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Microvolt T-Wave Alternans for Sudden Death Risk Stratification in Congestive Heart Failure

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Various studies have demonstrated that automatic implantable cardioverter-defibrillators (ICDs) reduce the risk of sudden cardiac death (SCD) in patients with heart failure. However, identifying which high-risk patients may benefit from an ICD is sometimes problematic. T-wave alternans (TWA) refers to alternating T-wave morphology on electrocardiogram (ECG). It is caused by various cardiac disturbances and linked with ventricular arrhythmias. This issue of *Cardiology Rounds* describes the changes in cardiac function that lead to the formation of T-wave alternans and how its presence may be used for risk stratification when determining which patients would benefit from ICD prophylaxis. The results of various clinical trials that have investigated microvolt TWA as a risk predictor of mortality are also presented.

Sudden cardiac death is estimated to comprise approximately half of the total annual incidence of cardiac mortality in North America.[1] The majority of SCDs are caused by ventricular arrhythmia, with acute myocardial ischemia generally considered the most common factor triggering these events. Epidemiological studies indicate that coronary artery disease and its consequences cause 80% of fatal arrhythmias, with dilated and hypertrophic cardiomyopathies accounting for the next largest proportion.[2] Left ventricular (LV) dysfunction and heart failure are both important predictors of the risk of sudden arrhythmic death (Figure 1). Clinical trials have demonstrated that antiarrhythmic drug therapy has only limited efficacy in reducing mortality for patients deemed at high risk for SCD.[2]

Automatic ICDs continuously monitor heart rhythm and deliver appropriate electrical therapy upon detection of a sustained ventricular arrhythmia. Implantation of these devices for survivors of cardiac arrest (ie, secondary prophylaxis) has been shown to prolong life and has been the standard of care for these patients for some time.[3] Survival after an out-of-hospital cardiac arrest is <5%, and this dismal prognosis provides a strong impetus to identify high-risk patients in order to implant an ICD *before* they experience a lethal arrhythmia (ie, primary prophylaxis).

The Multicentre Automatic Defibrillator Implantation Trial (MADIT), published in 1996, randomized 196 high-risk patients (eg, those with prior myocardial infarction [MI], LV ejection fraction [LVEF] ≤ 35%, asymptomatic nonsustained ventricular tachycardia [NSVT], and inducible VT on electrophysiologic study), to prophylactic ICD versus antiarrhythmic therapy. With 2 years of follow-up, the study was positive in favour of the ICD arm, with absolute and relative risk reductions of 25% and 56%, respectively.[4]

Three years later, the Multicenter Automatic Defibrillator Implantation Trial (MUSTT) was published. In this study, investigators randomized similarly high-risk patients,(eg, those with prior MI, LVEF ≤ 40%, NSVT, inducible VT on electrophysiologic study) to electrophysiologically-guided therapy (antiarrhythmic or ICD) versus conventional treatment. In the former arm, antiarrhythmic drugs were tested first and, at the physician's discretion, nonresponders received ICDs. A significant decrease in mortality was observed in the electrophysiologic study-guided therapy arm, and subgroup analysis revealed that the benefit was entirely due to the use of the ICDs. The robustness of these findings mirror those of MADIT, with a 30% decrease in absolute risk and 55% decrease in the relative risk.[5]

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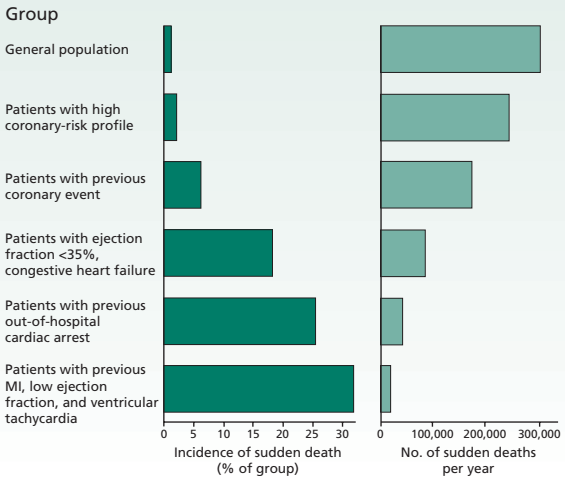
Figure 1: Predictors of sudden arrhythmic death



CHF = congestive heart failure; VT = ventricular tachycardia
SCD = sudden cardiac death; MI = myocardial infarction

The patient population that would benefit from ICD therapy expanded dramatically in 2002 with the publication of the MADIT-II study. This study randomized 1232 patients with a prior MI and systolic dysfunction (LVEF <30%) to ICD versus conventional therapy. After 2 years of follow-up, a significant reduction in total mortality was found in the ICD arm (hazard ratio 0.69, p = 0.02).[6]

Complementing these findings 3 years later was the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) that extended the survival benefit from ICDs to patients with systolic heart failure due to any etiology. Inclusion criteria for SCD-HeFT were LVEF ≤ 35% and New York Heart Association (NYHA) class II or III symptoms. Patients were randomized to conventional therapy (with or without amiodarone) or prophylactic ICD insertion, with all-cause mortality as the primary endpoint.[7] After 5 years of follow-up, there was a significant survival benefit in the ICD arm (hazard ratio = 0.77, p = 0.007). The benefit was present whether the etiology of heart failure was ischemic or nonischemic.

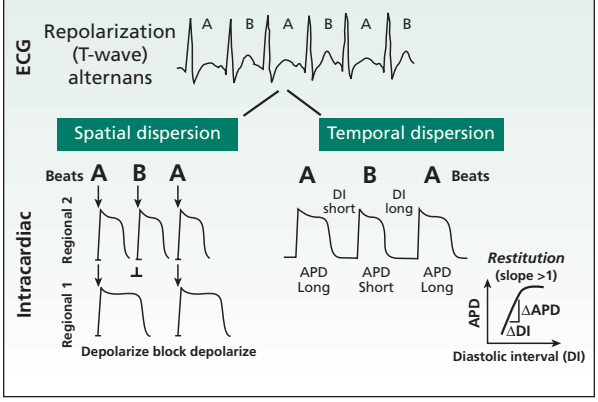
The results of MADIT-II and SCD-HeFT spurred a proliferation of research into risk-stratifying modalities that could help refine which heart failure patients were truly at the highest risk for SCD and who would therefore derive the most benefit from a prophylactic ICD.

Microvolt T-wave alternans

T-wave alternans refers to alternating T-wave morphology in sequential beats on the ECG. It is also called "repolarization alternans." Visible TWA was first reported in the early 1900s in patients during episodes of tachycardia and, subsequently, was reported in patients with ischemia, the long-QT syndrome, and electrolyte disturbances, and it has been consistently linked with ventricular arrhythmias.[8]

The technique for measuring microvolt T-wave alternans (MTWA) was developed to detect fluctuations in

Figure 2: Mechanisms underlying T-wave alternans



T-wave morphology at levels far below those observed on visual inspection of the ECG.

The presence of MTWA is believed to be related to alternations in action-potential duration in localized regions of the myocardium. This gives rise to localized delayed recovery on an alternate-beat basis.[9] The subsequent spatial dispersion of recovery leads to the fractionation of depolarization wave fronts and the development of re-entry. Spatial variations in repolarization (and therefore action potential duration) may prevent depolarization of myocytes that are still repolarizing from their last cycle (Figure 2). This can result in alternans behaviour, but can also lead to unidirectional block at sites of delayed repolarization, thus facilitating re-entry.[10] Animal studies have demonstrated that pro-arrhythmic events such as extrasystoles and ischemia can cause repolarization alternans by exaggerating spatial gradients in repolarization.[11]

In addition to spatial dispersion, TWA may also result from a complementary mechanism of *temporal* dispersion of repolarization (Figure 2). This refers to alternans of action potential duration, and is facilitated by the mechanism of *steep action potential duration restitution*.[12] Action potential duration (APD) restitution describes the relationship between the APD of one beat and its preceding diastolic interval (DI). When APDs are relatively long in comparison to the antecedent DI, the restitution slope is steep and, in this setting, small changes in DI cause large fluctuations in APD that facilitate alternans. Under the right conditions, this may lead to wave front fractionation and ventricular fibrillation.[9]

T-wave alternans is known to occur during tachycardia yet, the lower the heart rate at its onset, the higher the arrhythmic risk. Because TWA is heart rate-dependant, MTWA is usually measured while the heart rate is elevated for several minutes by means of exercise or cardiac atrial pacing. A positive test result occurs when TWA is sustained for >1 minute and occurs below an onset-heart rate of 110 beats/min (BPM). The test is negative in the absence of sustained TWA, as long as a heart rate >105 BPM is achieved. Tests that do not qualify as either "positive" or "negative" are classified as "indeterminate."[9]

While exercising is a more convenient strategy, pacing has been shown to reduce the number of indeterminate tests and prevent rate fluctuations that can falsely elevate TWA.[13] An MTWA test can be conducted by a trained technician in approximately 30 minutes, including the preparation of the patient. For the purpose of risk stratification, the important dichotomy in an MTWA result is *normal* vs *abnormal*. The former portends a good prognosis while, frankly, both a positive, as well as an indeterminate test, confers a higher risk for malignant arrhythmia.

MTWA clinical trial data

• In 2003, the results of a prospective study examining MTWA as a risk predictor in patients with nonischemic dilated cardiomyopathy (NIDCM) were published. The study population consisted of consecutive patients, all with NIDCM, who were referred to the Heart Failure clinic at J.W. Goethe University in Germany and underwent risk stratification for SCD with noninvasive modalities, including LVEF, Holter monitoring, baroreflex sensitivity assessment, signal-averaged ECG, and MTWA.[14] The primary endpoint was SCD, resuscitated cardiac arrest, or hemodynamically significant ventricular tachycardia. Mean follow-up was 14 months and 137 patients were enrolled. After multivariate analysis, MTWA was found to be the only independent predictor of arrhythmic events. Notwithstanding that this was a small, single-centre study, these findings were important in implicating the potential utility of MTWA as a risk stratification modality for malignant arrhythmia in patients with heart failure. The fact that the patients all had NIDCM is also of interest, since this is a patient population in which invasive electrophysiological testing is likely of fairly limited value.[15]

• The publication of the MADIT-II trial resulted in much controversy since it determined that patients with ischemic cardiomyopathy and an LVEF of ≤30% had decreased mortality when implanted with an ICD for primary prophylaxis. The cardiology community struggled with the implications of the findings of this trial in terms of financial, public health, legal, and ethical considerations. There was, therefore, substantial pressure to look for risk-stratifying factors to select patients from within the large MADIT-II population who would benefit the most from ICD implantation. A multivariate analysis of MADIT-II found that a QRS duration of >120 ms in this population was an independent predictor of mortality, with a hazard ratio of 1.90 (95% confidence interval (CI), 1.14 - 3.14, p=0.013).[16] Based on these data, the United States Centers for Medicaid and Medicare Services (CMS) made the decision to limit its funding of primary ICD insertion to patients with MADIT-II criteria, in whom QRS duration was >120 ms, since these would represent the highest risk stratum.[17]

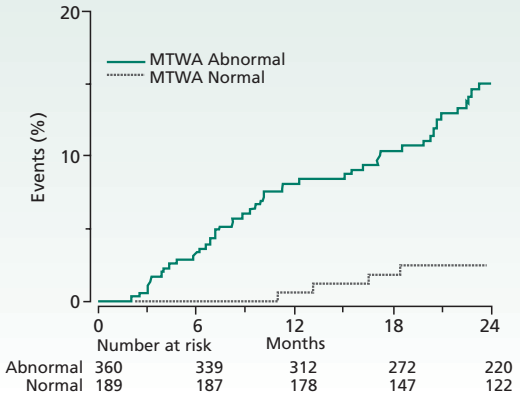
• In 2004, Dr Daniel Bloomfield et al at Columbia University, New York, published a paper that proposed a solution to the risk stratification conundrum caused by the MADIT-II trial. The group conducted a multicentre prospective study on the prognostic significance of MTWA in patients with LV dysfunction. These investigators, therefore, performed an analysis on a subgroup of their study patients, in those who would have met the MADIT-II entry criteria (ie, ischemic cardiomyopathy, LVEF ≤30%, >30 days post-MI, or >3 months post-revascularization).[18] They analyzed 177 patients, all of whom had exercise MTWA tests, with the results dichotomized as either normal (negative) or abnormal (positive or indeterminate). Their endpoint was all-cause mortality.

The QRS duration was >120 ms in 32% of the patients, while the MTWA test was abnormal in 68%. The 2-year actuarial mortality rate for patients with abnormal MTWA (17.8%) was significantly greater than for those with a normal result (3.8%, hazard ratio 4.8, p=0.02). Interestingly, the mortality rate for patients with a QRS duration of >120 ms (15.9%) was not significantly different than that for patients with a normal QRS duration (12.0%, p=0.367 hazard ratio 1.5, p=0.367). On the other hand, the mortality rate was substantially lower amongst patients with a normal MTWA test (3.8%) compared to those with a normal QRS (12.0%), suggesting that the negative predictive value of a normal MTWA test is superior to that of a QRS duration <120 ms. Of the 12 patients with normal QRS duration that died in this study, 11 had abnormal MTWA tests. Finally, in a multivariate Cox model, MTWA remained a strong predictor of mortality (hazard ratio 4.7, p=0.012) after adjusting for QRS duration.

Based on these results, the authors concluded that the CMS strategy of using QRS duration to determine funding eligibility for ICD in MADIT II-type patients was flawed, since its implicit assumption – that a normal QRS duration confers low-risk – appeared erroneous. MTWA not only identified high-risk patients, but was far superior to QRS duration in identifying low-risk patients, who would be unlikely to benefit from an ICD. In the MADIT-II trial, 18 ICDs had to be implanted to save 1 life. Bloomfield et al calculated that if an ICD was denied to patients with normal MTWA tests in the trial, only 7 ICDs would need to be implanted to save 1 life.[1]

• In 2006, the results of a large prospective trial by Bloomfield et al on the use of MTWA in the risk stratification of patients with LV dysfunction was published. These investigators hypothesized that MTWA improved the selection of patients for ICD prophylaxis, especially by identifying those who were unlikely to benefit.[19] The study was conducted at 11 centres in the US and patients were eligible if they had an LVEF that was ≤40%, no history of sustained arrhythmia, and were in sinus rhythm. All participants underwent an exercise MTWA test and were then followed for 20 months. The primary outcome was all-cause mortality or nonfatal sustained ventricular arrhythmia; 549 patients were included in the final analysis, 50% of whom had ischemia cardiomyopathy. The average LVEF of the entire cohort was 25%. All comparisons were made between normal (negative) MWTA tests and abnormal (positive or indeterminate)

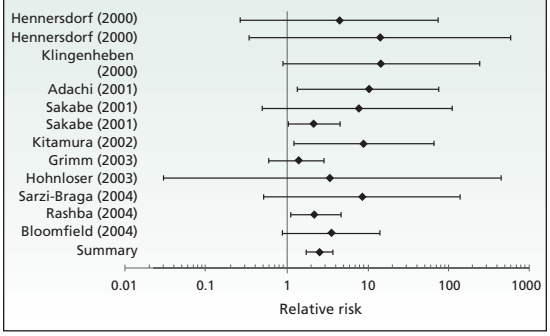
Figure 3: Kaplan-Meir mortality curves for patients with normal versus abnormal microvolt T-wave alternans (MTWA)[19]



tests. Sixty-six per cent of the patients had an abnormal MTWA test and their actuarial 2-year actuarial event rate was 15.0%, versus 2.5% for those with a normal test (hazard ratio 6.5, p<0.001) (Figure 3). There were no significant interactions with MTWA and other risk predictors (including LVEF, QRS duration, and functional class), indicating that MWTA is a robust risk predictor amongst various subgroups. The authors concluded that in patients with systolic dysfunction, MWTA can identify not only patients at high-risk for arrhythmic events, but also, more importantly, those truly low-risk patients who are unlikely to have an arrhythmic event over the next 2 years.

• In 2005, a group from Mount Sinai Hospital (New York) published a meta-analysis of studies evaluating the predictive value of exercise-induced MTWA for risk stratification of arrhythmic events.[20] These investigators examined 19 prospective studies published between 1990 and 2004; the result was an aggregate number of patients totaling 2,608. To be included in the meta-analysis, studies had to meet the following criteria: they were prospective cohort studies in >10 subjects who underwent exercise-induced MTWA testing for the prediction of cardiac death or ventricular arrhythmias; they provided primary data on results of MTWA and of clinical outcomes, including SCD, cardiac death, ventricular arrhythmias, and/or ICD shock; they provided a clear definition of normal or abnormal MTWA testing; and their follow-up time was ≥6 months. In the subgroup of patients with heart failure, the positive predictive value (PPV) during the average 18-month follow-up was 25%, and the negative predictive value (NPV) was 94%. As shown in Figure 4, abnormal MTWA increased the risk of adverse clinical outcomes. There was no significant difference in predictive values between ischemic or nonischemic heart failure. The positive predictive value varied significantly depending on the population being studied (Figure 5). Similarly, the negative

Figure 4: Summary estimates of the relative risk of abnormal microvolt T-wave alternans in subjects with congestive heart failure[20]



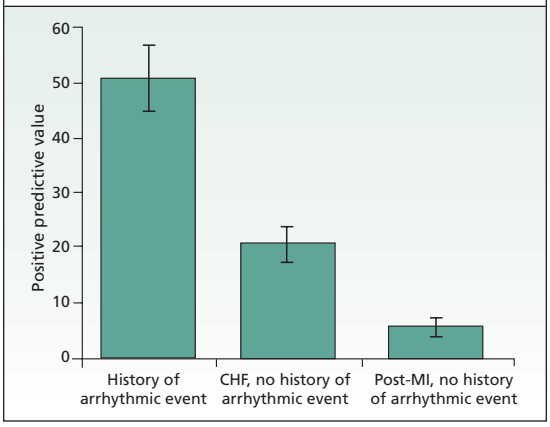
predictive value was even more robust (98%) when examining heart failure patients with no history of arrhythmia. The authors concluded that the negative predictive value of exercise-induced MTWA is excellent, while its positive predictive value is very dependant on baseline risk.

The current state of affairs

The 2005 American College of Cardiology/American Heart Association guidelines for the management of congestive heart failure have designated – as a Class I recommendation – that ICDs be offered to patients with LVEFs <30% if they have NYHA II or III symptoms.[21] This recommendation is obviously driven by the strongly positive MADIT-II and SCD-HeFT trials that demonstrated that patients with marked systolic dysfunction are at appreciable risk for dying suddenly. The problem is that these patients are also at increased risk for nonarrhythmic death and, as both functional class and systolic dysfunction deteriorate, the risk of death from pump failure may actually exceed that from fatal arrhythmia.[22] Furthermore, ICD implantation is invasive, expensive, and its effect on quality of life is neutral, and potentially even negative due to the risk of inappropriate shocks. In the post-SCD-HeFT era, the question cardiologists will face more frequently is not which heart failure patients need an ICD but, conversely, who does *not* need one. By detecting patients who are unlikely to benefit from an ICD because their baseline risk is low, resources could be directed towards more high-risk patients.

MTWA, with its excellent negative predictive value, appears to be a promising modality for detecting patients who are truly low-risk, at least over a 2-year period. This is contrary to QRS duration, which, while identifying high-risk patients, does *not* portend a low annual mortality in patients with a normal value. A reasonable approach may be one in which heart failure patients with normal MTWA studies have ICD implantation deferred, with repeat assessments done at 2-year intervals.

Figure 5: Positive predictive value of abnormal microvolt T-wave alternans in three populations of subjects[20]



CHF = congestive heart failure; MI = myocardial infarction

Conclusion

Over the past decade, it has become increasingly apparent that ICDs can prolong life in patients with systolic heart failure who have never had an episode of lethal arrhythmia. While LV function is an important predictor of SCD, it also confers a significant risk of nonarrhythmic death. MTWA provides a measure of the actual arrhythmic substrate of the heart and is, therefore, a much more precise tool. It appears to hold promise as a risk marker, particularly since its high negative predictive value in heart failure patients suggests it can identify individuals who are truly at low risk for SCD in the near future and who may be able to have device therapy deferred with re-assessments at 2-year intervals.

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Abstracts of Interest

Cost-effectiveness of a microvolt T-wave alternans screening strategy for implantable cardioverter-defibrillator placement in the MADIT-II-eligible population

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OBJECTIVES: This study was designed to compare the cost-effectiveness of implantable cardioverter-defibrillator (ICD) placement with and without risk stratification with microvolt T-wave alternans (MTWA) testing in the MADIT-II (Second Multicenter Automatic Defibrillator Implantation Trial) eligible population.

BACKGROUND: Implantable cardioverter-defibrillators have been shown to prevent mortality in the MADIT-II population. Microvolt T-wave alternans testing has been shown to be effective in risk stratifying MADIT-II-eligible patients.

METHODS: On the basis of published data, cost-effectiveness of three therapeutic strategies in MADIT-II-eligible patients was assessed using a Markov model: 1) ICD placement in all; 2) ICD placement in patients testing MTWA non-negative; and 3) medical management. Outcomes of expected cost, quality-adjusted life-years (QALYs), and incremental cost-effectiveness were determined for patient lifetime.

RESULTS: Under base-case assumptions, providing ICDs only to those who test MTWA non-negative produced a gain of 1.14 QALYs at an incremental cost of 55,700 dollars when compared to medical therapy, resulting in an incremental cost-effectiveness ratio (ICER) of 48,700 dollars/QALY. When compared with a MTWA risk-stratification strategy, placing ICDs in all patients resulted in an ICER of 88,700 dollars/QALY. Most (83%) of the potential benefit was achieved by implanting ICDs in the 67% of patients who tested MTWA non-negative. Results were most sensitive to the effectiveness of MTWA as a risk-stratification tool, MTWA negative screen rate, cost and efficacy of ICD therapy, and patient risk for arrhythmic death.

CONCLUSIONS: Risk stratification with MTWA testing in MADIT-II-eligible patients improves the cost-effectiveness of ICDs. Implanting defibrillators in all MADIT-II-eligible patients, however, is not cost-effective, with one-third of patients deriving little additional benefit at great expense.

J Am Coll Cardiol 2006;48(1):112-21.

Detection of T-wave alternans using an implantable cardioverter-defibrillator

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BACKGROUND: Microvolt T-wave alternans (TWA) increases acutely prior to ventricular tachycardia (VT) or ventricular fibrillation (VF) in computer simulations and animal models, suggesting that TWA may provide a warning for VT/VF in patients with an implantable cardioverter-defibrillator (ICD).

OBJECTIVES: The purposes of this study were to develop a method for analyzing TWA recorded from ICD electrograms (EGMs) and to evaluate the degree of concordance between EGM TWA and TWA recorded from the surface ECG.

METHODS: We developed a software program to measure EGM TWA in the frequency domain and then used simulated EGMs to determine the effects of ICD signal processing, electrical noise, and variation in the EGM fiducial point on the recorded amplitude and K score (signal-to-noise ratio) of TWA. We then applied this method to analyze TWA simultaneously using both surface ECGs and ICD EGMs during incremental pacing in 25 ICD patients. Pacing modes and EGM sources were varied in repeated trials. EGMs with dynamic range adjusted to achieve a large T wave were telemetered to a digital Holter recorder and measured offline. ECG TWA was analyzed using a commercial system. A positive (+) ECG test had sustained alternans ≥1.9 microV with K score ≥3. Stored EGMs were reviewed for VT/VF during a 6-month follow-up period.

RESULTS: Simulations demonstrated that the EGM method accurately identified TWA ≥10 microV. Overall, 10 (40%) patients had at least one ECG TWA+ test and 15 patients (60%) had no ECG TWA+ tests. The maximum value of TWA was greater in EGMs than in ECGs (median 64 microV vs 2.2 microV, P <.0001). EGM TWA was greater in ECG TWA+ tests than in ECG TWA- tests (169 ± 175 microV vs 71 ± 61 microV, P<.001). Using a sustained EGM TWA threshold of 30 microV, EGM TWA was concordant with ECG TWA in 63 (84%) of 75 analyzed tests (P<.0001) and predicted ECG TWA results with 85% sensitivity and 84% specificity. Both ECG and EGM TWA predicted VT/VF during follow-up (ECG: P=.006; EGM: P= .035).

CONCLUSION: The amplitude of TWA is at least 10 times greater on ICD EGMs than on surface ECGs. EGM and ECG TWA have substantial concordance and comparable predictive value for spontaneous VT/VF. These observations support the hypothesis that ECG and EGM TWA detect the same electrical alternans phenomenon.

Heart Rhythm 2006;3(7):791-7.

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11-15 March 2007
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Disclosure Statement: *Dr. Galiwango and Dr. Moe have no disclosures to declare in association with the contents of this issue.*

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