Use of Microvolt T-Wave Alternans Testing in Clinical Practice to Reduce Cardiac Arrest and Sudden Cardiac Death

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Abstract

Microvolt T-Wave Alternans (MTWA) is a new non-invasive method for identifying patients at increased risk of cardiac arrest and sudden cardiac death from ventricular arrhythmias. MTWA can be measured during a routine exercise stress test, during pharmacologic stress or during cardiac pacing. MTWA has been successfully applied to patients both with and without coronary artery disease. Its clinical performance compares favorably with that of other non-invasive risk stratifiers and invasive electrophysiologic study (EPS). The event rate during follow-up among patients who test MTWA positive is comparable to that of patients with a positive EPS, whereas the event rate among MTWA negative patients has tended to be lower than among EPS negative patients. In particular the low event rate during follow-up among patients with a negative MTWA test, renders MTWA a suitable non-invasive means for the initial evaluation of patients potentially at risk for ventricular arrhythmias. Patients suitable for MTWA testing include patients presenting with a history suggestive of ventricular arrhythmias, patients with left ventricular dysfunction, and patients at least 4-6 weeks after myocardial infarction. Patients who test MTWA positive can proceed to invasive study and/or therapy whereas patients who test negative in most cases can be managed conservatively. In addition, MTWA can be measured during cardiac pacing in the electrophysiology laboratory to provide an additional endpoint in addition to the outcome of programmed ventricular stimulation, or as a means to non-provocatively assess ventricular stability in patients being evaluated or treated for supraventricular arrhythmias. MTWA testing can increase referrals of appropriate patients for further electrophysiologic evaluation and/or therapy.

Sudden cardiac death (SCD) from ventricular tachyarrhythmia represents a major public health problem accounting for approximately 300,000 – 400,000 deaths per year in the United States[1]. In recent years there have been dramatic advances in therapy for the prevention of SCD due to ventricular tachyarrhythmias. Specifically, the development of the implantable cardioverter/defibrillator (ICD) has provided an effective and specific preventative treatment for patients known to be at high risk for sudden cardiac death[2-5]. The ICD however represents an expensive therapy that is applied only in patients known to be at high risk. Pharmacologic therapy also has advanced. Beta-blockers have been shown to reduce total mortality and arrhythmic death in patients with coronary artery disease[6]. Beta-blockers[6-7], angiotensin converting enzyme (ACE) inhibitors[8] , and aldosterone antagonists[9] have been shown to reduce total mortality and arrhythmic death in patients with left ventricular dysfunction. Amiodarone has been shown to reduce ventricular tachyarrhythmic events in patients with heart failure[10-12]. Sotalol has been shown to reduce the frequency of appropriate ICD discharges for ventricular tachycardia and ventricular fibrillation[13].

Advances in therapeutic modalities until recently have not been paralleled by advances in non-invasive diagnostic technologies to identify high risk patients. This may partially explain why sudden cardiac arrest and death remains at epidemic levels. Ideally, effective non-invasive diagnostic methods would identify those patients at increased risk of SCD, and then be used to guide prophylactic treatment.

The measurement of Microvolt T-Wave Alternans (MTWA) has recently been demonstrated to be a powerful non-invasive predictor of the risk of ventricular tachyarrhythmias

and sudden cardiac death in a number of different patient populations. In direct comparisons with prior non-invasive diagnostic risk stratification methods, MTWA has been a superior predictor of arrhythmic risk[14-18]. In direct comparisons with invasive electrophysiologic study (EPS) study, MTWA has been found to be either an equivalent or better predictor of ventricular tachyarrhythmic events and SCD[14,19,20]. Moreover, MTWA can now be conveniently measured during exercise or pharmacologic stress testing with commercially available equipment. MTWA testing has been cleared by the United States Food and Drug Administration on the basis of clinical data as a predictor of risk of ventricular tachyarrhythmias and sudden cardiac death. The question now arises how should MTWA testing be used currently in clinical practice?

Background

T-wave alternans is a type of electrical alternans in which there is a beat-to-beat variation in the morphology of the T-wave in an ABABAB… type of pattern. Electrical alternans was described at the very dawn of electrocardiography[22]. T-wave alternans as described in this paper refers to actual alternation in intrinsic cardiac repolarization processes and should be distinguished from *apparent* electrical alternans which results from alternating rotation of the cardiac electrical axis during mechanical alternans as occurs in the setting of pericardial effusion.

T wave alternans now is believed to be due to localized alternation in action potential morphology, in particular alternation in action potential duration[23- 24]. Alternation in action potential duration in turn occurs when the slope of the restitution curve (action potential duration as a function of preceding diastolic interval) exceeds unity at the current value of the diastolic interval (reference #25, see Figure 1).

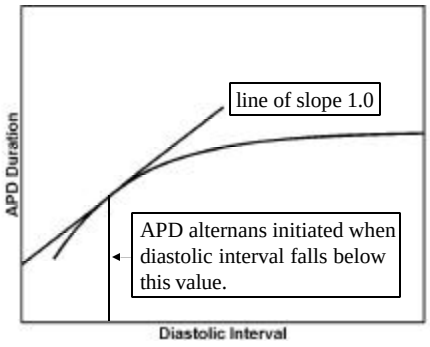

Figure 1. Restitution curve illustrating that action potential alternans is initiated when the diastolic interval falls to a value where the slope of the curve exceeds unity. (from reference #25, figure 25.3b)

Localized alternation in action potential duration in turn is reflected in the surface ECG as T-wave alternans. Localized alternation in action potential duration also results in localized regions of delayed recovery. The resulting spatial dispersion of recovery leads to depolarization wavefront fractionation leading to re-entry.

Clinical Interpretation

Localized action potential alternation sufficient to increase the risk of spontaneous tachyarrhythmia may result in T-wave alternans in which the variation in T-wave morphology is only a few microvolts in amplitude – T-wave alternans of this magnitude would not be detectable by visual inspection of the surface electrocardiogram. Thus sophisticated signal processing techniques were developed to reliably detect MTWA. The spectral method for detecting T-wave alternans[21] allows one to measure MTWA in terms of the alternans voltage, V_{alt}, and also determines the statistical significance of V_{alt} measured in terms of the alternans ratio, the number of standard deviations by which V_{alt} exceeds the noise level. Only values of V_{alt} which are greater than 1.9 microvolts and which are associated with an alternans ratio greater than three are considered statistically significant.

MTWA is highly heart rate dependent – presumably because the restitution curve tends to get steeper at shorter diastolic intervals. Clinical testing for MTWA involves elevating the patient's heart rate by means of exercise stress, pharmacologic stress or cardiac pacing. MTWA which is present at rest, or is consistently present above a patient specific onset heart rate which in turn is less than or equal to 110 bpm, is considered clinically significant (see Figure 2).

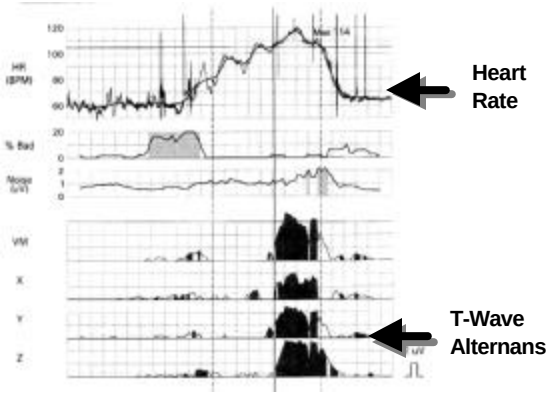

Figure 2. Trend plot of treadmill MTWA test in a patient with sustained alternans. Sustained alternans is defined as alternans with $V_{alt} \geq 1.9$ microvolts and alternans ratio ≥ 3 consistently present either at rest or above a patient specific onset heart rate. Tracings from top to bottom: Heart rate (smoothed and instantaneous), percent ectopic beats, noise level (microvolts) in vector magnitude lead, V_{alt} (microvolts) in vector magnitude and orthogonal leads X, Y, Z (precordial leads not shown) - shading indicates alternans ratio exceeds 3.0. Because the onset heart rate for sustained alternans is less than or equal to 110 bpm this is a positive test.

Sustained MTWA with an onset heart rate above 110 bpm has not been deemed clinically significant – presumably because heart rates above 110 bpm are reached only infrequently during ambient activity.

Patients with sustained MTWA with onset heart rate of 110 bpm or less are classified as having a positive test, patients who do not test positive and definitively do not have T-wave alternans at elevated heart rates are classified as negative. Remaining patients are classified as indeterminate. Causes of indeterminacy include inadequate heart rate elevation, and excessive

levels of ectopy or noise. In studies to date indeterminacy rates have generally exceeded 20 percent. A number of technical improvements are being implemented that promise to significantly reduce the indeterminacy rate.

Clinical Studies in Patients Presenting for Evaluation of Known or Suspected Cardiac Arrhythmias

A prospective study[19] of the predictive accuracy of MTWA measured during atrial pacing in 83 consecutive patients undergoing EPS revealed that 81% of patients testing T-wave alternans positive sustained a ventricular tachyarrhythmic event (sudden cardiac death, cardiac arrest, or electrocardiographically documented sustained ventricular tachycardia, or appropriate ICD discharge as documented by review of the stored electrocardiogram) within 20 months of follow-up whereas only 6% of patients who tested T-wave alternans negative sustained an event (see Figure 3). Invasive EPS yielded very similar predictive accuracy.

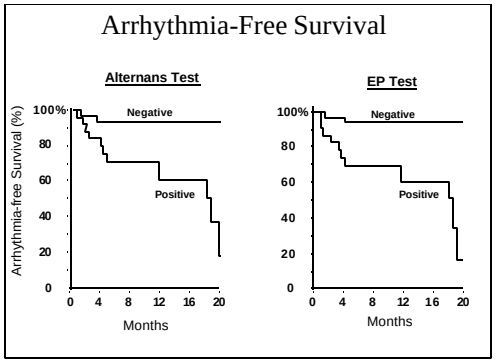

Figure 3. Left, the relation between T wave alternans and arrhythmia-free survival in 66 patients. Kaplan-Meier life table arrhythmia-free survival is compared in patients with and without significant T wave alternans. Note that the presence of T wave alternans strongly identifies those patients who are at risk for reduced arrhythmia-free survival. Right, arrhythmia-free survival in patients with positive electrophysiologic tests (+EP) is compared with survival in patients in whom ventricular arrhythmias were not induced at electrophysiologic testing.(-EP). Note that the predictive value of both electrophysiologic testing and T wave alternans is essentially indistinguishable in these plots. (from reference #19, figure 5)

The first study[14] to prospectively evaluate MTWA measured during exercise stress involved 95 patients receiving ICDs for clinical indications; the endpoint of this study was appropriate ICD discharge as documented by review of the stored electrograms. In addition to MTWA, patients also were risk stratified by means of EPS, left ventricular ejection fraction, baroreceptor sensitivity, signal averaged ECG, QT dispersion heart rate variability, mean RR interval over 24 hours, and the presence of non-sustained ventricular tachycardia during 24 hour Holter monitoring. Of all the risk stratifiers, including EPS, only MTWA was a statistically significant predictor of appropriate ICD discharge over 18 months of follow-up (see Figure 4).

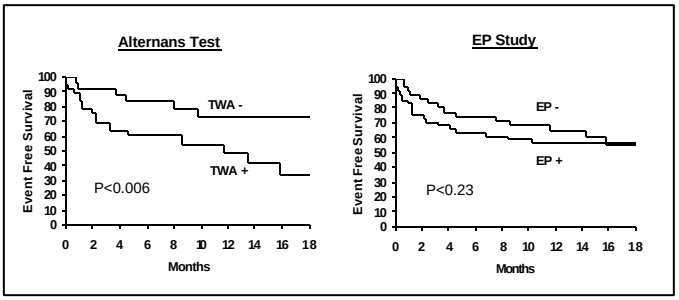

Figure 4. Arrhythmia-free survival in patients with implanted ICDs according to MTWA classification (left panel) and EPS classification (right panel). (from reference #14, figures 1a and 1b)

Gold et al[20] in a multi-center trial of 313 patients undergoing EPS found that MTWA was a highly significant predictor of ventricular tachyarrhythmic events. Forty-one percent of the patients were being evaluated for syncope or presyncope. During 14 month follow-up the presence of MTWA was associated with a relative risk of 10.9 compared to 7.1 for EPS for the endpoint of ventricular tachyarrhythmic events (see Figure 5). The relative risks for the combined endpoint of ventricular tachyarrhythmic events plus all cause mortality were 13.9 for MTWA and 4.7 for EPS.

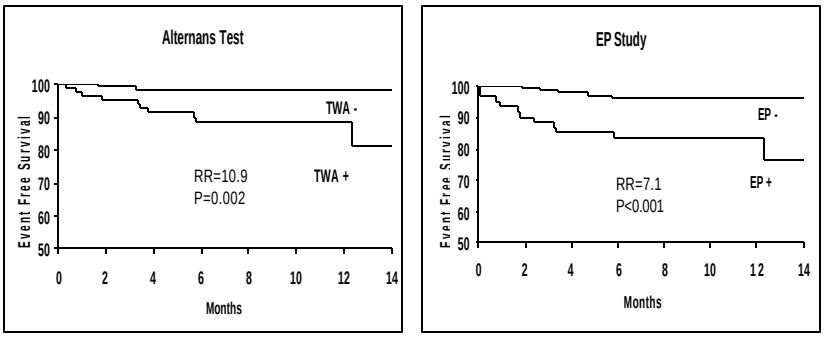

Figure 5. Arrhythmia-free survival in patients undergoing electrophysiologic testing according to MTWA classification (left panel) and EPS classification (right panel). (from reference #20, figures 1a and 1b)

Clinical Studies in Patients with Left Ventricular Dysfunction

Klingeheben[17] et al studied 107 consecutive patients with New York Heart Association congestive heart failure and no prior history of sustained ventricular arrhythmias. Two-thirds of the patients had coronary artery disease and one-third had non-ischemic dilated cardiomyopathy. MTWA was evaluated along with left ventricular ejection fraction, baroreceptor sensitivity, heart rate variability, signal averaged ECG, baroreceptor sensitivity, mean RR interval over 24 hours, presence of non-sustained ventricular tachycardia on 24 hour Holter monitoring. Of these seven measures, only MTWA was a statistically significant predictor of ventricular tachyarrhythmic events. Twenty-one percent of the patients who tested positive for MTWA had a ventricular

tachyarrhythmic event during 18 months of follow-up, whereas none of the patients who tested negative had an event (relative risk = ∞, see Figure 6).

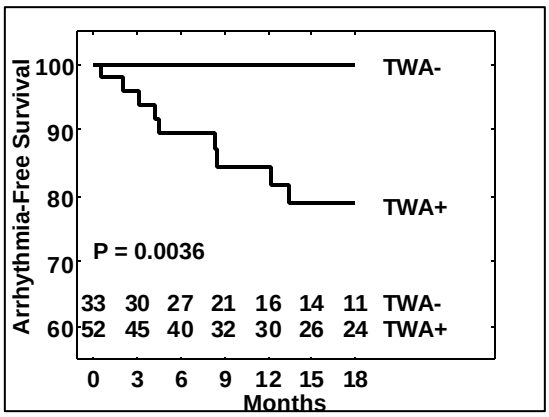

Figure 6. Arrhythmia-free survival in patients with heart failure according to MTWA classification. (from reference #17, figure)

Several studies[26-28] have evaluated patients with non-ischemic dilated cardiomyopathy. These studies have demonstrated a highly statistically significant association between the presence of MTWA and the occurrence of spontaneous ventricular tachycardia (see Figure 7).

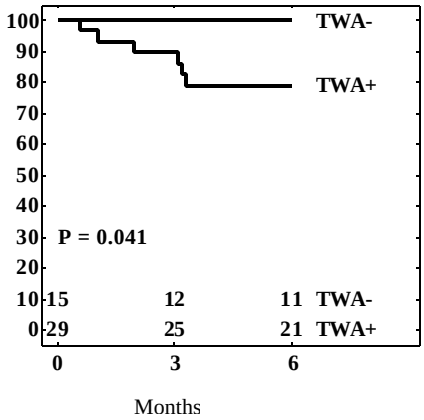

Figure 7. Arrhythmia-free survival in patients with non-ischemic dilated cardiomyopathy. (from reference #26, figure)

Clinical Studies in Patients with Recent Myocardial Infarction

Ikeda et al[18] studied 102 consecutive patients with acute myocardial infarction. Patients were studied a median of 20 days after myocardial infarction and were followed for twelve months for the occurrence of ventricular tachyarrhythmic events. T-wave alternans was a highly significant predictor ($p < 0.006$) of end-point events with a relative risk of 16. At the end of 12 months patients with a positive MTWA test had a 28% risk of sustaining a ventricular tachyarrhythmic event whereas patient who tested negative had a 2% risk (Figure 8).

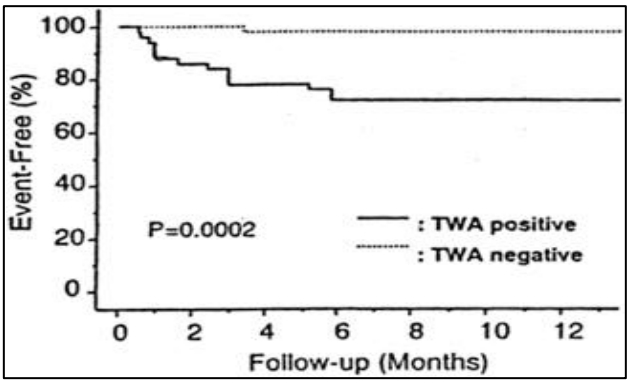

Figure 8. Arrhythmia-free survival in 102 post myocardial infarction patients based on MTWA classification. (from reference #18, figure 4a).

Hohnloser et al[29] in a multi-center trial found that T-wave alternans evolved substantially between the period 5-21 days after myocardial infarction and the period 28-56 after myocardial infarction. The concordance rate between determinate MTWA in the two periods being only 67%. Tapanainen et al[30] studied 379 patients a mean of 8.1 days after myocardial infarction and did not find a statistically significant elevation of cardiac deaths among patients who tested positive for MTWA. These three studies taken together suggest that T-wave alternans evolves rapidly during the acute post infarction period. Accordingly, MTWA is an accurate predictor of ventricular tachyarrhythmic events among patients after myocardial infarction only if the measurement is made after the acute post myocardial infarction period. It is suggested that MTWA be measured 4-6 weeks after infarction during the follow-up visit.

Comparison of Microvolt T-Wave Alternans with Electrophysiologic Testing

EPS generally is considered to be a useful predictor of ventricular tachyarrhythmic events only in patients with coronary artery disease. Data to date suggest that MTWA is a useful predictor of ventricular tachyarrhythmic events also in patients without coronary artery disease. Comparison of patients who test positive for MTWA and patients who are inducible during EPS indicate that during 12 to 24 month follow-up have similar event rates in the 20 – 30 percent range[14,19,20] (in non-ICD populations). Comparison of patients who test negative for the two tests[14,19,20] suggest that event rates among MTWA negative patients are at least as low (0 – 6%) and often substantially lower than among patients who are not inducible during EPS (5 – 12%).

Indications for Clinical Use of Microvolt Level T-Wave Alternans Testing

MTWA may be used as a useful non-invasive test for the initial evaluation of patients who may be at risk for sudden cardiac arrest and death from ventricular arrhythmias. Patients with coronary artery disease who test positive may be referred for invasive EPS and/or preventative therapy. Patients who test negative generally have a low risk of sudden cardiac arrest or death from ventricular arrhythmias and may in many cases be conservatively managed. Patients in whom MTWA testing is recommended include the following:

Patients Presenting for Evaluation of Known or Suspected Cardiac Arrhythmias

- *Syncope/Presyncope*
- *Non-sustained ventricular tachycardia, frequent ventricular ectopy, palpitations*
- *Family history of sudden cardiac death or conditions, such as long QT syndrome or hypertrophic cardiomyopathy, known to predispose to sudden cardiac death*
- *VT or VF associated with a possible reversible cause such as an acute ischemic episode*

Patients with the above histories may have an increased risk of cardiac arrest or sudden cardiac death due to ventricular arrhythmias. A microvolt level T-wave alternans test can be used to identify patients who are truly at high risk, and those patients who are not.

Patients with Left Ventricular Dysfunction

- *Heart Failure*
- *Cardiomyopathy (Ischemic or Non-ischemic)*
- *Left Ventricular Ejection Fraction £ 0.40*

Patients with left ventricular dysfunction have an increased risk of ventricular arrhythmias and sudden cardiac death. MTWA may be used to help identify those patients who are at high risk and require further study and/or therapy and those who are at low risk and can be managed conservatively.

Patients with Prior Myocardial Infarction

Patients with a prior myocardial infarction have an elevated risk of sudden cardiac death, particular during the first several years after the infarct. Microvolt level T-wave alternans may be performed in such patients to identify the high risk patients. It is important to perform this test no sooner than 4-6 weeks after the infarction to allow the patient's T-wave alternans status to stabilize.

Patients Undergoing Electrophysiology Study

- *Additional endpoint for patients undergoing programmed ventricular stimulation*

MTWA can be conveniently measured at the outset of an EPS during atrial pacing or atrio-ventricular sequential pacing at a cycle length of 550 msec. MTWA testing can provide an additional endpoint in addition to the outcome of programmed ventricular stimulation. This is particularly valuable when programmed ventricular stimulation results in a non-definitive result such as when polymorphic ventricular tachyardia or fibrillation are induced. Since EPS can have a high false negative rate (12% two year event rate among patients with a negative EPS compared to 18% among patients with a positive study in the MUSTT trial[4,5]), a T-wave

alternans test may be used to decide on therapy in patients with a compelling history for ventricular tachycardia but who are not inducible during programmed ventricular stimulation.

- *Evaluate risk of ventricular arrhythmia in patients with supraventricular arrhythmia and structural heart disease*

It is common to perform a limited ventricular stimulation study to rule out risk of ventricular arrhythmias in patients with structural heart disease undergoing EPS for evaluation or treatment of supraventricular arrhythmia. A complete ventricular stimulation protocol is generally not done in such patients for fear of inducing ventricular fibrillation which can be induced even in subjects with a completely normal ventricle. If T-wave alternans is measured during cardiac pacing at the outset of the study, then patients with a negative T-wave alternans test – because of the excellent negative predictive value of T-wave alternans – may not need to proceed to the limited ventricular stimulation study whereas patients who test positive for MTWA may proceed to a complete ventricular stimulation protocol.

What to Do with the Outcome of a Microvolt T-Wave Alternans Test?

Like any diagnostic test, the outcome of a MTWA test should be utilized only in conjunction with patient history and the results of other non-invasive or invasive tests.

Patients with a Negative Microvolt T-Wave Alternans Test

In populations that have been studied to date, the event rates among T-wave alternans negative patients have been extremely low – generally lower than the event rates among patients who are not inducible during programmed ventricular stimulation. Thus except for patients with prior cardiac arrest or who have a very compelling history suggestive of ventricular arrhythmias and/or severe left ventricular dysfunction, these patients in most cases may be conservatively managed. Conversely, patients with a positive MTWA test generally require further evaluation and/or treatment.

Patients with Coronary Artery Disease and a Positive Microvolt T-Wave Alternans Test

Patients with coronary artery disease and a positive T-wave alternans test, first need to be evaluated for the presence of active ischemia. Active ischemia is an extremely strong inducer of MTWA[21,31] (probably indicating increased risk of ventricular arrhythmias during the ischemic period). If active ischemia is present, then it should be treated and the T-wave alternans test repeated. If MTWA persists then the patient in most cases may proceed to invasive EPS. A positive EPS in most cases may lead to ICD therapy.

Patients with Coronary Artery Disease with Discrepant Microvolt T-Wave Alternans and Electrophysiology Study Results

The recently launched ABCD trial will be prospectively studying the efficacy of MTWA and EPS in guiding ICD therapy. In studies to date, the event rates are similar among patients with a positive T-wave alternans test and a positive EPS. Thus it would seem prudent to proceed

with therapy in patients with a positive EPS and a negative or indeterminate MTWA test. We do not yet have data on the effectiveness of ICD therapy based on T-wave alternans testing in patients with a negative EPS. However, it would seem reasonable to consider therapy in patients with a positive T-wave alternans test and negative EPS at least in those cases where the patient history is particularly compelling in suggesting ventricular tachycardia.

Patients without Coronary Artery Disease with a Positive Microvolt T-Wave Alternans Test

EPS is generally not considered to be a useful predictor of spontaneous ventricular arrhythmias in patients without coronary artery disease, for example patients with non-ischemic dilated cardiomyopathy. Thus there is not a second generally accepted test to be used to help make decisions in this group of patients. In patients with left ventricular dysfunction and a history suggestive of ventricular tachycardia it would seem prudent to proceed with ICD therapy. In other patients with structural heart disease but without a compelling history for ventricular tachycardia, one may wish to check that the dosage of medications used to treat the underlying condition have been optimized (e.g. ACE inhibitors, beta-blockers, aldosterone antagonists, and correction of any electrolyte abnormalities) and then repeat the T-wave alternans test if adjustments to the pharmacologic regimen have been made. If T-wave alternans is no longer present then one might wish to follow the patient, whereas if T-wave alternans persists one may wish to consider prophylactic anti-arrhythmic device or pharmacologic therapy.

How Often Should a Microvolt T-Wave Alternans Test be Repeated?

The follow-up period in studies conducted to date with T-wave alternans have mostly been in the 12 – 18 month range. Thus we do not know what the predictive value of T-wave alternans is for longer periods. Since in patients with structural heart disease, the disease itself may evolve over time, there is reason to believe that the predictive accuracy of T-wave alternans may degrade over longer follow-up periods. Thus it may be advisable to repeat T-wave alternans testing in patients who may be at risk at 12 to 18 month intervals.

Expected Impact of Microvolt T-Wave Alternans Testing on Cardiac Electrophysiology Practice

Use of MTWA testing makes it possible to identify patients at potential risk of cardiac arrest and sudden cardiac death from ventricular arrhythmias, that would not now normally come to the attention of the electrophysiologist – such as patients with left ventricular dysfunction and patients with recent myocardial infarction. Furthermore, physicians are generally reluctant to refer a patient for invasive EPS and/or ICD therapy even when the patient meets approved indications, such as patients who meet MADIT/MUSTT indications of coronary artery disease, left ventricular dysfunction and non-sustained ventricular tachycardia. In such patients a positive T-wave alternans test provides a specific arrhythmic indicator which may motivate both patient and physician for referral to an electrophysiologist. Patients who proceed to EPS following a positive T-wave alternans test, are more likely to be inducible in the electrophysiology laboratory than patients who are not so tested. Thus T-wave alternans may increase the yield of positive ventricular stimulation studies. The net effect of T-wave alternans testing should be to increase the number of patients appropriately referred for EPS and ICD implantation.

Conclusions

The measurement of MTWA is a non-invasive test for the assessment of susceptibility to ventricular arrhythmias. It may be incorporated into standard exercise or pharmacologic stress testing protocols to identify patients who are at risk for ventricular arrhythmias. It may also be measured during cardiac pacing in patients with pacemakers or in the electrophysiology laboratory. MTWA testing may be used for the initial evaluation of patients with a history suggestive of ventricular arrhythmias, identifying patients who are at high risk and require further evaluation and/or treatment and also identifying those who are at low risk. MTWA may also be used to identify patients with heart disease or who are at increased risk of ventricular arrhythmias and require electrophysiologic attention.

Despite the advances in anti-arrhythmic therapy, mortality from sudden cardiac death remains at epidemic levels. A prime reason may be that we have until now had non-invasive means to identify patients who are at greatest risk so that they could be properly evaluated and treated. The advent of MTWA testing promises to help remedy this situation, so that appropriate patients may identified and appropriately treated.

Bibliography

1. Zipes DP, Wellens HJJ. Sudden cardiac death. Circulation 1998; 98:2334-2351.

2. Antiarrythmics Versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997; 337:1576-1583.

3. Moss AJ, Hall J, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. N Engl J Med 1996; 335:1933-1940.

4. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley GH. A randomized study of the prevention of sudden death in patients with coronary artery disease. N Engl J Med 1999;341:1882-90.

5. Buxton AE, Lee KL, DiCarlo L, Gold MR, Greer GS, Prystowsky EN, O'Toole MF, Tang A, Fisher JD, Coromilas J, Talajic M, Hafley G. Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. N Engl J Med 2000;342:1937-45.

6. Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. N Engl J Med 1998; 339:489-497.

7. Packer P, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med 1996;334:1349-55.

8. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr, Cuddy TE, David BR, Geltman EM, Goldman S, Flaker GC. Effect on captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med 1992; 327:669-677.

9. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J, for the Randomized Aldactone Evaluation Study Investigators. Effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999; 341:709-717.

10. Singh SN, Fletcher RD, Gisher SG, Singh BN, Lewis HD, Deedwania PC, Massie BM, Colling C, Lazzeri D. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. N Engl J Med 1995; 333:77-82.

11. Cairns JA, Connolly SJ, Roberts R, Gent M. Randomized trial of outcomes after myocardial infarction in patients with frequent or repetitive ventricular premature depolarization: CAMIAT. Lancet 1997; 349:675-682.

12. Julian DG, Camm AJ, Frangin G, Janse MG, Munoz A, Schwartz PJ, Simon P. Randomized trial of effect of amiodarone on mortality in patients with left ventricular dysfunction after recent myocardial infarction: EMIAT. Lancet 1997; 349:667-674.

13. Pacifico A, Hohnloser SH, Williams JH, Saksena TB, Henry PD, Prystowski EN. Prevention of implantable-defibrillator shocks by treatment with sotalol. d,l-sotalol implantable cardioverter-defibrillator study group. N Engl J Med 1999;340:1910-1912.

14. Hohnloser SH, Klingenheben T, Yi-Gang L, Zabel M, Peetermans J, Cohen RJ. T Wave Alternans as a Predictor of Recurrent Ventricular Tachyarrhythmias in ICD Recipients: Prospective Comparison with Conventional Risk Markers. J Cardiovasc Electrophysiol 1998;9:1258 – 1268.

15. Armoundas A, Rosenbaum DS, Ruskin JN, Garan H, Cohen RJ. Prognostic significance of electrical alternans versus signal averaged electrocardiography in predicting the outcome of electrophysiological testing and arrhythmia-free survival. Heart 1998: 80: 251-256.

16. Armoundas AA, Osaka M, Mela T, Rosenbaum DS, Ruskin JN, Garan H, Cohen RJ. T-Wave Alternans and Dispersion of the QT Interval as Risk Stratification Markets in Patients Susceptible to Sustained Ventricular Arrhythmias. Am J Cardiol 1998; 82: 1127 – 1129.

17. Klingenheben T, Zabel M, D'Agostino RB, Cohen RJ, Hohnloser SH. Predictive Value of T-wave alternans for Arrhythmic Events in Patients with Congestive Heart Failure. The Lancet 2000; 356:651-52.

18. Ikeda T, Takami M, Kondo N, Tezuka N, Nakae T, Mahito N, Enjoji Y, Abe Ryoji, Sugi K, Yamaguchi T. Combined assessment of T-wave alternans and late potentials used to predict arrhythmic events after myocardial infarction. J Am Coll Cardiol 2000;35 722-30.

19. Rosenbaum DS, Jackson LE, Smith JM, Garan H, Ruskin JN, Cohen RJ: Electrical alternans and vulnerability to ventricular arrhythmias. N Engl J Med 1994;330:235-241.

20. Gold MR, Bloomfield DM, Anderson KP, et al. A Comparison of T-wave alternans, Signal Averaged Electrocardiography and Programmed Ventricular Stimulation For Arrhythmia Risk Stratification. J Am Coll Cardiol, 2000: 36, 2247-53.

21. Smith JM, Clancy EA, Valeri CR, Ruskin JN, Cohen RJ: Electrical alternans and cardiac electrical instability. Circulation 1988;77:110-121.

22. Hering HE. Experimentelle studien an saugethieren uber das elektrocardiogram. Zchr f exper path u therapie 1909;7:363-378.

23. Chinushi M, Restivo M, Caref EB, and El-Sherif N. Electrophysiological Basis of Arrhythmogenicity of QT/T Alternans in the Long QT Syndrome. Circ Res 1998;83:614-28.

24. Pastore JM, Girouard SD, Laurita KR, Akar FG, Rosenbaum DS. Mechanism linking T-wave alternans to the genesis of cardiac fibrillation. Circulation 1999;99:1385-94.

25. Bloomfield DM, Cohen RJ. Repolarisation Alternans. In: Malik M, editor. Risk of Arrhythmia and Sudden Death London: BMJ Books; 2001; p.256-265.

26. Kingenheben T, Credner SC, Bonsignore M, Mauss O, Hohnloser SH. Exercise Induced Microvolt Level T-Wave Alternans Identifies Patients with Non-Ischemic Dilated Cardiomyopathy at High Risk of Ventricular Tachyarrhythmic Events. PACE 1999;22 Supple II: 860.

27. Adachi K, Ohnishi Y, Shima T, Yamashiro K, Takei A, Tamura N, Yokoyama M. Determinant of microvolt-level T-wave alternans in patients with dilated cardiomyopathy. J Am Coll Cardiol 1999;34:374-80.

28. Hennersdorf MG, Perings C, Niebch V, Vester EG, Strauer B. T Wave Alternans as a Risk Predictor in Patients with Cardiomyopathy and Mild-to-Moderate Heart Failure. PACE 2000;23:1386-1391.

29. Hohnloser SH, Huikiri H, Schwartz PJ, Vijgen J, Pedretti RF, Levy S, Klingenheben T, Tapanainen J, Vanoli E, Camm J, Zipes DP, Cohen RJ. T wave alternans in post myocardial infarction patients (ACES pilot study). J Am Coll Cardiol 1999;33:144a, abstract 847-1.

30. Tapanainen JM, Aino-Maija S, Airaksinen KEJ, Huikuri HV. Prognostic significance of risk stratifiers of mortality, including T wave alternans, after acute myocardial infarction: results of a prospective follow-up study. J Cardiovasc Electrophsyiol 2001;12:645-52.

31. Verrier RL, Nearing BD. Electrophysiologic basis for T-wave alternans as an index of vulnerability to ventricular fibrillation. J Cardiovasc Electrophysiol 1994;5:445-465.