

# Microvolt T-wave alternans in patients undergoing elective coronary artery bypass grafting: a pilot study

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## ABSTRACT

**Introduction:** We designed a prospective observational study targeting a selective population of patients undergoing elective coronary artery bypass grafting with normal systolic function. In this study we looked at the prevalence of pre-operative microvolt T-wave alternans and if it predicts atrial fibrillation after surgery.

**Methods:** The inclusion criteria included all patients referred to the cardiothoracic outpatient clinic for elective bypass, who can perform aerobic exercise, with a recent exercise stress test exercising at least to 85 % of the maximal predicted heart rate (220 - age) and with non-limiting chest pain at maximal exercise. Twenty patients met the inclusion/exclusion criteria between May 2008 and February 2010. The hospital course of those patients was followed, and in-hospital events were recorded.

**Results:** Nine out twenty (45 %) of patients had a non-negative microvolt T-wave alternans tracing. Six patients (30 %) developed new onset atrial fibrillation post surgery. Patients with non-negative microvolt level T-wave alternans are more likely to develop atrial fibrillation post coronary artery bypass grafting than patients with negative microvolt level T-wave alternans ( $p = 0.05$ ).

**Conclusions:** This pilot study provides the first clinical evidence that patients with ischemic heart disease and normal systolic function have a high prevalence of abnormal microvolt T-wave alternans and might be at higher risk of sudden cardiac death. In addition our results show that microvolt level T-wave alternans predicts post coronary artery bypass grafting new onset atrial fibrillation.

**Keywords:** microvolt T, wave alternans, atrial fibrillation, sudden cardiac death.

## INTRODUCTION

T-wave alternans is characterized by beat-to-beat change in the morphology, amplitude and/or polarity of the T wave. Microvolt level T-wave alternans (MTWA) has been proposed to assess the abnormalities in ventricular repolarization, which favors the occurrence of reentrant arrhythmias (1). In 1994, a first clinical study by Rosen-

baum and coworkers demonstrated that MTWA is closely related to arrhythmia induction in the electrophysiology laboratory as well as to the occurrence of spontaneous ventricular tachyarrhythmias during follow-up (2, 3). Microvolt TWA analysis has been implicated as one of the strongest predictors of ventricular arrhythmias and sudden cardiac death (also superior to other non-invasive markers of ventricular repolarization, such as QTc interval prolongation) in several trials including patients with myocardial infarction, heart failure and implantable defibrillators (3 -5). Two main hypotheses have been proposed for

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the mechanism of MTWA, the action potential restitution and the calcium cycling hypothesis. There is considerable experimental and clinical trials that do not support the restitution hypothesis (6, 7) on the other hand there is considerable evidence to support the abnormal calcium cycling hypothesis (8).

Patients undergoing elective coronary artery bypass grafting (CABG) tend to be relatively healthy and subsequently their surgery is significantly delayed when compared to urgent cases. The cumulative pre-surgical risk of death from cardiovascular disease was found to be similar in the semi-urgent and elective CABG cases due to the longer wait for surgery in the later group (9). The in-hospital death was also shown to be significantly higher when the surgery is delayed beyond the recommended time of 12 weeks in non-urgent cases (10). However there is no data that reports on the risk of sudden cardiac death in elective CABG patients with no structural heart disease. Also, none of the studies looked at the prevalence of MTWA as a predictor of sudden cardiac death (SCD) in this population.

Also, in patients undergoing CABG, new onset post operative atrial fibrillation (Afib) is a very common complication (11). Patient with this complication were found to have a significant higher mortality at 10 years of follow up (11). Recently Afib was linked to abnormal calcium handling, a mechanism proposed for abnormal MTWA tracing (12, 13). Although MTWA and Afib may share a similar underlying mechanism, there are no reports on the risk of new onset Afib in patients with abnormal T wave alternans testing.

We designed a prospective observational study targeting a selective population of patients undergoing elective CABG with normal systolic function. In this study we looked at the prevalence of pre-operative MTWA. We followed these patients

throughout their hospital stay and looked at the incidence of new onset Afib in patients with normal and abnormal MTWA tracing.

## METHODS

This study was conducted at a 700 bed University Affiliated urban teaching hospital. It is an observational study. The institutional review boards approved the study protocol. All patients signed an informed consent after a detailed explanation of the study aim and purpose. The inclusion criteria included all patients referred to the cardiothoracic outpatient clinic for elective CABG, who can perform aerobic exercise, and agree to have a MTWA testing prior to the scheduled surgery. Since MTWA testing involves a submaximal treadmill exercise test, and our population involves patients with significant coronary artery disease (CAD), we pre-specified a safety measure in our protocol. We only considered patients with a recent exercise stress test who reached at least 85% of the maximal predicted heart rate (220 - age) and non-limiting chest pain at maximal exercise. The exclusion criteria included any of the following criteria; age less than 18, pregnancy, left ventricular ejection fraction (LVEF) less than 50%, Patients on any antiarrhythmic medications, baseline electrolyte abnormalities, known history of atrial fibrillation, stage 5 chronic kidney disease (CKD), and inability to perform a submaximal treadmill test.

The patients were recruited between May 2008 and February 2010 at an outpatient cardiothoracic office at Staten Island University Hospital. In this study we used the Heartwave System (Cambridge Heart Inc., Cambridge, MA, USA). Heartwave® II System detects the presence of MTWA By electrocardiogram (EKG) measurements during rest, exercise, and then rest again. Fourteen

sensors - 7 Micro-V Alternans Sensors and 7 standard electrodes - are placed in the Frank-lead configuration. The electrodes are connected to the digital EKG amplifier that leads back to the MTWA enabled system.

After checking the system for correct lead placement, the patient is directed to begin walking on a treadmill to raise the heart rate. The exercise part consists of two levels. The first aims to maintain the heart rate at 100-110 bpm for a total 90 seconds, while the second goal is to achieve a heart rate of 110-120 for the same time interval. The total time of submaximal exercise can range between 5-10 minutes to achieve and adequate recording. The patients were instructed to hold calcium channel blockers or beta-blockers on the day of testing to achieve adequate heart rate with minimal exercise.

Based on the previously defined criteria by Bloomfield et al., MTWA tracing was interpreted as either negative or non-negative which included patient with positive or intermediate tracing (14). Studies have well shown that intermediate and positive MTWA tracing, have similar prognostic value (15, 16). Each test was analyzed by the same electrophysiologist (cardiologist),

and confirmed by a trained technician from the company, who was blinded to the study and patients.

The hospital course of all patients included in the study was followed, and in-hospital events were recorded. This included, post surgery Afib, sustained ventricular tachycardia, ventricular fibrillation, cardiac arrest, arrhythmias requiring anti-arrhythmic treatment, and hospital death.

In order to assess the prevalence of atrial fibrillation in patients with a non-negative MTWA we divided the sample into two groups. The first involved all patients with non-negative test MTWA (+), while the second included all with a negative test MTWA (-). We also studied variables that were shown to predict atrial fibrillation post CABG. Based on a study done by Amar et. al, 4 variables were shown to predict Afib post CABG. These included older age, prior history of Afib, P-wave duration > 110 ms on surface EKG, and low cardiac output defined as cardiac index < 2 l/min/m<sup>2</sup> for > 8 h after surgery (17). In that study a point score was developed to predict the probability of post CABG Afib. In our study we used this validated score to compare the risk of post-CABG Afib in the MTWA groups (*Table 1*).

**Table 1 - Clinical characteristic and outcome by Microvolt T-wave Alternans (MTWA) groups.**

|                              | MTWA (+) test<br>(n = 9) | MTWA (-) test<br>(n = 11) | p-value |
|------------------------------|--------------------------|---------------------------|---------|
| History of MI                | 1 (11%)                  | 3 (27%)                   | 0.4     |
| History of DM                | 3 (33%)                  | 4 (36%)                   | 1.0     |
| GFR (ml/min/m <sup>2</sup> ) | 75* (35-105)**           | 90* (43-115)**            | 0.1     |
| Ejection fraction (%)        | 58* (50-70)**            | 58* (55-65)**             | 0.8     |
| Post CABG Afib               | 5 (55%)                  | 1 (9%)                    | 0.05    |
| Point score                  | 68* (50-80)              | 64* (45-80)**             | 0.3     |
| for risk of post CABG Afib   |                          |                           |         |
| Post CABG cardiac arrest     | 1 (11%)                  | 0 (0%)                    | 0.4     |

\*Mean, \*\*Range

MTWA = Microvolt level T-wave alternans; MI = myocardial infarction; DM = diabetes mellitus; GFR = glomerular filtration rate; CABG = coronary artery bypass graft; Afib = atrial fibrillation.

*Statistical analysis.* Continuous variables were expressed as a mean  $\pm$  standard deviation (SD) and were compared using an unpaired two-tailed Student's t-test.

Unpaired categorical variables were compared using Fisher's exact test. A probability cutoff of  $p < 0.05$  was considered significant for all statistical determinations.

A multivariate logistic regression model was used to evaluate the independent contribution of baseline clinical characteristics to the development of the end point in a forward stepwise manner.

At each step, a significance of 0.10 was required to enter into the model while those with probabilities less than 0.05 were considered statistically significant. All analyses were performed using SPSS 19.0 (SPSS Inc., Chicago, IL).

## RESULTS

Sixty three patients were initially considered for enrollment. Only 36 met the inclusion criteria that were specified in our study protocol. Out of those, twenty four consented and were further followed. Of the 24 patients, 4 did not show up on the day of the MTWA testing and were dropped out of the study. The characteristics of the studied sample population are listed in *Table 2*. The mean age was  $62.3 \pm 10.97$  years. The majority were male (90%), and white (75%). Hypertension and hyperlipidemia were highly prevalent (90%). The average number of bypassed vessels was 3.5.

The median and mean time elapse from coronary angiography to bypass surgery was 29 and 23 days, respectively. All MTWA tests were performed within a week prior to the scheduled surgery. The results are shown in *Table 1*. Nine out twenty (45%) patients had a non-negative MTWA tracing. The mean age of MTWA (+) group was 64 years slightly older than the MTWA

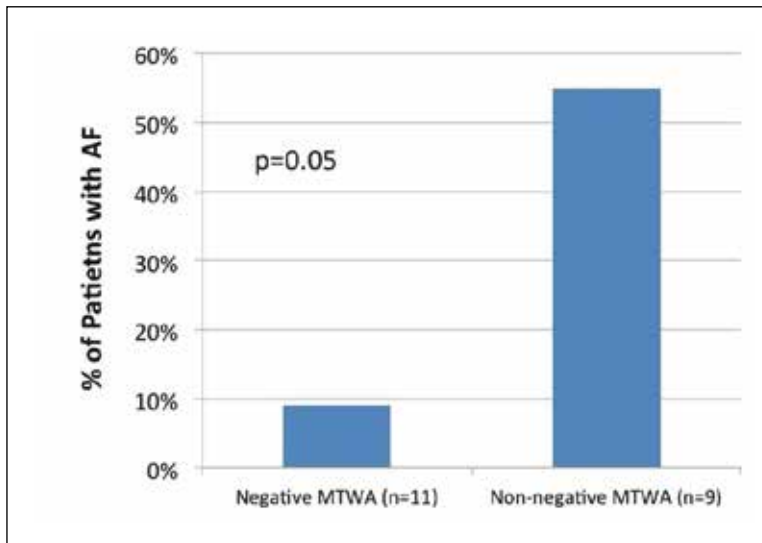
**Table 2 - Demographics and hospital events.**

| <b>Demographics</b>                |              |                |
|------------------------------------|--------------|----------------|
| <b>Sex</b>                         | <b>Count</b> | <b>Percent</b> |
| Male                               | 18           | 90 %           |
| Female                             | 2            | 10 %           |
| <b>Race</b>                        |              |                |
| White                              | 15           | 75 %           |
| All Other                          | 5            | 25 %           |
| <b>Past Medical History</b>        |              |                |
| Hypertension                       | 18           | 90 %           |
| History of dysrhythmias            | 0            | 0 %            |
| Diabetes Mellitus                  | 7            | 35 %           |
| Hyperlipidemia                     | 18           | 90 %           |
| Myocardial Infarction              | 4            | 20 %           |
| History of atrial fibrillation     | 0            | 0 %            |
| <b>Medications</b>                 |              |                |
| Beta Blocker                       | 16           | 80 %           |
| Aspirin                            | 18           | 90 %           |
| Clopidogrel                        | 12           | 60 %           |
| ACE/ARB                            | 13           | 65 %           |
| CCB                                | 4            | 20 %           |
| <b>Social History</b>              |              |                |
| Smoking                            | 13           | 65 %           |
| <b>Post Surgical Complications</b> |              |                |
| Cerebrovascular Accident           | 0            | 0 %            |
| Atrial Fibrillation                | 6            | 30 %           |
| Myocardial Infarction              | 0            | 0 %            |
| Asystole                           | 1            | 5 %            |

ACE = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker.

(-) group which was 61years. Diabetes mellitus (DM) and prior history of myocardial infarction (MI) was slightly higher in the MTWA (-) group. The mean glomerular filtration rate was lower in the MTWA (+), but none of the patients had a stage 5 CKD, as this was one of the exclusion criteria. The Point score that predicts the risk of post CABG Afib was similar in both groups (*Table 1*).

All patients were followed throughout the hospital course. The mean hospital stay



**Figure 1** - The incidence of post-coronary artery bypass graft atrial fibrillation by Microvolt T-wave Alternans (MTWA) groups. AF = atrial fibrillation.

was 4 and 7 days among MTWA (-) and MTWA (+) groups, respectively. The hospital stay did not differ between the 2 groups. There was no in-hospital death. One patient in the MTWA (+) group had a cardiac arrest post surgery and was successfully resuscitated. There were no events of sustained ventricular tachycardia or ventricular fibrillation in both groups. One (9%) patient with negative MTWA developed AF in comparison to 5 (55%) patients with non-negative MTWA. Patients with non-negative MTWA are more likely to develop AF post CABG than patients with negative MTWA ( $p = 0.05$ ) (Table 1, Figure 1). In multivariate logistic regression, a non-negative MTWA was the only predictor of AF ( $p = 0.042$ ). Two patients with Afib required electrical cardioversion, while the others were converted chemically. Finally we looked at the 30 months mortality using the national death registry. There was no reported death in any of the groups.

## DISCUSSION

In MADIT-2 trial MTWA was shown to have a better risk stratification for SCD

when compared to QRS duration on EKG in patients with ischemic heart disease (18). In several studies, MTWA was shown to have a prognostic value after acute myocardial infarction (19, 20).

In our study we found that the prevalence of abnormal MTWA is very high when compared to previous reports on healthy adults. In this study we aimed to assess the prevalence of abnormal cardiac repolarization in patients with ischemic heart disease scheduled for elective CABG. All of our patients had a systolic function of more than 50%, and none of them had a significant CKD as we specified in our study protocol (Table 1). The reported prevalence of abnormal MTWA in healthy adults ranged between 4 and 5% (21, 22). Post MI it was reported to be abnormal in up to 44% of patients (20). Abnormal MTWA was also reported to be high in diabetics, in patients with uremic cardiomyopathies, and in patients on hemodialysis (23-27). Neither ischemic, nor uremic cardiomyopathy can explain the high prevalence of abnormal MTWA in our studied population (45%). Moreover, looking at other potential clinical predictors for abnormal MTWA, there was more patients with history of DM and prior MI in the

MTWA (-) group. In the MTWA (+) group, one patient had history of MI, and 3 had DM. None of those patients had a concomitant history of MI and DM. On the other hand in the MTWA (-) group, three had a prior history of MI, and 4 were diabetic. Of those, two had DM and MI. There was no statistically significant difference in any of the known clinical predictors of abnormal MTWA in both groups (*Table 1*). For this reason, although DM and prior history of MI could have contributed to the MTWA test results in this population, it does not exclusively explain the high prevalence noted in our population.

Animal studies have shown that regional myocardial ischemia in structurally normal hearts can lead to regional action potential alternans (28, 29). This can lead electrical dispersion and arrhythmias (29). Regional Ischemia induced by exercise might explain the prevalence of abnormal MTWA in this population. There are no previous studies that looked at MTWA as a predictor of SCD in patients with ischemia but normal systolic function. One patient with abnormal MTWA tracing had a post surgical asystole, and was successfully resuscitated. There was no recorded death in both groups at 30 months of follow up.

Although our observation may suggest that patients awaiting elective CABG are at high risk of arrhythmias and SCD, Further studies are needed to assess the potential risk in this population before drawing further conclusion.

The incidence on new onset atrial fibrillation post CABG varies between 11% and 40% depending on the study cohort and method of detection used (11, 30). In this study we excluded patients with history of Afib. Post-op, 30% of patients developed new onset atrial fibrillation. Interestingly, most of those had an abnormal MTWA tracing. Patients with non-negative MTWA are more likely to develop atrial fibrillation

(AF) post CABG then patients with negative MTWA with a significant p value ( $p = 0.05$ ) (*Table 1, Figure 1*). In multivariate logistic regression, a non-negative MTWA was the only predictor of AF ( $p = 0.042$ ).

There is growing evidence that links atrial fibrillation to abnormal calcium handling/calcium alternans (12, 13). Similarly, there are considerable evidence that abnormal calcium cycling/calcium alternans is the mechanism behind action potential and T wave alternans. Since MTWA tracing in patients with atrial fibrillation is not feasible, no studies have looked at the prevalence of abnormal MTWA in patient with Afib. Also there no previous reports on the risk of new onset Afib in patients with abnormal T wave alternans testing. Knowing that both Afib and abnormal MTWA might have a common electrical mechanism, this study presents the first direct link between the two. We think that the risk of post-CABG atrial fibrillation might be further stratified by pre-CABG MTWA in groups with comparable other risk scores. Although this finding is very interesting we only suggest a potential association between abnormal MTWA and Afib, and further studies with more patients are needed to consolidate our finding.

There are several limitations to this study. The sample size is small and limits us from generalizing our results. Although this is a significant limitation we think that our results are very interesting to report especially that we targeted a very specific group of patients.

We had many exclusion criteria to assure patient safety, which limited our ability to recruit a larger sample. A multicenter study will be needed to recruit a larger and more representative sample. Another limitation is that the prognosis of abnormal MTWA testing is not well established in patients with ischemic heart disease with normal systolic function. For this reason even with

this high prevalence of abnormal MTWA results, the risk of SCD is still unknown. Furthermore, there was no difference in mortality at any interval follow up in both groups. For this reason no assumption can be drawn on the risk of SCD in this population until we have more data.

## CONCLUSION

This pilot study provides the first clinical evidence that patients with ischemic heart disease and normal systolic function have a high prevalence of abnormal MTWA and might be at higher risk of SCD.

In addition our results shows that MTWA predicts post CABG new onset atrial fibrillation. MTWA might be studied as a potential factor in future Afib risk scores. Despite our interesting findings, we suggest a multicenter study with a larger representative sample to confirm our findings.

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