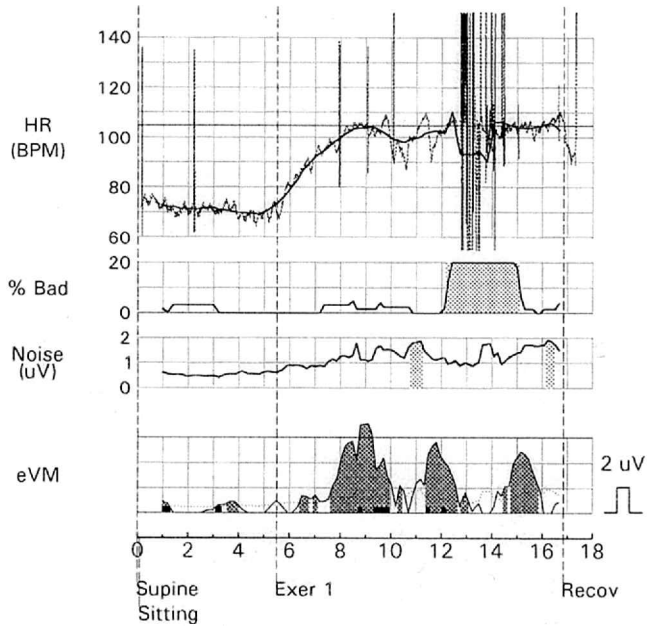

Figure 4. *Example of ectopic beat squelching alternans. Sustained alternans is present with an onset heart rate of ~92 beats/min at minute ~7:50. As the heart rate increases from 92 to 105 beats/min, the magnitude of the alternans voltage increases. At minute 10:00, there is an ectopic beat as well as a rapid fall in heart rate that is associated with a marked reduction in the magnitude of alternans. As the heart rate increases, alternans returns but then disappears again at minute 12:30 when frequent ectopic beats are present (>10% of the 128 beat segments were labeled bad beats, causing the Bad Beat Indicator to be shaded in gray). After the burst of ectopic beats, alternans returns. This tracing is an example of how sustained alternans may be interrupted by artifacts that obscure alternans. Despite these artifacts, however, there is enough evidence on this tracing to interpret the tracing as having sustained alternans.*

the noise indicator will be shaded in gray, indicating the possibility that noise is obscuring alternans. In addition, noise levels are displayed in each lead, which allows evaluation of the relationship of noise levels to alternans in any single lead.

Ectopic beats can have an unpredictable effect on the measurement of alternans levels. As mentioned earlier, ectopic beats can produce brief periods of alternans. More commonly, ectopic beats will attenuate or eliminate alternans. When >10% of the beats in a 128-beat segment are ectopic beats, it is possible that the ectopic beats are potentially obscuring true alternans and the ectopic beat indicator will be shaded in gray. In addition, a single premature beat can change the phase of alternans (i.e., from an A-B-A-B pattern to a B-A-B-A pattern). When this occurs, a premature beat (denoted by "**P**") changes the pattern or phase of alternans (i.e., A-B-A-B-**P**-B-A-B-A). If this type of phase reversal occurs, a segment of 128 beats with the premature beat exactly in the center will show zero alternans, because the alternans before and after the premature beat will cancel. It is common, therefore, to see a high level of alternans that disappears in a portion of the trend centered on an ectopic beat (Figs. 4 and 5).

Rapid changes in heart rate can obscure alternans. Rapid changes in heart rate are most likely to occur early at the start of exercise, during a change in stage of exercise, or in the first minute of recovery after the person has stopped exercising.

Lead malfunction can obscure alternans. If there is an indication that one or more leads are disconnected or malfunction during exercise, then it is possible that true alternans present in those leads has been obscured.

The presence of artifacts that can obscure alternans impacts on the interpretation of microvolt TWA studies in two ways. First, the interpretation of a microvolt TWA study requires determination of the *maximum negative heart rate,* which is defined as the highest smoothed heart rate on the tracing above which you are confident that alternans is not present. To be confident that alternans is not present above a given smoothed heart rate, the subject must be at or above that smoothed heart rate for 1 minute (to give alternans time to develop) and there must not be artifact in that minute that could potentially obscure true alternans. An interval that meets these conditions is called a *negative interval* and is defined as a 1-minute interval without significant alternans in any lead, with a noise level <1.8 μV in the vector magnitude lead, with <10% ectopic beats, and without lead malfunction. The lowest smoothed heart rate in a 1-minute interval is defined as the interval heart rate (this ensures that the alternans has had 1 min to develop at that heart rate). In practice, we will interpret an interval as negative even if it has a very short period of alternans (i.e., 5 to 10 sec) or if the noise levels are slightly >1.8 μV as long as the magnitude of alternans is low (i.e., the sum of the noise level and alternans is <2.5 μV in the vector magnitude lead). If there

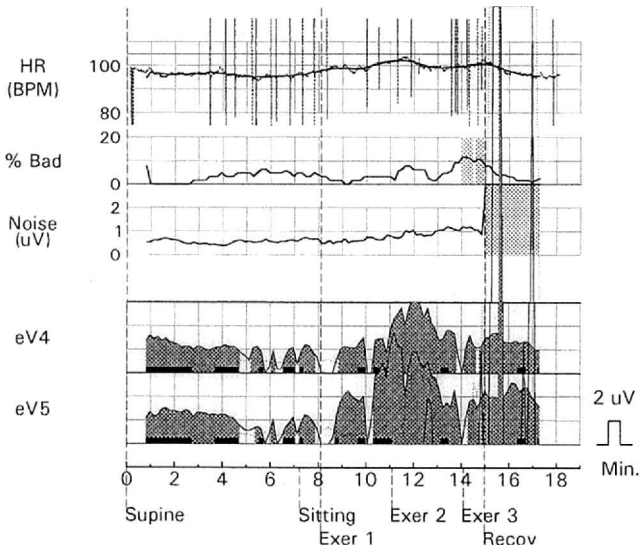

Figure 5. *Example of ectopic beats reducing alternans voltage. At the onset of the study, alternans is present at a heart rate of 98 beats/min. From minute 5:00 to 9:00, the magnitude of alternans is markedly reduced possibly related to ectopic beats. Note that the ectopic beats are not frequent (i.e, <10% of 128 beat); thus, the Bad Beat Indicator is not shaded in gray. However, the ectopic beats are occurring every 30 to 45 seconds, which is sufficient to attenuate the magnitude of alternans. As the heart rate increases from 98 to 102 beats/min, the magnitude of alternans increases. There are two places (minutes 10:00 and 14:00) where high levels of alternans rapidly disappears centered on an ectopic, presumably due to an alternans phase change centered on the ectopic beat. Because alternans is present at the lowest heart rate on the tracing, rest alternans is present and the tracing would be classified as positive.*

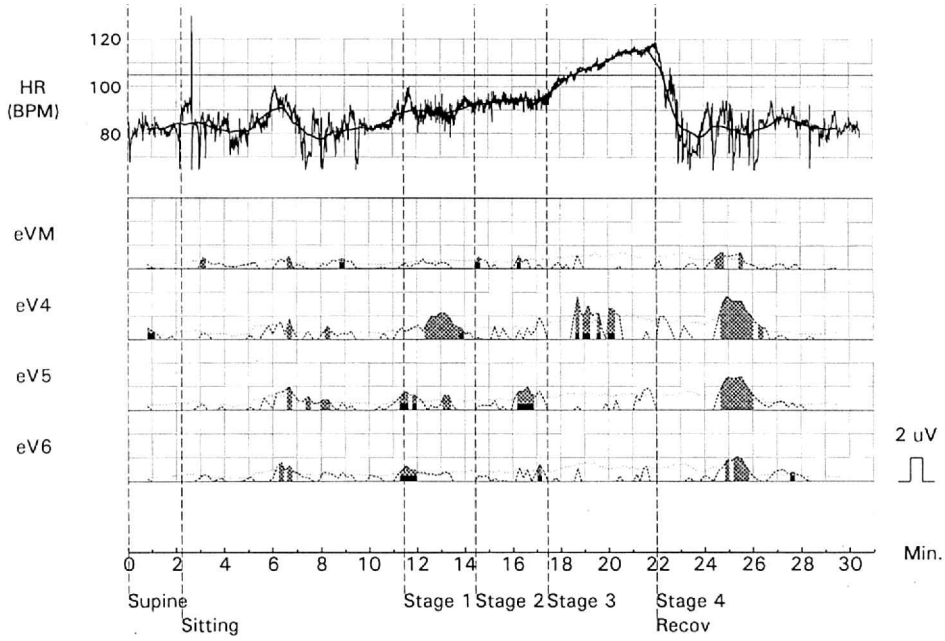

Figure 6. *Example of a negative tracing. In this tracing there is no significant alternans. The maximum heart rate is 114 beats/min. In the minute corresponding to the maximum heart rate (21:00 to 22:00), there is no significant alternans, there are no ectopic beats, and the noise levels are <1.8 μV. Therefore, this 1-minute interval is a negative interval minute and the maximum negative heart rate is the same as the maximum heart rate for this tracing. There are period of nonsustained alternans in the precordial leads, although these periods of alternans are not confirmed in adjacent leads and are not sustained above a threshold onset heart rate.*

is no negative interval present in the tracing, the maximum negative heart rate is by definition zero. The maximum negative heart rate can never exceed the onset heart rate.

Actual determination of the maximum negative heart rate is done by evaluating each 1-minute interval in the tracing starting at the highest interval heart rate. If the 1-minute interval corresponding to the maximum heart rate does not have alternans and there are no artifacts present that could potentially obscure alternans, then the maximum negative heart rate is equal to the maximum heart rate (the lowest smoothed heart rate in the 1-min interval with the highest interval heart rate). For example, in Figure 6, the subject exercised to a maximum heart rate of 113 beats/min and there is neither alternans present nor any artifacts that could potentially obscure alternans. Therefore, we are confident that the subject does not have alternans at a heart rate of 113 beats/min and thus the maximum negative heart rate equals the maximum heart rate of 113 beats/min.

In contrast, the subject shown in Figure 7 exercised to a maximum heart rate of 119 but has frequent ectopic beats during the period when his heart rate is >110. Our confidence that alternans is not present during this period is reduced. Determination of the maximum negative heart rate involves examining 1-minute intervals at lower heart rates until a negative interval is found. In this example, between minute 9:00 and 10:00, there is no significant alternans, there are no ectopic beats, and the noise levels are <1.8 μV. This 1-minute interval is a negative interval minute with an interval heart rate of 95 beats/min (the lowest smoothed heart rate in the interval), which defines the maximum negative heart rate for this tracing. Therefore, even though this subject exercised to a maximum heart rate of 119 beats/min, frequent ectopic beats at the end of exercise shift the maximum negative heart rate down to 95 beats/min. This indicates that even though the subject exercised to a maximum heart rate of 119 beats/min, we are only confident that alternans is not present up to a heart rate of 95 beats/min. We then accept the possibility that alternans potentially could be present (but potentially masked by frequent

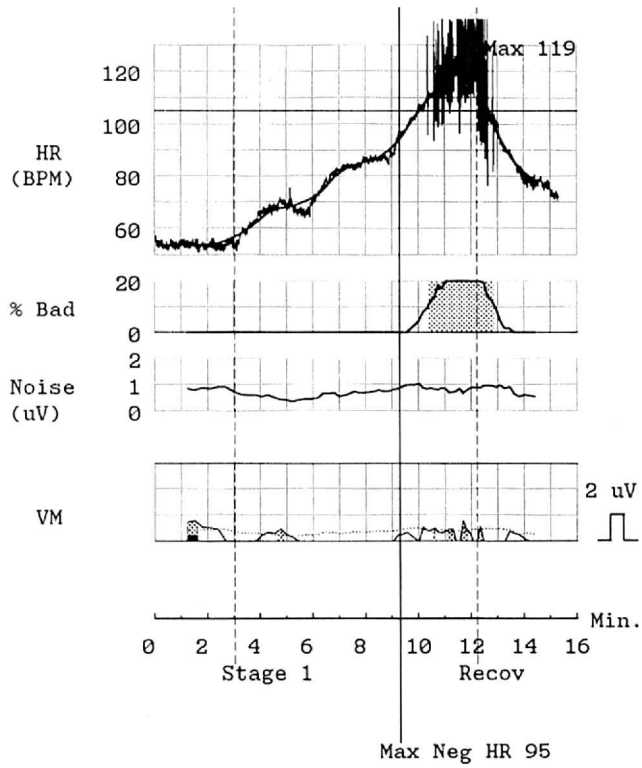

Figure 7. *Example of a gap between maximum heart rate and maximum negative heart rate. In this tracing, the maximum heart rate is 119 beats/min. However, during the minute corresponding to the maximum heart rate, frequent ectopic beats are present and the bad beat flag is turned on (% Bad Trend is shaded in gray) between 10:15 and 12:55. The maximum negative heart rate is 95 beats/min, corresponding to the interval heart rate of the minute prior to the onset of frequent ectopic beats (9:15 to 10:15). The tracing would be classified as indeterminate because we cannot be confident that alternans is not present at or above a heart rate of 105 beats/min (the negative heart rate threshold). In this case, we are only confident that alternans is not present at 95 beats/min.*

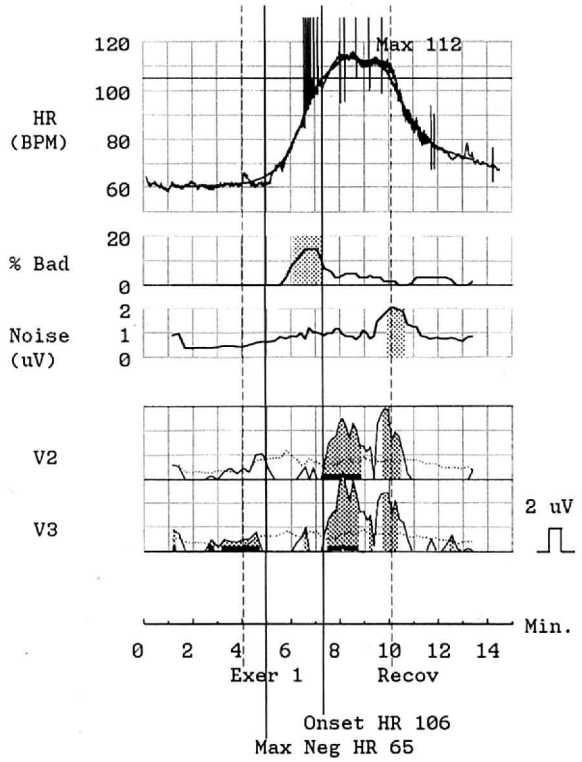

Figure 8. *Example of a gap between onset heart rate and maximum negative heart rate. See text for details of the interpretation.*

ectopic beats) at heart rates between 95 and 119 beats/min. The tracing would be classified as indeterminate because we cannot be confident that alternans is not present at or above a heart rate of 105 beats/min (the TWA classification algorithm is discussed in the next section). In this case, we are only confident that alternans is not present at 95 beats/min.

Another example of how ectopic beats can affect the maximum negative heart rate is shown in Figure 8. Sustained alternans is present with an onset heart rate of ~106 beats/min at minute 7:15. The alternans voltage increases rapidly as the heart rate increases >106 beats/min and is consistently present >106 beats/min except for a brief drop in alternans voltage likely caused by ectopic beats. The minute prior to the onset of alternans, however, has frequent ectopic beats; this prevents us from having confidence that alternans does not start at a lower heart rate. These ectopic beats cause a shift in the maximum negative heart rate to 65 beats/min, indicating that we are confident that alternans is not present below 65 beats/min and that we are unsure if alternans is present between 65 and 106 beats/min. Despite this "gap" between onset heart rate and maximum negative heart rate, the tracing still is interpreted as positive because alternans is present at an onset heart rate ≤110 beats/min.

If the interval immediately preceding the onset of microvolt TWA is a negative interval, the maximum negative heart rate is set to the onset heart rate even though this may not be the lowest smoothed heart rate in the interval. For example, in Figure 2, both the onset heart rate and the maximum negative heart rate are 95 beats/min.

The presence of artifacts that can potentially obscure alternans also impacts on the determination of whether sustained alternans is present. The definition of sustained alternans requires that alternans be consistently present above a patient specific heart rate threshold (onset heart rate). However, it is common for alternans to be interrupted by artifacts (gaps) that can obscure alternans. When this occurs, it appears as if alternans is broken up and, therefore, may not appear to be consistently present above the onset heart rate. In this situation, the important question to answer is whether the alternans represents true sustained alternans that is interrupted by artifacts, or if the period in question contains a few bursts of nonsustained (i.e., potentially artifactual) alternans. When the period of alternans is long (>4 min) and the gaps are short (<1 min), then the alternans is more likely to be true physiologic alternans. If the gaps in alternans correspond to ectopic beats on the heart rate trend, then this potential explanation for the gaps may enhance our confidence that the alternans is real and broken up by ectopic beats. In addition, if the alternans voltage increases with increasing heart rate, the alternans is more likely to be real rather than artifactual.

Figure 4 is an example of this phenomenon. Despite the large gaps in the alternans, we interpret the alternans as sustained because we have an explanation for most of the gaps on the tracing (a sudden drop in heart rate between minutes 10:00 and 12:00 and frequent ectopic beats between minutes 12:30 and 15:00). In contrast, Figure 9 is an example of significant alternans with amplitude consistently ≥1.9 μV starting after minute 19 that persists for <1 minute and then disappears without explanation prior to it reappearing for 20 seconds. In this case, given that the gap in the alternans is unexplained and accounts for a large portion of time relative to the amount of time that alternans is present, our confidence that these two short bursts of

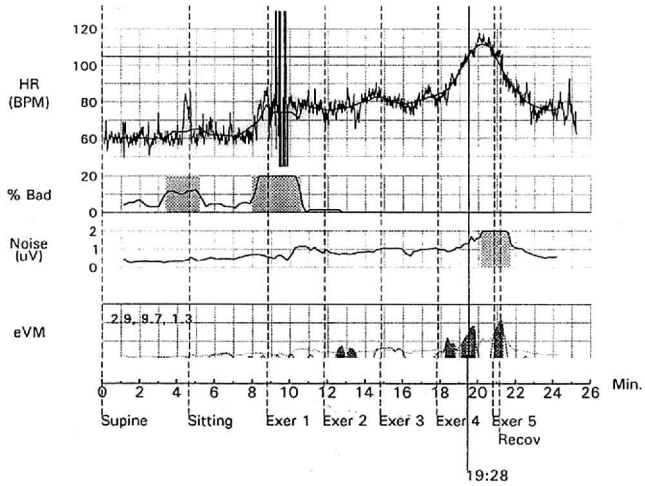

Figure 9. *Example of an indeterminate tracing because of nonsustained alternans and either noise or ectopic beats. There is significant alternans at minute 19:00 that persists for nearly 1 minute but is not sustained. There is a 1-minute gap in the alternans followed by another 20 seconds of alternans. There are no ectopic beats to explain the gap. The alternans voltage falls just prior to a mild increase in noise levels that are just over 2 μV. Modestly elevated noise levels should not cause such a marked reduction in alternans voltage. There is not enough evidence to call this sustained alternans with a gap; the two short bursts of alternans may be artifactual. On the other hand, these two bursts of significant alternans shift the maximum negative heart rate to ~82 beats/min (the negative interval with the highest interval heart rate), resulting in an indeterminate classification.*

TABLE 2
Predictive Accuracy of Classification Schemes

Study	Total N	N+ (%)	N− (%)	N Ind (%)	Survival+ (%)	Survival− (%)	Relative Risk
Klingenheben et al.[15] (2000)							
A rules	107	52 (48.6)	23 (21.5)	32 (29.9)	78.7	100	∞
B rules	107	52 (48.6)	33 (30.8)	22 (20.6)	78.7	100	∞
C rules	107	55 (51.4)	33 (30.8)	19 (17.8)	80.0	100	∞
Hohnloser et al.[14] (1998)							
A rules	88	36 (40.9)	26 (29.5)	26 (29.5)	33.4	73.2	2.49
B rules	88	36 (40.9)	31 (35.2)	21 (23.9)	33.4	72.0	2.38
C rules	88	38 (43.2)	31 (35.2)	19 (21.6)	31.6	72.0	2.44
Gold et al.[11] (2000)							
A rules	283	83 (29.3)	121 (42.8)	79 (27.9)	81.2	98.3	11.0
B rules	283	83 (29.3)	135 (47.7)	65 (23.0)	81.2	98.4	12.1
C rules	283	100 (35.3)	135 (47.7)	48 (17.0)	79.3	98.4	13.2

A, B, and C rules are defined in the text.
N+ = number of patients with a positive T wave alternans (TWA) test; N− = number of patients with a negative TWA test; NInd = number of patients with an indeterminate TWA test, Survival+ = proportion of patients with a positive test surviving without a ventricular tachyarrhythmic event for 1 year; Survival− = proportion of patients with a negative test surviving without a ventricular tachyarrhythmic event for 1 year.

alternans are real is diminished. In this example, the period of significant but nonsustained alternans lowers the maximum negative heart rate to 82 beats/min, indicating that we are not confident that alternans is not present above a heart rate of 82 beats/min.

Classification of Microvolt TWA Tracings

Microvolt TWA tracings are classified as positive, negative, or indeterminate. The classification of a microvolt TWA tracing as positive requires only the determination of whether sustained alternans is present and a determination of the onset heart rate. The distinction between tracings that are negative or indeterminate is made by the determination of the maximum negative heart rate as well as the maximum heart rate. Once these patient specific heart rates are known, the classification of a microvolt TWA tracing is straightforward.

Positive Tracings

If sustained alternans is present with an onset heart rate ≤110 beats/min, then the tracing is classified as positive. The choice of the threshold heart rate of 110 beats/min is based upon the observation that normal healthy subjects may develop alternans at high heart rates, suggesting that alternans at high heart rates is not prognostically significant. There are some data suggesting that the risk of an arrhythmic event is greater in patients with lower onset heart rates,[21] although this needs confirmation in larger studies. If a tracing has sustained alternans but the onset heart rate is >110 beats/min, then the tracing will be either negative or indeterminate based on the patient's maximum negative heart rate (see later). One exception to the onset heart rate threshold of 110 beats/min is if the patient has alternans at rest (i.e., at the lowest heart rate on the tracing; Fig. 5). Whenever a tracing has sustained alternans starting at the lowest smoothed heart rate on the tracing, then it is classified as positive regardless of the onset heart rate (the maximum negative heart rate in this case is zero). If there are ectopic beats or noise at the resting heart rate that obscures the interpretation of alternans, alternans can still be considered rest alternans if the onset heart rate is within 10 beats/min of the true resting heart rate and the maximum negative heart is zero (no negative interval with an interval heart rate below the onset heart rate).

Negative Versus Indeterminate Tracings

All tracings that are not positive are either negative or indeterminate. The distinction between tracings that are negative or indeterminate is based on the maximum negative heart rate, the highest heart rate on the tracing in which you are confident that alternans is not present. The original classification (*A rules*) used prospectively in a number of studies[11,14] required that the maximum negative heart rate must be ≥105 beats/min in order to classify a tracing as negative. This threshold is based on the concept that alternans tends to occur at increased heart rates (90 to 110 beats/min). If a tracing has excessive levels of ectopy above a heart rate of 95, then we cannot be confident that alternans is not present above a heart rate of 95 and we cannot consider the tracing to be negative (an example of this type of tracing is Fig. 7). The maximum negative heart rate is 95 and the tracing is classified as indeterminate. Perhaps if the noise levels were reduced, alternans would be "unmasked" at heart rate of 100 beats/min. For this reason, tracings without sustained alternans and with a maximum negative heart rate <105 beats/min are considered indeterminate. Similarly, tracings with sustained alternans with an onset heart rate >110 beats/min (i.e., alternans that it is not prognostically significant) also are classified as indeterminate if the maximum negative heart rate is <105 beats/min.

Application of this classification (A rules) can result in indeterminate results of up to 25% to 30% in some populations.[11,14,15] Many of the tracings were classified as indeterminate because the patient's maximal heart rate was <105 beats/min and, therefore, the tracing had no chance of being classified as negative (the maximum negative heart rate cannot be greater than the maximal heart rate).

Alternative Classification Schemes

In an attempt to reduce the number of indeterminate test results, a number of alternative classification schemes have been developed. A comparison of these different classification schemes is presented in Table 2. One way of reducing the number of indeterminate tracings is to lower the maxi-

mum negative heart rate threshold required to call a tracing negative. In *B rules,* a test can be classified as negative with a maximum negative heart rate as low as 80 beats/min (instead of 105 beats/min) as long as two other conditions are satisfied. First, the difference between the maximum negative heart rate and the maximum heart rate must be ≤5 beats/min. Second, a test can only be called negative with a maximum negative heart rate ≤105 beats/min only if the patient exercised to his or her maximal effort during the test. These conditions are based on the following scenario. If a patient exercises to a maximum heart rate of 110 beats/min but has noise or ectopy between a heart rate of 90 and 110 beats/min, then the maximum negative heart rate would be 90 beats/min. We cannot call this tracing negative because we could not be confident that alternans is not present between a heart rate of 90 beats/min and the maximum heart rate of 110 beats/min given that there is noise or ectopy above a heart rate of 90 up until the patient's maximum heart rate. However, if the patient's maximum heart rate during a maximal exercise test is 90 beats/min and if the maximum negative heart rate is also 90 beats/min (or within 5 beats/min of the maximal heart rate), then, according to B rules, the test can be classified as negative.

B rules were applied prospectively to a study of patients with congestive heart failure,[15] and we have applied them retrospectively to two other published studies[11,14] with follow-up data. In Table 2, a comparison of the predictive accuracy of A and B rules demonstrates that there is an 18% to 31% reduction in the proportion of indeterminate test results without any loss of predictive accuracy. It is important to emphasize, however, that in order to classify a tracing as negative using B rules with a maximum negative heart rate that is <105 beats/min requires that a patient has completed a maximal effort exercise test.

A study by Tapanainen et al.[22] might appear to call into question the adoption of B rules. In this study of 379 patients after MI, Tapanainen et al. reported that TWA was not predictive of mortality. In addition, patients who were classified as "incomplete" because they could not achieve a heart rate of 105 beats/min had a significantly increased risk of cardiac death. This study is flawed, however, because the TWA test was performed too early after MI (8.1 ± 2.4 days after MI) when TWA is thought to be unstable and unreliable.[12,13,23] In addition, it is difficult to determine whether the patients in this study by Tapanainen et al. who were classified as "incomplete" would have been classified as "negative" according to B rules. B rules require a heart rate of 80 beats/min, a maximum negative heart rate that is within 5 beats/min of the maximum heart rate, and B rules require that the exercise test was a test of maximal effort (many physicians would hesitate to perform a maximal exercise test within 1 week of an acute MI). Finally, the primary endpoint of this study was all-cause mortality rather than arrhythmic events. It is possible that TWA did not perform well in part because it may not identify patients at risk for noncardiac or pump failure death.

When TWA is measured later after MI, it appears to be a potent predictor of arrhythmia risk. In contrast to the study by Tapanainen et al., Ikeda et al.[13] demonstrated that TWA measured 2.7 ± 5.4 months after MI was strongly associated with arrhythmic events after MI (relative risk 5.9, P = 0.007) in a large study of 850 consecutive patients after MI. In another study by Ikeda et al.,[12] TWA was measured 20 ± 6 days after MI in 102 patients and was also strongly associated with arrhythmic events (relative risk 16.8, P = 0.006). Taken together, these studies suggest that a TWA study should be performed no earlier than 3 weeks after MI.

TABLE 3
T Wave Alternans Interpretation Schemes

A Rules	
Is sustained alternans present at rest?	
Yes ⇒	Positive
If **No,** is onset of sustained alternans ≤110 beats/min?	
Yes ⇒	Positive
If **No,** is MaxNegHR ≥105 beats/min?	
Yes ⇒	Negative
No ⇒	Indeterminate
B Rules	
Is sustained alternans present at rest?	
Yes ⇒	Positive
If **No,** is onset of sustained alternans ≤110 beats/min?	
Yes ⇒	Positive
If **No,** is MaxNegHR ≥105 beats/min?	
Yes ⇒	Negative
If **No,** is MaxHR ≥80 beats/min?	
No ⇒	Indeterminate
If **Yes,** did patient stop exercise due to fatigue or symptoms?	
No ⇒	Indeterminate
If **Yes,** is (MaxHR − MaxNegHR) ≤5 beats/min?	
Yes ⇒	Negative
No ⇒	Indeterminate

Another classification scheme *(C rules)* attempts to further reduce the number of indeterminate test results by classifying tracings as positive that are indeterminate because of frequent ventricular ectopy that persisted during exercise. This scheme is motivated by data showing that patients with ventricular ectopy during exercise are at an increased risk of dying.[24] In most patients, ventricular ectopy decreases during exercise because of overdrive suppression by the sinus node. C rules therefore reduce the number of indeterminate tests in two ways. Like B rules, some indeterminate tests are classified as negative if the maximum negative heart rate is within 5 beats/min of the maximum heart rate, which in turn is ≥80 beats/min, and if the patient exercised to a maximal effort. In addition, C rules classifies some of the indeterminate tests as positive if ventricular ectopy persisted for >30% of the time during the exercise portion of the test. Comparing A and C rules (Table 2), the predictive accuracy increases slightly (more events are captured by tests classified as positive) and the proportion of indeterminate tests is reduced by 27% to 40%. C rules require that one identify which *bad beats* are ventricular ectopic beats.

Given that B rules have been tested prospectively in one study and retrospectively in two other studies and that they do substantially reduce the indeterminacy rate, it seems reasonable to adopt them in clinical use. C rules have not yet been tested prospectively and require further investigation. A number of large-scale epidemiologic studies currently in progress will prospectively compare these different classification schemes. Table 3 provides flow sheets for application of A and B rules.

Use of Beta-Blockers and TWA Testing

It remains a matter of controversy whether beta-blockers should be withheld prior to TWA testing. In three studies

with follow-up data, beta-blockers were not withheld prior to testing,[12,14,15] and in one study beta-blockers were withheld for 24-hours prior to testing.[11] All three studies demonstrated that TWA was strongly associated with an increased risk of arrhythmic events. There are data demonstrating that beta-blockers reduce the magnitude of TWA independent of their effects on heart rate (atrial pacing was used to measure alternans).[25,26] However, it is not clear how often the reduction in the magnitude of alternans results is sufficient to change the classification of a test from positive to negative. In addition, it is not known whether the prognostic significance of TWA is improved or weakened depending on whether beta-blockers are held or continued at the time of testing.

With regard to the classification of TWA tests, testing patients who are taking beta-blockers may result in a greater number of indeterminate studies when A rules are used because some patients will not achieve a maximal heart rate of 105 beats/min while taking beta-blockers (the maximum negative heart rate must be $\geq$105 beats/min in order for a test to be classified as negative in A rules). The reduced maximum heart rate in patients taking beta-blockers should not result in an increased number of indeterminate tests when B rules are used because a test can be classified as negative if the maximum negative heart rate is $\geq$80 beats/min.

Software Tools for Guiding Interpretation of Microvolt TWA Tests

Software has recently been developed that aids in the interpretation of microvolt TWA tracings. The software will evaluate a microvolt TWA tracing from a CH2000 or HeartWave system (Cambridge Heart, Inc.) and determine whether sustained alternans is present and, if so, the onset heart rate. The software also will determine the maximum negative heart rate and the maximum heart rate for all tracings. Figures 7 and 8 are examples of microvolt TWA tracings processed using these software tools. With these tools, the classification of a microvolt TWA tracing is straightforward. These software tools were developed using 300 TWA tracings and subsequently were validated by comparing its classification with our classification in a dataset of 311 tracings. The classification of tracings using these software tools and the classification of tracings by the consensus interpretation of two of the authors of this manuscript (D.M.B. and R.J.C.) were highly concordant. Of the 297 of 311 tracings with a determinate classification (positive and negative), the concordance of the classification was 97% (κ 0.95). Among all 311 tracings (positive, negative, and indeterminate), the concordance was 91% (κ 0.86). Despite the accuracy of these software tools, physicians should evaluate all tracings and reclassify tracings when appropriate.

Importance of the Exercise Protocol

Interpretation and classification of microvolt TWA tracings depend heavily on the determination of the presence of alternans within a heart rate window between 105 and 110 beats/min. For this reason, it is imperative that the heart rate increases slowly and smoothly through this window. Ideally, the increase in heart rate from 90 to 110 should occur slowly (3 to 5 min) in order to obtain at least 2 minutes between a heart rate of 105 and 110 beats/min. This will provide a sufficient period of time for determination of the onset heart rate if alternans is present. Then, an additional 2 minutes should be collected between a heart rate of 110 and 120 beats/min in order to allow the alternans to continue to develop at a higher heart rate. In some tracings, the heart rate rises through this heart rate window (from 90 to 120 beats/min) in $<$1 minute. This steep increase in heart rate may not only obscure alternans but also makes the determination of the onset heart rate extremely difficult. Utilization of an exercise protocol that allows for a greater time period between a heart rate of 105 and 110 beats/min will significantly reduce the rate of indeterminate TWA tests.

The ideal exercise protocol for the measurement of microvolt TWA will vary from patient to patient depending on the patient's level of fitness and resting heart rate. The fundamental goal of an exercise protocol for the measurement of microvolt TWA is to provide a gradual increase in workload when the heart rate reaches 90 beats/min such that the heart rate remains between 105 and 110 beats/min for a few minutes. In patients whose exercise tolerance is limited either by deconditioning or disease, the Naughton Protocol or modified Bruce Protocol should be used if the patient is exercising on a treadmill. If a bicycle ergometer is being used, a ramp protocol is optimal because the workload (resistance) increases by only 5 W every minute and results in a gradual and smooth increase in heart rate. The starting workload in a ramp protocol depends on the patient. Some patients can comfortably start at 10 to 15 W, whereas others find it uncomfortable to pedal against such a light workload and should start at 30 to 40 W. Ultimately, the exercise protocol being used can be modified in response to the patient's heart rate. If the heart rate begins to increase rapidly, the workload can by manually reduced. Once the heart rate reaches 95 to 100 beats/min, it often is useful to hold the stage (or keep the workload constant) for 1 to 2 minutes and allow the heart rate to gradually increase at that workload.

On occasion, the patient's heart rate will rapidly increase to 120 to 130 beats/min immediately after the onset of exercise. This may be due to the patient's discomfort with, or anxiety about, exercise. When this occurs, the patient should be told to stop exercising and should recover until the heart rate returns to baseline. Some patients need additional training or additional time to adjust to the equipment and type of exercise. In addition, the protocol can be changed if the initial workload was set too high. Optimization of the exercise protocol will result in a greater proportion of determinate microvolt TWA classifications.

Recent Improvements and Future Directions of Microvolt TWA Testing

There have been a number of recent improvements in the analysis of microvolt TWA, e.g., prefiltering of data to suppress noise at repetitive frequencies that may, as a result of aliasing, overlap with the alternans frequency. The effect of this prefiltering of data is to remove alternans that is likely to be artifactual, which appears to reduce the number of false-positive alternans tests. Another enhancement in the analysis has been to accept alternans only when the peak at 0.5 cycles per beat is sharp. This "sharpness" enhancement further eliminates alternans that is likely the result of motion

artifact, which tends to have a broader peak rather than the sharp peak characteristics of physiologically significant alternans. These two improvements in the analysis of microvolt TWA, which both remove artifactual alternans, have made it possible to measure alternans during treadmill exercise. Preliminary data suggest that the results of microvolt TWA tests using bicycle and treadmill exercise are equivalent.[27]

For those patients who cannot exercise or who cannot increase their heart rate sufficiently during exercise, microvolt TWA can be measured during pharmacologic stress testing. Preliminary data suggest that the results of microvolt TWA measured during bicycle exercise and pharmacologic stress testing are highly concordant.[28]

Conclusion

Measurement of microvolt level microvolt TWA during routine exercise stress testing now is possible as a result of sophisticated noise reduction techniques and analytic methods that have become commercially available. Although this technology is new, the available data suggest that microvolt TWA is a potent predictor of arrhythmia risk in diverse disease states. Based on these data, the measurement of stress-induced microvolt level TWA has been approved by the United States Food and Drug Administration for the following indication: "The presence of microvolt T-wave alternans in patients with known, suspected or at risk of ventricular tachyarrhythmia predicts increased risk of a cardiac event (ventricular tachyarrhythmia or sudden death). TWA should be used only as an adjunct to clinical history and the results of other non-invasive and/or invasive tests."

As this technology becomes more widely available, physicians will be called upon to interpret microvolt TWA tracings. We hope that this review will help establish uniform standards for the clinical interpretation of microvolt TWA tracings.

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