Review of Key Clinical Literature on Microvolt T-Wave Alternans

August 2002

Overview

The Microvolt T-Wave Alternans Test™ is a non-invasive diagnostic test designed to identify patients at risk of life threatening heart rhythm disturbances and sudden cardiac death. It was the first, and remains the only, non-invasive test cleared by the FDA to evaluate patients' increased risk of these conditions.

Sudden cardiac death is a leading cause of death in the United States claiming over 400,000 lives each year. One in seven individuals in the general population will eventually die of sudden cardiac death. In many cases, sudden cardiac death is the very first symptom of heart disease.

Most people who suffer cardiac arrest have an underlying, pre-identifiable, electrical disorder that puts them at risk. The proximate cause of sudden cardiac death in a majority of cases is ventricular tachyarrhythmia. However, the clinical dilemma is that there has not been a non-invasive diagnostic test that accurately identifies those individuals at risk for sudden cardiac death prior to their having a cardiac event. As a result, only a very small percentage of patients at risk receive specific preventative therapy, and therefore the ability to reduce the rate of sudden cardiac death has been severely limited.

Conventional non-invasive tests, such as exercise stress testing and echocardiography, do not specifically identify risk of ventricular arrhythmia. Likewise, tests such as holter monitoring, event recording or SAECG have not proven to be adequate in stratifying patient's risk of fatal ventricular arrhythmia. The most definitive method for detecting risk for sudden cardiac death today is the electrophysiology study (EP study), however, the study has limitations due to its cost and invasiveness. The non-invasive Microvolt T-Wave Alternans (MTWA) Test has consistently been demonstrated in studies to be comparable or superior to EP study in the prediction of sudden cardiac death and is currently being used to support further appropriate testing and treatment. Moreover, MTWA has been demonstrated to be up to three times better than EP study in ruling out those patients that do not go on to have events and is being used to avoid unnecessary EP procedures and costly treatment.

The Microvolt T-Wave Alternans Test is a provocative test conducted while the patient's heart rate is elevated through exercise, pharmacological stress or pacing. In order to perform the test and analyze microvolt patterns of the T-wave, it is necessary to use unique equipment incorporating proprietary algorithms, highly specialized alternans sensors and trained personnel. The test can be performed in a number of settings including the stress-testing lab, the pacing clinic, the nuclear testing lab, the echocardiography lab and EP lab. It can be performed as a "stand-alone" service and often is performed in this manner. In other instances it is performed in conjunction with electrophysiology testing or stress testing.

BASIC SCIENCE

T-wave alternans is an electrocardiographic pattern in which the morphology of the T-wave alternates on an every other beat basis (Figure 1). T-wave alternans visible in the electrocardiogram is a rare finding associated with a variety of pathophysiologic conditions[1-6] which are in turn associated with increased risk of ventricular arrhythmias such as acute ischemia, Prinzmetal's angina, electrolyte abnormalities, and the long QT syndrome.

Visible T-wave alternans, often associated with immediate ventricular arrhythmia

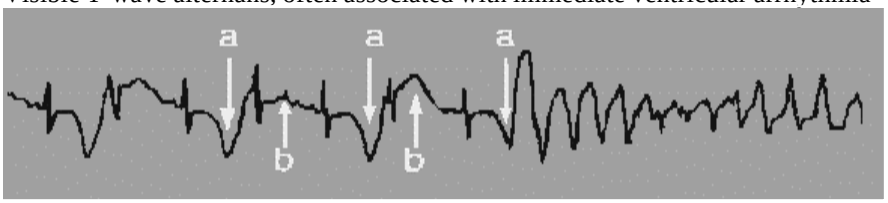


Figure 1

The advent of advanced signal processing methods have made it possible to measure Microvolt T-Wave Alternans, [7] which cannot be detected by visual inspection of the electrocardiogram. Microvolt T-Wave Alternans was demonstrated in animal studies to be a powerful predictor of susceptibility to ventricular tachycardia and fibrillation.[8]

Electrophysiologic mapping studies[9-12] demonstrated that t-wave alternans is caused by localized alternation in the duration of the action potential. Localized action potential alternans in turn leads to spatial dispersion of recovery leading to fractionation of depolarization wave fronts and the development of reentrant arrhythmias - ventricular tachycardia and fibrillation (Figure 2).

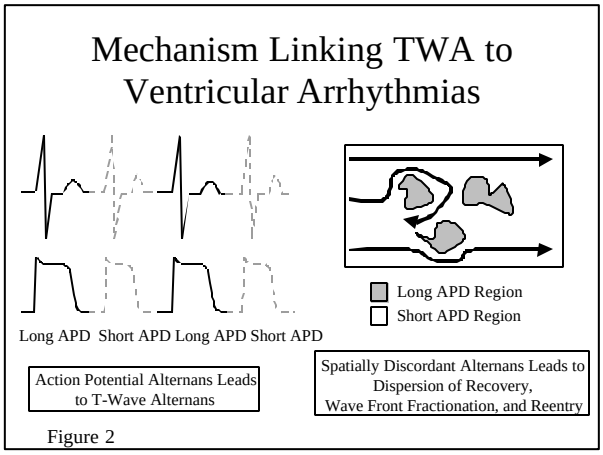


Figure 2

A large body of work now demonstrates a mechanistic link of MTWA and the onset of ventricular tachyarrhythmias and ventricular fibrillation at the cellular level.[12-17, 21,22] This research supports MTWA not just as a marker of events but an underlying cause.

CLINICAL STUDIES

Over 4,000 patients have been studied and reported using MTWA. The results have consistently demonstrated MTWA to be a powerful predictor and can clearly stratify those patients unlikely to have events and those that are at high risk. The patient populations that demonstrate the highest incidence of SCD include post MI, congestive heart failure (left ventricular dysfunction), syncope or cardiomyopathy. Many studies have been published using MTWA in each of these populations that demonstrate its value as a powerful predictor.

PATIENTS WITH PRIOR MYOCARDIAL INFARCTION

Ikeda T, Saito H, Tanno K, et al. T-Wave Alternans as a Predictor for Sudden Cardiac Death After Myocardial Infarction. Am J Cardiol 2002; 89:79-82.

In a multi-center trial of 850 post MI patients, MTWA was compared to other non-invasive risk stratifiers. In the 25-month follow up only MTWA was and LVEF met statistical significance and were independent predictors. MTWA was the most powerful predictor. Patients testing positive for MTWA in the trial were 11.4 times more likely to have sudden death or cardiac arrest than those who tested negative. MTWA had a negative predictive value of 99.5%. (Figure 3-graph represents Post-MI and EF≤40%)

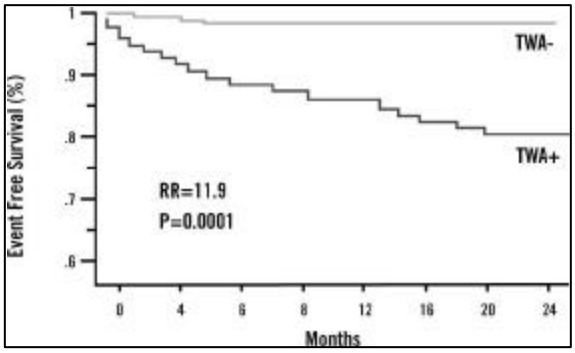


Figure 3

PATIENTS WITH KNOWN OR SUSPECTED ARRHYTHMIAS (INCLUDING SYNCOPE PATIENTS)

Rosenbaum DS, Jackson LE, Smith JM, et al. Electrical Alternans and Vulnerability to Ventricular Arrhythmias. N Engl J Med 1994; 330: 235-41.

This study involved 83 patients undergoing invasive electrophysiologic study (EPS) for clinical indications. Kaplan-Meier survival analysis revealed that at 20 months of follow-up 81% of the patients who had tested positive for Microvolt T-Wave Alternans had had a ventricular tachyarrhythmic event (sudden death, cardiac arrest, electrocardiographically documented sustained ventricular tachycardia, or ventricular fibrillation) whereas only 6% of patients who tested negative had had such an event. In this study MTWA was equivalent to invasive electrophysiologic testing as a predictor of ventricular tachyarrhythmic events. (Figure 4)

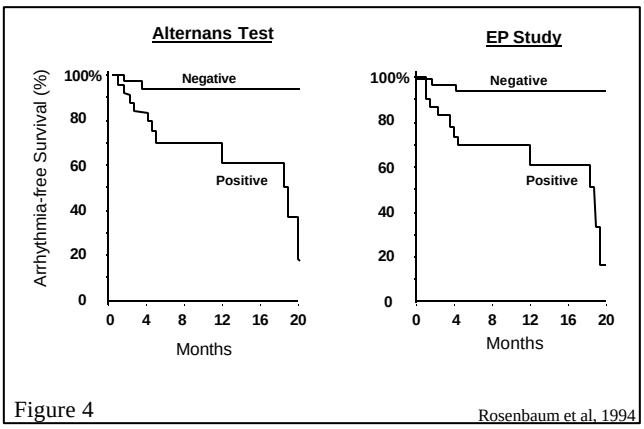


Figure 4

Rosenbaum et al, 1994

Hohnloser SH, Klingenheben T, Yi-Gang L, et al. T-wave alternans as a Predictor of Recurrent Ventricular Tachyarrhythmias in ICD Recipients. J Cardiovascular Electrophysiol 1998; 9: 1258-68.

This study compared Microvolt T-Wave Alternans to 9 other measures of arrhythmic risk in 95 patients receiving implantable cardioverter defibrillators (ICDs) for clinical indications. This population was chosen because the event rate was expected to be high and the ICD served as a 24-hour per day monitor for documenting ventricular tachyarrhythmic events. Of all ten measures only T-wave alternans ($p < 0.006$) and, to a lesser extent, left ventricular ejection fraction ($p < 0.04$) were statistically significant univariate predictors of appropriate ICD discharge (Figure 5). EP testing failed to achieve statistical significance as a predictor of events.

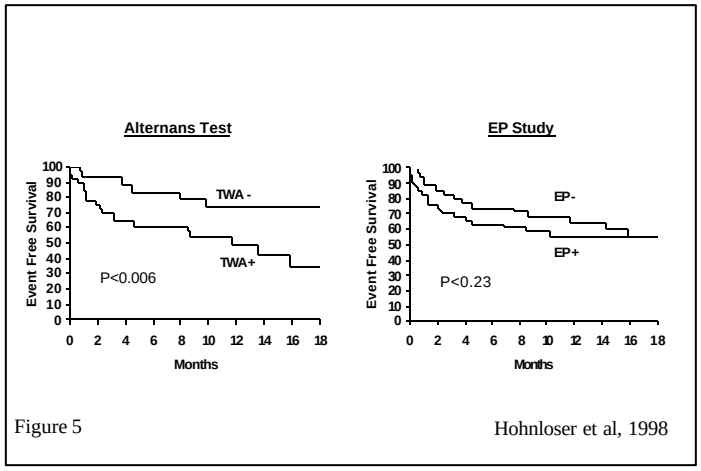
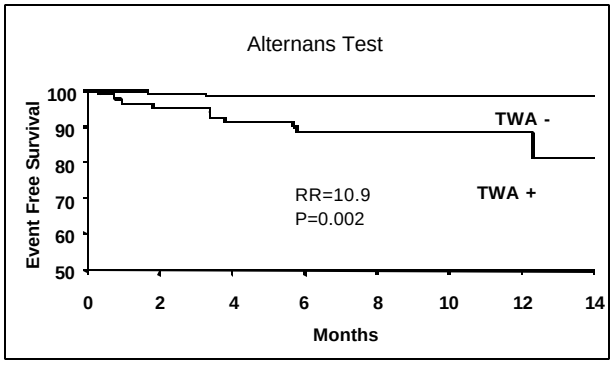


Figure 5 Hohnloser et al, 1998

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.

In this multi-center study conducted for FDA regulatory approval, of 313 patients undergoing electrophysiology study, Microvolt T-Wave Alternans was a highly significant predictor of ventricular tachyarrhythmic events. The relative risk of TWA for arrhythmic events was 10.9 compared to 7.1 for electrophysiologic testing (Figure 6).



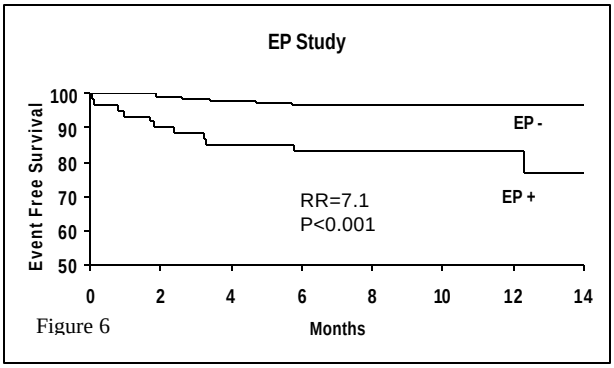


Figure 6

PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION

Klingenheben T, Zabel M, D'Agostino RB, et al. Predictive Value of T-Wave Alternans for Arrhythmic Events in Patients with Congestive Heart Failure. The Lancet 2000; 356:651-52.

This is a study of 107 patients with New York Heart Association class II and III congestive heart failure but with no prior history of sustained ventricular arrhythmias. In this population of patients, Microvolt T-Wave Alternans was a highly significant predictor of ventricular tachyarrhythmic events ($p < 0.0036$) whereas none of the other six measures of arrhythmic risk achieved statistical significance. Not only did MTWA identify a high risk group, but it also identified a very low risk group - in fact, no ventricular tachyarrhythmic events occurred among the MTWA negative patients (Figure 7).

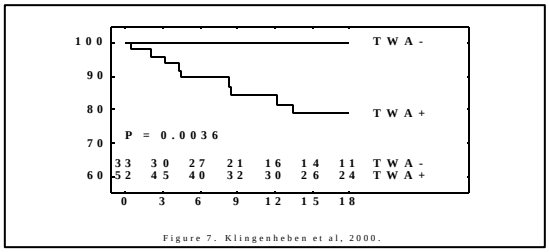


Figure 7. Klingenheben et al, 2000.

Adachi K, Ohnishi Y, Shima T, et al. Determinant of Microvolt T-wave Alternans in Patients with Dilated Cardiomyopathy. J Am Coll Cardiol 1999; 34: 374-80.

This paper examined the ability of Microvolt T-Wave Alternans to predict the occurrence of spontaneous ventricular tachycardia or fibrillation in 58 patients with non-ischemic dilated cardiomyopathy. Microvolt T-Wave Alternans was highly correlated with the occurrence of spontaneous ventricular tachycardia or fibrillation ($p < 0.001$). This patient population is important clinically because invasive electrophysiologic testing is generally not regarded a useful predictor of spontaneous ventricular tachyarrhythmias in this population.

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

This study evaluated 60 patients with cardiomyopathy but nearly normal ejection fractions, in whom absence of coronary artery disease was documented angiographically. MTWA was positive in twelve of the patients; sixteen patients had had sustained ventricular tachyarrhythmic events. Eighty-three percent of MTWA positive patients had had a ventricular tachyarrhythmic event versus 12.5% of TWA negative patients, $p < 0.00001$. Three patients had ventricular tachyarrhythmic events during six-month follow-up, all of whom had had a positive MTWA Test. In a subset of patients studied with electrophysiologic testing, a statistically significant correlation was found between inducibility of tachyarrhythmia and a positive MTWA Test.

Kitamura H, Ohnishi Y, Okajima K, et al. Onset Heart Rate of Microvolt-Level T-Wave Alternans Provides Clinical and Prognostic Value in Nonischemic Dilated Cardiomyopathy. J Am Coll Cardiol 2002; 39:295-300.

In this study of 104 patients with nonischemic dilated cardiomyopathy, Kitamura et al., demonstrated that MTWA was a powerful predictor if events in this difficult to diagnose population. During the 21 month follow up MTWA was the best predictor of events with a positive predictive value of 23.9%, negative predictive value of 97.3% and relative risk of 8.8

COMPARISON OF MTWA WITH INVASIVE EPS

Review of a number of prospective studies conducted in a variety of clinically relevant patient populations, indicates that occurrence of ventricular tachyarrhythmic events in patients with a positive MTWA Test is equivalent to the ventricular tachyarrhythmic event rate among patients with a positive EPS. The event rate among patients with a negative MTWA Test is at least as low, and in many cases lower, than the event rate among patients with a negative EPS (see Tables 1 and 2).

Table 1 Events among MTWA & EP Positives

Study	Patient Population	Follow-Up (months)	TWA+	EP+
Rosenbaum, et al NEJM, 1994	EP	20	81%	~81%
Ikeda, et al JACC, 2000	Post MI	12	28%	
Gold MR, et al FDA, 1999	EP	13	23%	25%
Gold MR, et al JACC, 2000	Known or Suspected Ventricular Arrhythmia (EP)	13	25%	25%
Bloomfield, et al Circ, 1999 (abs)	Syncope (EP)	13	19%	21%
Klingenheben, et al The Lancet, 2000	CHF	18	21%	
Kitamura, et al JACC, 2002	Non-Ischemic DCM	21	24%	
Klingenheben, et al Circ., 2002	Non-Ischemic DCM	12	30%	
Ikeda, et al AJC, 2002	Post MI	24	18%	

Table 2 Events among MTWA & EP Negatives

Study	Patient Population	Follow-Up	TWA-	EP-
Rosenbaum, et al NEJM, 1994	EP	20	6%	~6%
Ikeda, et al JACC, 2000	Post MI	12	2%	
Gold MR, et al FDA, 1999	EP	13	2%	5%
Gold MR, et al JACC, 2000	Known or Suspected	13	3%	8%
Bloomfield, et al Circ, 1999 (abs)	Syncope (EP)	13	3%	6%
Klingenheben, et al The Lancet, 2000	CHF	18	0%	
Kitamura, et al JACC, 2002	Non-Ischemic DCM	21	3%	
Klingenheben,et al Circ., 2002	Non-Ischemic DCM	12	7%	
Ikeda, et al AJC, 2002	Post MI	24	2%	

Conclusion, MTWA is an effective non-invasive predictor of risk of ventricular tachyarrhythmias and sudden death, with an efficacy that appears at least comparable to invasive electrophysiologic testing.

REFERENCES

1. Kleinfeld MJ, Rozanski JJ: Alternans of the ST segment in Prinzmetal's angina. Circulation 1977;55:574-577.

2. Reddy CVR, Kiok JP, Khan RG, El-Sherif N: Repolarization alternans associated with alcoholism and hypomagnesemia. Am J Cardiol 1984;53:390-391.

3. Shimoni Z, Flatau E, Schiller D, Barzilay E, Kohn D: Electrical alternans of giant U waves with multiple electrolyte deficits. Am J Cardiol 1984;54:920-921.

4. Salerno JA, Previtali M, Panciroli C, Klersy C, Chimienti M, Regazzi Bonora M, Marangoni E, Falcone C, Guasti L, Campana C, Rondanelli R: Ventricular arrhythmias during acute myocardial ischaemia in man. The role and significance of R-ST-T alternans and the prevention of ischaemic sudden death by medical treatment. Eur Heart J 1986;7 Suppl A:63-75.

5. Schwartz P, Malliani A: Electrical alternation of the T wave: clinical and experimental evidence of its relationship with the sympathetic nervous system and with the long Q-T syndrome. Am Heart J 1975;89:45-50.

6. Shimizu W, Antelevitch C. Cellular and ionic basis for T-wave alternans under long-QT conditions. Circulation 1999;99:1499-1507.

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

8. Rosenbaum DS, Albrecht P, Cohen RJ. Predicting sudden cardiac death from T-wave alternans: promise and pitfalls. J Cardiovasc Electrophysiol, 1996;7:1095-1111.

9. Konta T, Ikeda K, Yamaki M, Nakamura K, Honma K, Kubota I, Yasui S: Significance of discordant ST alternans in ventricular fibrillation. Circulation 1990;82:2185-2189.

10. 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.

11. 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.

12. Pastore JM, Rosenbaum DS, Role of Structural Barriers in the Mechanism of Alternans-Induced Reentry. Circ. Res. 2000;87:1157-1163.

13. 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.

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. 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.

16. 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.

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. 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.

19. Bloomfield DM, Gold MR, Anderson KP, et all. T-Wave Alternans Predicts Events in Patients with Syncope Undergoing Electrophysiolgic Testing. Circulation 1999; 100: I-508.

20. Kingenheben T, Credner SC, Bender B, Cohen RJ, 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.

21. 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.

22. 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.

23. Ikeda T, Saito H, Tanno K, et al. T-Wave Alternans as a Predictor for Sudden Cardiac Death After Myocardial Infarction. Am J Cardiol 2002; 89:79-82.

24. Kitamura H, Ohnishi Y, Okajima K, et al. Onset Heart Rate of Microvolt-Level T-Wave Alternans Provides Clinical and Prognostic Value in Nonischemic Dilated Cardiomyopathy. J Am Coll Cardiol 2002; 39:295-300.

1 Oak Park Drive
Bedford, MA 01730
www.cambridgeheart.com
888.226.9283

P/N 30-0055-001 Rev B