Review of Key Clinical Literature on Microvolt T-Wave Alternans

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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](image)

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).

![Mechanism Linking TWA to Ventricular Arrhythmias](image)

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


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%)

PATIENTS WITH KNOWN OR SUSPECTED ARRHYTHMIAS (INCLUDING SYNCOPE PATIENTS)


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)

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.


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).
PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION


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).


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.


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.


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

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population</th>
<th>Follow-Up (months)</th>
<th>TWA+</th>
<th>EP+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenbaum, et al NEJM, 1994</td>
<td>EP</td>
<td>20</td>
<td>81%</td>
<td>~81%</td>
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<tr>
<td>Ikeda, et al JACC, 2000</td>
<td>Post MI</td>
<td>12</td>
<td>28%</td>
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<td>Klingeneheben, et al The Lancet, 2000</td>
<td>CHF</td>
<td>18</td>
<td>21%</td>
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<tr>
<td>Kitamura, et al JACC, 2002</td>
<td>Non-Ischemic DCM</td>
<td>21</td>
<td>24%</td>
<td></td>
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<tr>
<td>Klingeneheben, et al Circ., 2002</td>
<td>Non-Ischemic DCM</td>
<td>12</td>
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</table>
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


