T-Wave Alternans and Arrhythmia Risk Stratification

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In spite of recent improvement in overall cardiovascular mortality, sudden cardiac death (SCD) remains a formidable clinical challenge. Given the magnitude of the problem of SCD—representing up to 50% of all cardiac deaths—cardiologists have long struggled to identify individuals at specific risk for SCD.[1] Traditional strategies have focused on the very high-risk subgroups in which SCD rates are high. These include survivors of acute myocardial infarction (AMI), and populations such as those studied in MADIT[2] and AVID[3] trials. This strategy has limited population impact, however, because it addresses only a small part of the spectrum of SCD risk. For example, 20-30% of the population with known or unsuspected coronary artery disease experience SCD as the first clinically recognized manifestation of the disease.[1]

Management strategies of SCD—which in the majority of cases is due to malignant ventricular tachyarrhythmias (VT) defined as hypotensive ventricular tachycardia and ventricular fibrillation—have centered over the years on two closely related aspects:[4] (1) how to identify those at risk of SCD, and (2), what are the best management modalities, vis-à-vis pharmacotherapy or the implantable cardioverter-defibrillator (ICD). Following recent publications of the results of several multicenter studies, pharmacotherapy, mainly antiarrhythmic drugs, has not proven, so far, to be an effective management modality for those at risk of SCD. This cleared the way for more widespread use of the ICD as the sole, or main, management modality. Primarily because of the high cost of the ICD, and the invasive nature of this therapeutic modality, the prophylactic use of the device for primary prevention of SCD did not gain momentum until recently. This aspect of management strategy for SCD is still in the clinical research domain with several primary ICD prevention trials currently underway. However, this trend has highlighted the urgent need for more powerful risk stratification algorithms for SCD. Further, the recent results of the MADIT[2] and AVID[3] trials on one hand and the CABG-PATCH trial[5] on the other hand, underscored the point that the ICD works only when implanted in patients at high risk of arrhythmic death.

In order to impact on a significant proportion of the total population at risk, methods that allow increased resolution of SCD risk within more general populations will be required. Besides the invasive electrophysiology study (EPS), noninvasive risk stratifiers that have been commonly utilized include: left ventricular ejection fraction (LVEF), ventricular arrhythmias on ambulatory Holter recording, signal averaged electrocardiography (SAECG), heart rate variability (HRV), baroreflex sensitivity (BRS), and QT dispersion. In addition, there are a number of other less commonly utilized markers of arrhythmic death, e.g., the recently introduced heart rate turbulence.[6] However, with the exception of LVEF, none of the other tests, at present, has proven to be solely adequate as a powerful risk stratifier.[4] An optimal algorithm that

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combines more than one index of high risk has not yet been identified or agreed upon.

A new noninvasive technique that detects microvolt levels of T-wave alternans (TWA), has attracted increased interest in recent years.[7] Although overt TWA in the electrocardiogram (ECG) is not common,[8] digital signal processing techniques capable of detecting subtle degrees of TWA have suggested that TWA is more prevalent than previously recognized and may represent an important marker of vulnerability to VT.[9] This review will examine the electrophysiologic basis that links TWA to electrical vulnerability and the recent clinical data that investigated TWA as a risk stratifier of VT.

ELECTROPHYSIOLOGIC BASIS OF TWA

Tachycardia-Dependent Alternans of Normal Cardiac Fibers

Alternans of the action potential duration (APD) of normal Purkinje and ventricular muscle fibers under physiologic conditions can consistently be induced by a critical short cycle length. In Purkinje fibers, alternans induced by a decrease in cycle length always declined progressively and disappeared before the APD reached the new steady state. In ventricular muscle fibers, the magnitude of alternans induced by a decrease in cycle length also tended to decrease progressively because of declining memory effect. However, at very rapid rates, alternans of the action potential shape in ventricular muscle fibers could continue indefinitely without a change in diastolic interval.[10] Alternation of APD of Purkinje fibers is explained by the differences in the recovery of membrane currents generated by the preceding action potential. The two recovery processes that could be curtailed by a reduction of the interval between successive action potentials are the recovery of the slow inward calcium current (I_{ca}) from inactivation and the difference in magnitude of the decaying time dependent outward current (I_k).[11,12] Although the same factors may also influence the alternation of APD of muscle fibers, the latter seem to have an independent mechanism for action potential alternans associated with tension alternans. The alternans in muscle fibers may be related to differences in the concentration and/or handling of intracellular calcium.[10] Action potential alternans of muscle fibers can be limited to alternation of the configuration of the plateau without changes in APD or diastolic intervals.[10] It is important to emphasize the differences between the mechanisms of alternans in Purkinje and muscle fibers because it is the alternans of myocardial fibers that predominantly influence the duration and configuration of the repolarization wave of the body surface ECG.

Electrophysiologic Mechanisms of the Arrhythmogenicity of TWA

Interest in repolarization alternans is attributed to the hypothesis that it may reflect underlying dispersion of repolarization in the ventricle, a well-recognized electrophysiologic substrate for reentrant VT.[13] Investigations of the arrhythmogenicity of QT/T wave alternans in experimental models of the long QT syndrome (LQTS) have provided significant insight into the role of dispersion of ventricular repolarization in the generation of reentrant VT. Chinushi et al.[14] studied an in vivo canine surrogate model of LQTS utilizing the neurotoxin anthopleurin-A (AP-A) and analyzed tridimensional repolarization and activation patterns during tachycardia-induced QT/T alternans (Fig. 1). The arrhythmogenicity of QT/T alternans was primarily due to the greater degree of spatial dispersion of repolarization during alternans than during slower rates not associated with alternans. The dispersion of repolarization was most marked between midmyocardial (M) and epicardial zones in the LV free wall. In the presence of a critical degree of dispersion of repolarization, propagation of the activation wavefront could be blocked between these zones to initiate reentrant excitation and polymorphic VT. Two factors contributed to the modulation of repolarization during QT/T alternans, resulting in greater magnitude of dispersion of repolarization between M and epicardial zones at critical short cycle lengths: (1) differences in restitution kinetics at M sites, characterized by larger differences of the activation recovery interval (ARI), an accurate in vivo marker of the duration of repolarization, and a slower time constant (τ) compared with epicardial sites; and (2) differences in the diastolic interval that would result in different input to the restitution curve at the same constant cycle length. The longer ARI of M sites resulted in shorter diastolic interval during the first short cycle, and thus a greater degree of ARI shortening.

An important observation was that marked repolarization alternans could be present in local elec-

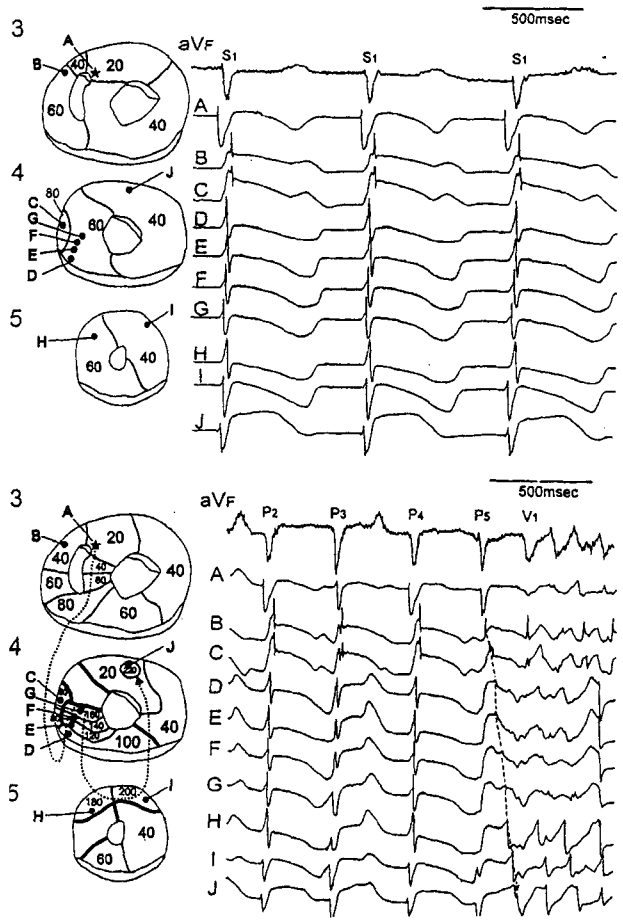

Figure 1. Recordings obtained from a canine experiment in the presence of AP-A to create a surrogate model of LQT3. T-wave alternans in ECG lead aVF was induced by abrupt shortening of ventricular paced cycle length (CL) from 700 ms (top panel) to 350 ms (bottom panel). Following the fifth paced beat at short CL (P5), polymorphic VT developed, the first beat of which is labeled V_1. The figure illustrates the tridimensional activation map during control paced rhythm at 700 ms (S1) (top). Activation began at the pacing site (indicated by star) in section 3. The total ventricular activation time was 80 ms, and there were no arcs of functional conduction block. Selected unipolar electrograms are shown on the right panel. There was no QT/T alternans at this CL at any site. Recordings from the same experiment during abrupt shortening of the cycle length to 350 ms (P) (bottom). The activation map of the P5 beat that initiated reentrant excitation is shown on the left. Selected electrograms along the reentrant pathway that demonstrate complete diastolic bridging are shown on the right. Note the development of QT/T alternans which was more marked at Mid sites E to H compared to Epi sites B,C,I and J. The reentrant wavefront circulated around arcs of functional conduction block between Epi and Mid sites in sections 4 and 5 (represented by heavy solid lines) before reactivating a subepicardial site in section 4 at the 220-ms isochrone. (From Chinushi et al. Circ Res 1998;83:614-628, with permission of the American Heart Association).

trograms without manifest alternation of the QT/T segment in the surface ECG. The latter was seen at critically short cycle lengths associated with reversal of the gradient of repolarization between epicardial and M sites, with a consequent reversal of polarity of the intramyocardial QT wave in alternate cycles. This observation provides the rationale for the digital processing techniques that attempt to detect subtle degrees of TWA.

The association of TWA with a greater degree of dispersion of repolarization was later confirmed in two other experimental models. Shimizu et al.[15] studied an in vitro surrogate model of LQTS utilizing the neurotoxin ATX-II and a perfused wedge preparation of canine LV wall. Simultaneous transmembrane action potentials were recorded from epicardial, mid-myocardial, and endocardial cells, together with a simulated unipolar ECG. When the preparation was paced at a critical fast rate, there was pronounced alternation of APD of M cells, resulting in a reversal of repolarizing sequence across ventricular wall leading to alternation in the polarity of the T wave in the unipolar ECG (Fig. 2). The authors concluded that TWA observed at rapid rates under long QT conditions is largely the result of alternation of the M-cell APD, leading to exaggeration of transmural dispersion of repolarization during alternate beats, and thus the potential for development of torsade de pointes. The data also suggested that, unlike transient forms of TWA that damp out quickly and depend on electrical restitution factors, the steady-state electrical and mechanical alternans demonstrated in their study appears to be largely the result of beat-to-beat alternans of I_{ca}.

Pastore et al.[16] investigated TWA in a Langendorff-perfused guinea pig heart using optical mapping of epicardial action potentials and showed that repolarization alternans at the level of the single cell accounts for TWA on the surface ECG. They also showed that discordant alternans produces spatial gradients of repolarization of sufficient magnitude to cause unidirectional block and reentrant VT.

MEASUREMENT OF MICROVOLT TWA

A spectral technique is utilized to detect microvolt TWA.[7,17] The technique involves measuring the amplitude of the T wave, at a fixed offset from the QRS complex, in sequential beats in order to

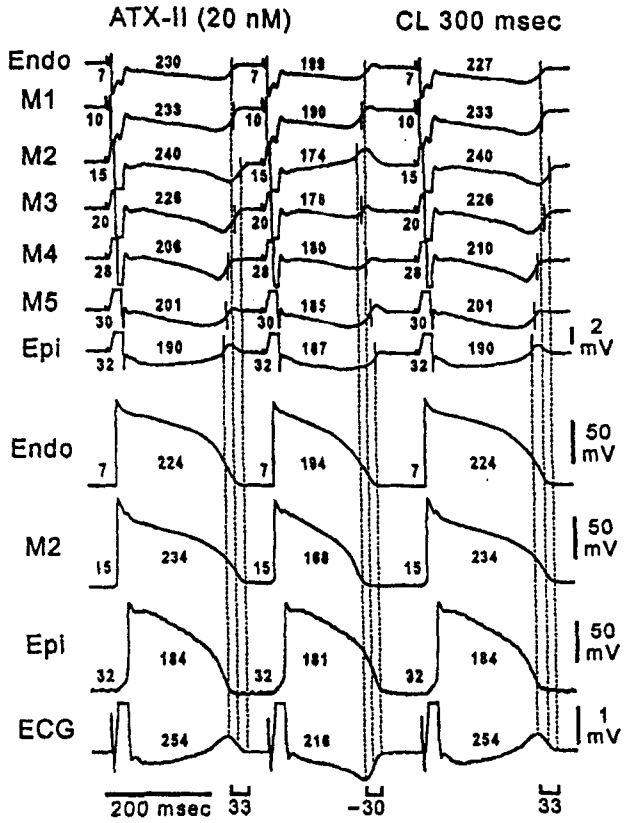

Figure 2. Cellular basis for alternans in T-wave polarity from a canine perfused wedge preparation in the presence of ATX-II (20 nM). The figure shows 7 intramural unipolar electrograms recorded from endocardial (Endo), mid-myocardial (M sites: M1-M5), and epicardial (Epi) regions, transmembrane action potentials recorded from M (M2) and epicardial sites together with a transmural ECG. Numbers before and after depolarization of each unipolar electrogram indicate activation time (AT) and activation-recovery intervals (ARI). Numbers before and after upstroke of each action potential indicate AT and APD_{90}. Numbers associated with each ECG denote transmural dispersion of repolarization. Horizontal lines in each unipolar electrogram show time maximum of the first derivative (V_{max}) of T wave. Note that the epicardium is the first to repolarize and the M region is the last when the T wave is positive (first and third beats). When in alternate beats repolarization gradients reverse (the M region repolarizes first and epicardium last), the T wave becomes negative (second beat). Traces were obtained under steady-state conditions (15 seconds after decreasing CL from 500 to 300 ms). (From Shimizu and Antzelevitch, Circulation 1999;99:1499-1507, with permission of the American Heart Association.)

create a time-series. This time-series is analyzed using a Fast Fourier Transform in order to generate a power spectrum (Fig. 3). Applying this technique to a series of points in the T wave, each with a different offset from the QRS, creates a set of power spectra. All of these power spectra are then averaged to generate a composite power spectrum for the entire T wave. One may use this composite power spectrum to detect any type of fluctuation in T-wave morphology that occurs on an every other beat basis. Alternans appears in this spectrum as a peak at the last point in the spectrum, at a frequency of 0.5 cycles per beat. From the composite power spectrum, two numerical measures can be obtained for application to clinical evaluations. The first is the alternans voltage (V_{alt}), the square root of the alternans power (i.e., the height of the peak above the background noise level). The second is the alternans ratio (k), which is the alternans power measured in units of standard deviations of the background noise. Thus the alternans ratio is a measure of the statistical significance of the alternans peak representing the number of standard deviations by which it exceeds the background noise level.

The original application of the technique of TWA utilized atrial pacing to increase heart rate.[18] Although the study was the first to demonstrate the predictive value of microvolt TWA as a marker for electrical vulnerability, the technique was limited by the need of invasive atrial pacing to produce a fixed heart rate at an elevated level. In order to make the technique fully noninvasive, a methodology was developed to permit measurement of TWA while the heart rate is elevated by means of bicycle (and later treadmill) exercise. Exercise complicates the measurement of TWA because it introduces movement artifact and because the heart rate is not fixed. Electrode systems and signal processing techniques were developed to minimize the movement artifact, and pedaling was controlled to keep the frequency of the motion artifact far from the frequency of alternans. These strategies successfully enable the measurement of TWA during exercise. Noise, premature beats, rapid changes in heart rate, or prominent beat-to-beat variability of RR intervals, may all mask true alternans.[17] All these factors, besides the inability to achieve a target heart rate may result in an "indeterminate" result of the TWA test.

OPTIMAL TARGET HEART RATE FOR EXERCISE-INDUCED TWA

TWA is a threshold phenomenon, tending to appear abruptly when the heart rate exceeds a pa-

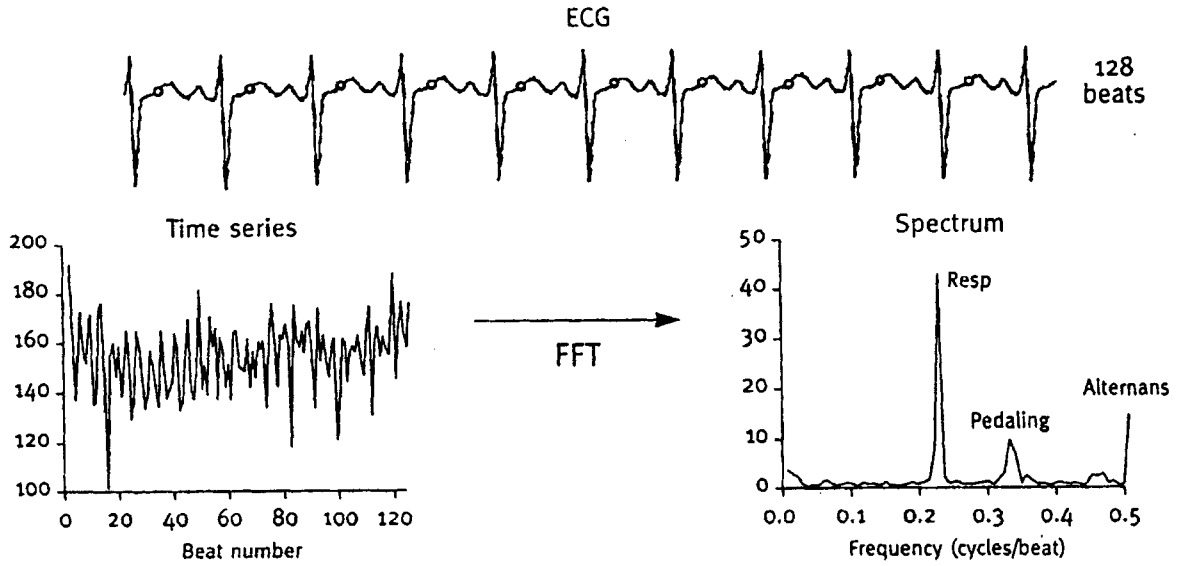

Figure 3. T-wave alternans measurement: spectral method.

tient-specific onset heart rate threshold. Sustained TWA is defined as TWA which is present continuously while the patient's heart rate is above his/her onset heart rate. The occurrence of sustained TWA is the clinically predictive phenomenon. Because experimental evidence suggests that TWA is dependent on both heart rate and the sympathetic nervous system,[19,20] the difference in the electrophysiologic mechanisms of rate-dependent TWA when HR is increased by exercise versus atrial pacing was investigated. The prevalence and heart rate threshold for TWA were compared in the same group of patients during exercise and atrial pacing.[21] This study showed that, during both exercise and atrial pacing, TWA developed when the heart rate reached a patient-specific threshold and that the average threshold for TWA was similar whether the heart rate was increased by exercise or with pacing. This would suggest that the increase in heart rate rather than autonomic changes is primarily responsible for TWA. However, in this study a submaximal exercise was utilized that may not have been associated with significant activation of the sympathetic nervous system.[22]

TWA is a rate-dependent phenomenon and microvolt TWA could develop in normal subjects at sufficiently high heart rate. The onset heart rate for sustained TWA in patients susceptible to VT tends to be relatively low. In clinical studies of TWA, a voltage $> 1.9\ \mu V$ and an alternans ratio > 3 at a heart rate < 110 beats/min was empirically utilized as the criterion of a positive test[18] (Fig. 4). Recently, the optimal heart rate for the use of TWA as an index of ventricular vulnerability was systematically investigated.[23] Two groups of age-matched elderly subjects were studied: Group I, 50 patients with malignant VT who received an ICD, and constituted a "true positive" high-risk group, and Group II, 55 normal subjects considered "true negative" for arrhythmic risk. The best sensitivity and specificity could be achieved at a target heart rate of 115 beats/min (100% and 96%, respectively) (Fig. 5). A target heart rate of 110 beats/min had a similar specificity (98%), but a lower sensitivity (82%). Lower target heart rates were associated with rapid decline of the sensitivity of the test, while maintaining a relatively high specificity.

This study was not designed to investigate the predictive value of exercise-induced TWA for malignant VT at large nor to compare it with other indices of arrhythmic risk, such as programmed stimulation or the SAECG. However, in Group I, that comprised patients at very high risk for arrhythmic death in whom the ICD was indicated according to currently approved guidelines, a TWA utilizing a target HR of 115 beats/min had only a 61% positivity. On the other hand, 11% of these patients had false negative results, while in the remaining 28% the test was indeterminate, because the patients could not exercise up to a target heart rate of 115 beats/min. In this group, it could be argued that the use of a pharmacologic agent,

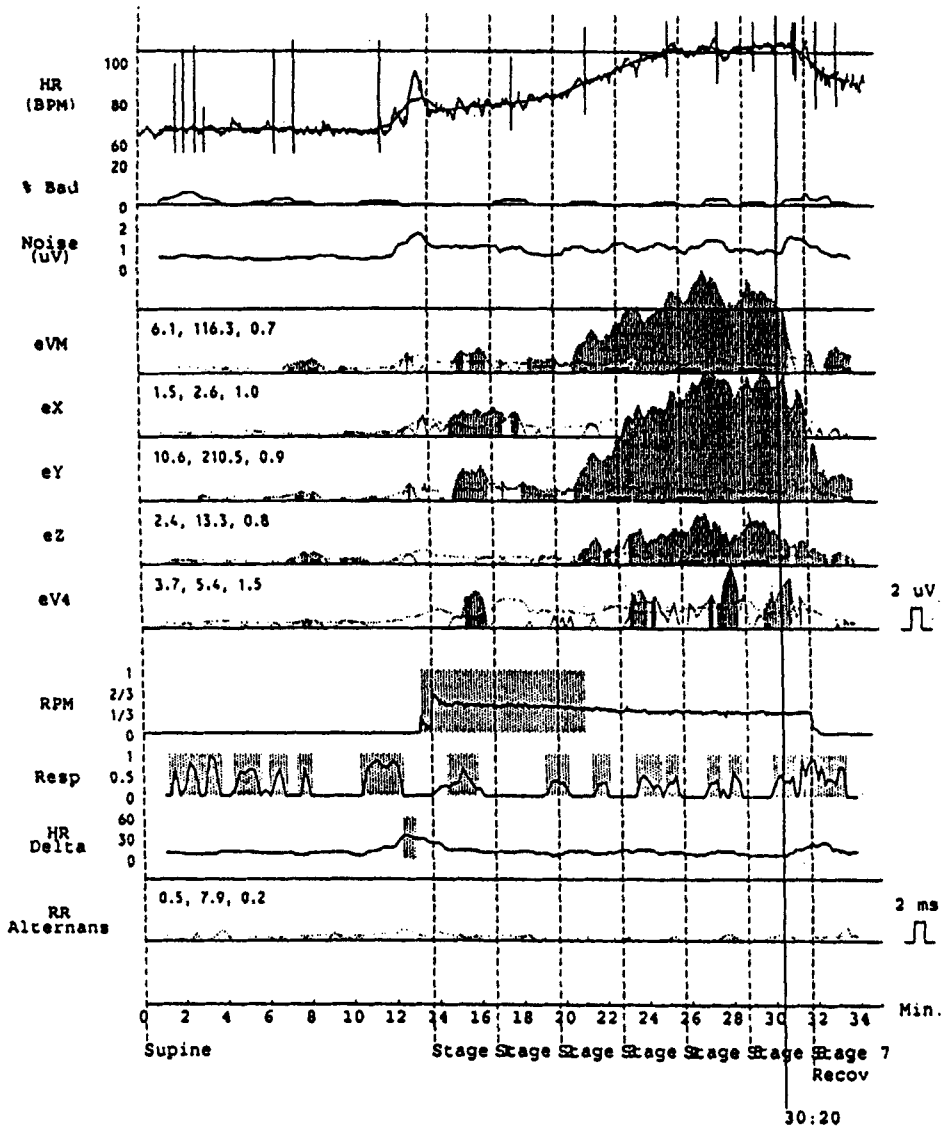

Figure 4. A representative case of a trend graph of TWA during bicycle exercise test in a 62-year-old male patient with coronary artery disease, prior myocardial infarction, spontaneous and inducible sustained monomorphic ventricular tachycardia. Marked TWA (voltage > 1.9 μV with alternans ratio > 3) developed when the patient's heart rate reached 85 beats/min during stage I of exercise, increased until peak exercise, and gradually decreased during the recovery phase (shaded area in X,Y, Z leads and the vector magnitude eVM). (From Turitto et al, Ann Noninvasive Electrocardiol 2001;16: xxx-xxx).

e.g., isoproterenol, to increase heart rate to the target level may be advised and could conceivably enhance the sensitivity of the test. However, a comparison of the sensitivity/specificity of TWA induced by exercise versus pharmacological means is yet to be reported. It should be emphasized, however, that the two study groups with markedly contrasting arrhythmic risk are not appropriate for evaluating the predictive value of TWA for malignant VT, nor for comparing TWA with other potential risk stratifiers. Further, the study utilized an analysis algorithm for defining TWA that has been previously reported.[24] It is possible that a different algorithm would have resulted in a different optimal target heart rate. For example, a recent study has shown that the use of individual orthogonal

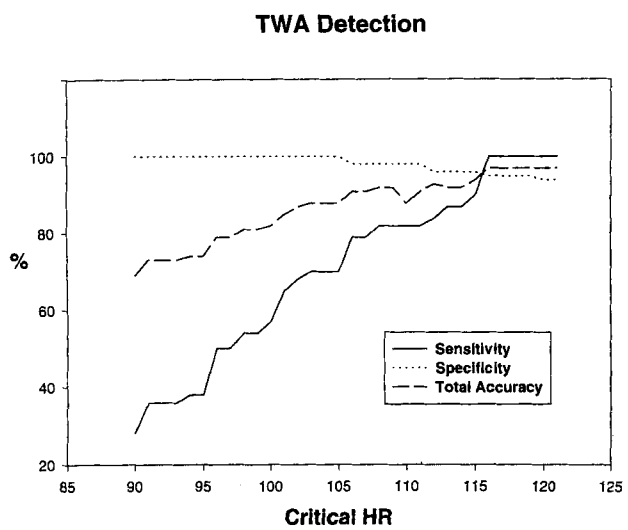

Figure 5. Sensitivity, specificity, and total accuracy curves plotted to identify the optimal target heart rate for TWA detection. HR = heart rate (in beats/min). (From Turitto et al., Ann Noninvas Electrocardiol 2001;6:123-128.)

leads plus a vector magnitude lead (as was utilized in the above study) results in increased sensitivity of the test as a predictor of VT inducibility.[25] On the other hand, the study raises the important issue of sensitivity versus specificity of a diagnostic test in relation to the degree and severity of the risk investigated in a given population. For example, if TWA is to be used as a screening test for malignant VT in a population with low-to-moderate risk, it is comforting to know that the specificity of the test remains high up to a heart rate of 115 beats/min. However, in a high-risk population, e.g., those with coronary artery disease and LV dysfunction, to achieve a high degree of sensitivity for identification of those at risk (and who could, for example, receive a prophylactic ICD) it may be necessary to reach a high target heart rate.

CLINICAL STUDIES OF TWA FOR RISK STRATIFICATION

The first study to demonstrate the value of TWA for arrhythmic risk stratification was published in 1994. Rosenbaum et al.[18] showed that microvolt level TWA measured during atrial pacing prior to EPS identified patients at high risk of VT events (defined as sustained ventricular tachycardia, ventricular fibrillation, or SCD). Patients who did not have significant levels of TWA had only a 6% event rate over the following 20 months, while those with significant levels of TWA had an 81% rate of VT events. TWA performed equivalently to EPS as a predictor of VT events.

In subsequent studies of TWA, the increased heart rate was achieved by bicycle exercise test. In a pilot study of 27 patients who presented with sustained VT and underwent EPS, the TWA measured at rest and during exercise had a sensitivity of 89% and a specificity of 75%, and an overall clinical accuracy of 80% in predicting inducibility during EPS.[24] Based on the results of this study, a multicenter trial of 313 patients in sinus rhythm who were undergoing EPS was conducted.[26] TWA, assessed with bicycle ergometry, and the SAECG were measured before EPS. The primary endpoint was SCD, sustained VT, or appropriate ICD therapy, and the secondary endpoint was any of these arrhythmias or all-cause mortality. All follow-up data were censored at 400 days. Kaplan-Meyer survival analysis of the primary endpoint showed that TWA predicted events with a relative risk of 10.9, EPS had a relative risk of 7.1, and SAECG had a relative risk of 4.5. The relative risk for the secondary endpoint were 13.9, 4.7, and 3.3, respectively ($P < 0.05$). Multivariate analysis of 11 clinical parameters identified only TWA and EPS as independent predictors of events. In the prespecified subgroup with known or suspected VT, TWA predicted primary endpoints with a relative risk of 6.1 and secondary endpoints with a relative risk of 8.0. The study concluded that TWA is a strong independent predictor of spontaneous VT or death. It performed as well as programmed stimulation and better than the SAECG in risk stratifying patients for life-threatening VT.

Several other clinical studies of TWA were published in the last few years.[27-30,32-35] One study focused on patients receiving ICDs.[27] At the time of implantation of the ICD, 95 patients underwent a battery of diagnostic tests involving essentially all the arrhythmic risk stratifiers currently in use. These tests included TWA and invasive EPS, as well as measurement of LVEF, BRS, 24-hour HRV, the presence of nonsustained ventricular tachycardia during 24-hour ECG monitoring, and QT dispersion. The endpoint of the study was the first appropriate discharge of the ICD as documented by review of stored ECGs. Of all the diagnostic tests, only TWA and LVEF were statistically significant predictors of appropriate ICD therapy. Other studies investigated the predictive value of TWA

for arrhythmic risk in patients with organic heart disease other than coronary artery disease. Murda'h et al.[28] measured TWA noninvasively in 64 patients with hypertrophic cardiomyopathy in an attempt to predict arrhythmic events in this high-risk patient population. A positive TWA was found in 34 out of 64 patients. TWA was the only significant marker with respect to identification of patients who survived a VT event. The predictive power could be increased by combining TWA with the clinical history (sensitivity: 86%; specificity: 79%). Adachi et al.[29] investigated the value of TWA in 58 patients with nonischemic dilated cardiomyopathy. In this group of patients, EPS as well as many other noninvasive markers of arrhythmic risk are known to have less predictive accuracy compared to patients with ischemic heart disease. In this study, the sensitivity, specificity, and predictive accuracy of TWA for VT were 88, 72, and 77%, respectively. Multivariate analysis showed that the presence of VT was a major independent determinant of TWA in patients with nonischemic dilated cardiomyopathy. The study concluded that TWA is a useful noninvasive test for identifying high-risk patients with dilated cardiomyopathy who have VT. Hennersdorf et al.[30] investigated the correlation of TWA and resuscitated SCD in patients with nonischemic cardiomyopathy, including dilated cardiomyopathy, chronic myocarditis, and LV hypertrophy. The study found a significant correlation between a positive TWA and a history of resuscitated arrhythmic event, with a sensitivity of 65% and a specificity of 98%.

There are currently a number of ongoing multicenter SCD primary prevention trials in patients with ischemic or nonischemic cardiomyopathy.[31] In some of the trials the only requirements for entering the study are LVEF < 35% and class II/III NYHA symptoms. The annual cardiac mortality in this group of patients is high and it is generally considered that approximately half of the deaths are sudden and presumably due to malignant VT, while the rest of the deaths are due to terminal pump failure.[32] It is obvious that a strategy that requires a prophylactic ICD in all of these patients represents significant redundancy, since at least half of the patients would not have benefited from such a highly expensive therapeutic modality. It comes to reason that a better risk stratification in these patients is an important requirement before recommending the ICD as primary prophylaxis for SCD in this population. With this goal in mind, a recent report from Klingenheben et al.[33] investigated the predictive value of TWA for arrhythmic events in 107 patients with congestive heart failure and no history of sustained VT. The patients were followed up for arrhythmic events during the next 18 months. Of the patients with events, 11 had positive and 2 indeterminate TWA results; there were no arrhythmic events among patients with negative TWA results. Of seven different noninvasive risk stratifiers, only TWA was a significant ($P = 0.0036$) and independent predictor of arrhythmic events.

TWA AND THE SAECG

The concept of combining more than one risk index for serious arrhythmic events in order to increase their combined predictive accuracy is a valid one. However, the combination of more than one risk index should be based on thorough understanding of their relationship to the underlying electrophysiologic mechanism(s) of malignant VT. In this regard, the combined application of the SAECG and TWA for risk stratification of malignant VT makes the most sense. The SAECG can provide evidence of ventricular conduction disorders while TWA detects underlying inhomogeneity of ventricular repolarization. These two electrophysiologic parameters contribute to a varying degree to the development of reentrant VT. A number of recent studies that examined the predictive value of these two techniques in the same group of patients reported inconsistent results.[26,34,35] For example, in the report by Gold et al.[26], both TWA and SAECG predicted arrhythmic events in univariate analysis with a relative risk of 10.9 and 4.5, respectively. However, in a multivariate analysis only TWA (and EPS) were independent predictors of events. On the other hand, Ikeda et al.[35] examined the combined predictive power of TWA and the SAECG in post-AMI patients. In this study, the event rate was significantly higher in patients with TWA, late potentials in the SAECG, and low LVEF. The negative predictive accuracy of TWA was very high whereas the positive value was lower than those of late potentials and LVEF. The study concluded that the combined indices of positive TWA and late potentials were associated with a high positive predictive value for arrhythmic events in the post-AMI patient. It is also important to emphasize that all the studies that examined both SAECG and TWA in the same group of patients utilized

time-domain analysis of the SAECG. There are several studies that showed that combined time-domain and frequency-domain analysis of the SAECG can significantly increase its positive predictive accuracy.[36]

SOME LIMITATIONS OF TWA

There are several technical and electrophysiologic limitations of the TWA that should be considered in the design of the best strategy for risk stratification of serious arrhythmic events. The two most obvious technical limitations are: 1) TWA could not be measured in patients with atrial fibrillation, a relatively common arrhythmia in patients with organic heart disease, and 2) the presence of frequent ectopic beats, motion artifacts, and in particular the inability of patients to achieve the target heart rate would render the results "indeterminate". Unfortunately, indeterminate results approach 20 to 25% in most of the published studies. Some of these technical limitations could be reduced by refinement of the technique and by investigating, for example, exercise-induced versus pharmacologic-induced increase in heart rate. On the electrophysiologic aspect, there is evidence that the test may lose much of its predictive power when applied in the first few weeks post-AMI, a period of time known to be associated with a relatively high incidence of SCD.

EPILOGUE

The detection of rate-dependent microvolt TWA seems to be a powerful marker for the risk of malignant VT. This concept has a solid electrophysiologic basis. The combination of this technique with other established risk indices such as SAECG (with combined time- and frequency-domain analysis) may provide a strong algorithm for risk stratification, especially in patients with organic heart disease. More importantly, the noninvasive nature and the relative low cost of both techniques make them ideal as screening tests in the much larger group of patients with only moderate risk for arrhythmic events. However, the real challenge is to prove the validity of the test in a prospective multicenter ICD primary prevention trial of SCD. Such a trial (Alternans Before Cardioverter Defibrillator -ABCD-) is currently underway.

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