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T-wave Alternans as an Arrhythmic Risk Stratifier: State of the Art

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Abstract

Microvolt level T-wave alternans (MTWA), a phenomenon of beat-to-beat variability in the repolarization phase of the ventricles, has been closely associated with an increased risk of ventricular tachyarrhythmic events (VTE) and sudden cardiac death (SCD) during *medium-* and *long-term* follow-up. Recent observations also suggest that heightened MTWA magnitude may be closely associated with *short-term* risk of impending VTE. At the sub-cellular and cellular level, perturbations in calcium transport processes likely play a primary role in the genesis of alternans, which then secondarily lead to alternans of action potential morphology and duration (APD). As such, MTWA may play a role not only in risk stratification but also more fundamentally in the pathogenesis of VTE. In this paper, we outline recent advances in understanding the pathogenesis of MTWA and also the utility of T-wave alternans testing for clinical risk stratification. We also highlight emerging clinical applications for MTWA.

Keywords

repolarization alternans; arrhythmia risk stratification; arrhythmia prevention; sudden cardiac death; T-wave alternans

Introduction

Electrocardiographic alternans, a phenomenon of beat-to-beat oscillation in electrocardiographic waveforms, was first described by Hering in 1908¹. Much of the interest in the alternans phenomenon has focused on alternans during the repolarization phase of the cardiac action potential (AP), also known as repolarization alternans (RA). Over the last several decades, physiologic studies have demonstrated that alternans is an important marker of cardiac electrical instability and ventricular tachyarrhythmic events (VTE)^{2, 3}.

Specifically, the presence of microvolt level beat-to-beat alternation in T-wave morphology during low level exercise has been identified as a marker of ventricular arrhythmia

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Conflict of Interest

Faisal M. Merchant, Omid Sayadi, Kasra Moazzami, Dheeraj Puppala, and Antonis A. Armoundas declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

susceptibility in patients with structural heart disease and lead to the advent of microvolt T-wave alternans (MTWA) testing for clinical risk stratification. Since the seminal publication by Rosenbaum et al. demonstrating the efficacy of MTWA testing in risk-stratifying patients for VTE⁴, an extensive body of literature has evolved on the clinical utility and the underlying pathophysiologic mechanisms of MTWA. In this paper, we aim to provide a contemporary perspective on clinical MTWA testing for arrhythmia risk stratification and also provide a review of emerging applications for alternans.

Emerging insights on the pathophysiology of MTWA

T-wave alternans likely occurs as a result of beat-to-beat alternation in AP duration (APD) at the cellular level. Two prevailing hypotheses have emerged to explain alternation of APD: the APD restitution hypothesis and the calcium restitution hypothesis (Figure 1).

The APD restitution hypothesis suggests that alternation in sarcolemmal currents, membrane voltage and AP morphology lead to beat-to-beat fluctuations in intracellular calcium concentration ($[Ca^{2+}]_i$). The calcium restitution hypothesis posits that alternation of $[Ca^{2+}]_i$ is the primary event which then secondarily leads to alternans of membrane voltage and AP morphology⁵⁻¹². According to the second hypothesis, $[Ca^{2+}]_i$ alternans can result from stress-induced^{5, 13} perturbations in any number of Ca^{2+} transport processes including Ca^{2+} entry into the cytoplasm¹⁴, recovery of ryanodine receptors (RyRs) from inactivation, triggering of sarcoplasmic reticulum (SR) Ca^{2+} release^{6, 10}, SR Ca^{2+} uptake¹⁵, intra-SR Ca^{2+} redistribution^{16, 17} and linking of intracellular Ca^{2+} handling to surface membrane voltage⁸.

Early work demonstrated significant variation across species in the ability to induce alternans and also demonstrated that APD alternans is more easily induced at lower temperatures¹⁸, which tend to prolong APD, therefore suggesting a primary role for membrane voltage dynamics in alternans at the tissue level. Further support of this hypothesis comes from data showing that modulation of sarcolemmal Ca^{2+} ¹⁹ and K^+ ^{14, 20} currents based on changes in AP morphology⁸ has a significant effect on the stability of Ca^{2+} handling processes and the transition to stable alternans^{21,22}. These results are in agreement with the findings of Weiss et al²³ in computer simulations which have shown that at the cellular level, both steep APD restitution (the relationship between APD and the previous diastolic interval) slope and $[Ca^{2+}]_i$ cycling dynamics cause APD and $[Ca^{2+}]_i$ to alternate.

However, despite the demonstration that sustained APD alternans occurs when the APD restitution slope is >1 at a given cycle length, additional experimental evidence indicates that the onset of APD alternans is primarily attributable to an instability in $[Ca^{2+}]_i$ cycling dynamics rather than steep APD restitution^{23, 24}. Voltage clamp experiments in isolated myocytes⁷ have demonstrated that $[Ca^{2+}]_i$ exhibits alternans despite a constant beat-to-beat AP (voltage) waveform, suggesting that APD alternans is typically driven by $[Ca^{2+}]_i$ dynamics and not by voltage dynamics (i.e. steep APD restitution slope). Furthermore, in both isolated ventricular myocytes⁵ and intact tissue²⁵, the onset of APD alternans has been demonstrated at a constant cycle length at which APD restitution slope is still considerably <1 and interventions that suppress $[Ca^{2+}]_{SR}$ cycling have eliminated AP alternans irrespective of the APD restitution⁵. Overall, a preponderance of recent data has emerged in support of the calcium restitution hypothesis, suggesting the primacy of perturbations in Ca^{2+} handling processes as the fundamental event in the genesis of cellular alternans (for a detailed review of the calcium cycling hypothesis, see Merchant and Armourdas²⁶).

Optical mapping experiments in isolated perfused hearts^{11, 13, 27-32} and single cell electrophysiological studies^{5-12, 14, 19, 20, 33}, have shown that cardiac alternans has its origin

at the single cell level. Weiss et al²³ have demonstrated that at the tissue level, additional factors such as conduction velocity restitution and ectopic beats promote spatially discordant alternans, a condition where adjacent regions of myocardium demonstrate long and short APD sequences which oscillate out-of-phase with each other. Overall, it is believed that localized regions of AP alternans (spatial alternans), exhibiting delayed recovery on an every other beat basis, are intrinsically related to increased repolarization gradients sufficient to produce unidirectional block, wave break, reentry and arrhythmia on-set (Figure 2). This mechanism linking alternans and arrhythmogenesis has been explored by Kuo et al³⁴ who have shown that increased dispersion of repolarization (DR) is an important condition for the development of reentrant arrhythmias. The mechanistic link between the onset of alternans and the substrate for reentrant arrhythmias also lends support to the notion that beyond medium- and long-term risk stratification, MTWA may also play a role in predicting *short-term* arrhythmia susceptibility. In aggregate, evidence supports the idea that at a minimum, the mechanisms that generate alternans (functional spatial dispersion of refractoriness^{11, 13, 27-32, 35, 36}) are likely to also lead to ventricular tachycardia/ventricular fibrillation (VT/VF), such that the heart either passes through a state of heightened alternans on the way to VT/VF or heightened alternans occurs in close conjunction with developing VT/VF.

The preponderance of data in support of the calcium restitution hypothesis may also have important clinical implications. Impairments in intracellular calcium cycling machinery have been identified as a major cause of contractile dysfunction/heart failure and may provide a common mechanism linking contractile dysfunction with electrophysiologic risk. In support of this idea, it has recently been demonstrated in animal models that impairment of sarcoplasmic reticulum Ca²⁺ ATPase 2a (SERCA 2a) function is associated with enhanced susceptibility to alternans³⁷ and SERCA 2a gene transfer improves both contractile function and reduces arrhythmia susceptibility^{38, 39}. Extension of these findings holds the exciting promise of developing therapeutic strategies that not only improve myocardial contractile function but also reduce the risk of VTE. Improved understanding of the pathophysiology of T-wave alternans and the specific cellular and sub-cellular defects which lead to alternans may also shed light on which patients are at particularly high, or low, arrhythmic risk.

Another area of emerging interest in the pathogenesis of malignant arrhythmias is the role of the autonomic nervous system. The effect of sympathetic nervous system stimulation on the heart is complex and is governed by the state of the myocardium. In the normal ventricle, sympathetic stimulation shortens the APD and reduces the dispersion of repolarization, both associated with a decrease in arrhythmogenic tendency⁴⁰. However, in pathological states associated with reductions in repolarizing capacity of the ventricular myocardium, such as congestive heart failure, sympathetic stimulation is a potent stimulus for the generation of arrhythmias, perhaps by enhancing the dispersion of repolarization, which may be why β -adrenergic blockade reduces sudden death mortality in patients with heart failure^{41, 42}. Consistent with these observations, pre-clinical studies have demonstrated that sympathetic stimulation tends to reduce the threshold for RA and increase arrhythmia susceptibility whereas parasympathetic stimulation has the opposite effect^{43, 44}. In this context, interventions that reduce cardiac sympathetic activity have been shown to protect against arrhythmias⁴⁵⁻⁴⁷, whereas those that enhance sympathetic activity provoke malignant arrhythmias^{45, 46, 48, 49}.

Clinical MTWA testing

The presence of microvolt level beat-to-beat alternation in T-wave morphology (Figure 3) during low-level exercise has been identified as a marker of ventricular arrhythmia susceptibility and has led to the advent of MTWA testing for clinical risk stratification.

Over the last two decades, numerous studies have assessed the ability of MTWA testing to predict risk of VTE in both ischemic and non-ischemic heart failure and other forms of structural heart disease^{50, 51}. In general, patients with a positive MTWA test have consistently been found to have a significantly increased risk of ventricular arrhythmias during follow-up whereas those with negative MTWA tests have a very low arrhythmic risk. In the era of primary prevention ICD therapy, there has been widespread recognition that new tools, beyond LVEF, are necessary to better risk stratify patients and determine which patients are most, or least, likely to benefit from ICDs. Specifically, among patients who are currently candidates for primary prevention ICD therapy (i.e. LVEF $\leq 35\%$), only a small percentage of patients ($\sim 2\text{-}5\%$ per year) will suffer a ventricular arrhythmia resulting in sudden cardiac death (SCD)⁵². Conversely, the majority of SCD events occur in patients with only mildly impaired or even preserved LV systolic function^{53, 54}.

Two studies have specifically assessed the utility of MTWA testing to predict arrhythmic risk in patients implanted with ICDs. The Microvolt T-wave Alternans Testing for Risk Stratification of Post-Myocardial Infarction Patient trial (MASTER)⁵⁵ studied 575 patients meeting Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) criteria⁵⁶, all of whom underwent MTWA testing followed by ICD implantation. During an average follow-up of just over 2 years, MTWA status (negative vs. non-negative) was not found to be a significant predictor of VTE (defined as SCD or appropriate ICD therapy). However, a non-negative MTWA test result was associated with a significantly heightened risk of all-cause mortality. The MTWA sub-study of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) reported on 490 patients enrolled in a sub-study of the larger trial⁵⁷. Again, MTWA status was not found to be a significant predictor of the primary composite endpoint of SCD, sustained VTE or appropriate ICD therapy. In large, part due to these results, there has been a dampening of enthusiasm for clinical MTWA testing as a tool to guide ICD implantation.

What might account for the discrepancy between the results of MASTER and the SCD-HeFT MTWA sub-study and the majority of earlier studies documenting a robust role for MTWA testing in predicting arrhythmic risk? One plausible explanation may lie in the confounding effect of including “appropriate” ICD therapy as a clinical endpoint. It is well recognized that many “appropriate” ICD therapies treat arrhythmias that would have self-terminated or that ICDs may induce arrhythmias that they subsequently treat⁵⁸⁻⁶⁰. In fact, the number of “appropriate” ICD therapies may overestimate the true incidence of SCD in the placebo arm of primary prevention ICD trials by a factor of 2 or greater⁵⁹. In light of this, a recent meta-analysis has suggested that MTWA testing maintains robust predictive capacity in studies where relatively few patients are implanted with ICDs (i.e. $\leq 15\%$) and “appropriate” ICD therapies account for a small percentage of the overall outcome events, whereas the predictive capacity of MTWA is significantly obscured when a larger percentage of patients are implanted with ICDs⁵⁸. These data suggest that MTWA testing is not as good a predictor of “appropriate” ICD therapy, as it is a predictor of VTE/SCD in patients without ICDs. It is likely that MTWA testing is best utilized for patients who do not already have ICDs in order to determine whether they are at risk and should be considered for ICD therapy.

To overcome the potential confounding influence of ICD therapy on clinical endpoints, we have recently shown that in a pooled cohort of 2883 patients without ICDs, a negative MTWA test in patients with LVEF $\leq 35\%$ predicts a very low risk for SCD (0.9% per year), whereas the risk of SCD was significantly increased among patients with positive MTWA tests (approximately 4% per year)⁶¹ (Figure 4A). In this study, MTWA testing was also a significant predictor of SCD risk among patients with LVEF $> 35\%$ with annual SCD rates of 3.0% in the positive MTWA cohort versus 0.3% in the negative MTWA group (Figure

4B). Further data in support of this idea come from a prospective study of patients with LVEF $\leq 35\%$ which showed that ICD therapy reduced annual mortality by approximately 50% among patients with a non-negative MTWA test and provided no benefit among those with a negative test⁶².

A generally consistent finding in the MTWA literature is that patients with a negative MTWA test are at very low risk of arrhythmic death during follow-up^{51, 55, 58, 63, 64}. In the Alternans Before Cardioverter Defibrillator (ABCD) Trial, among patients with LVEF 40%, coronary artery disease and non-sustained ventricular tachycardia, a negative MTWA test demonstrated a negative predictive value of approximately 95% and 90% at 1 and 2 years, respectively, for the primary endpoint of SCD or appropriate ICD discharge⁶⁴. The negative predictive value of a negative MTWA test in the ABCD trial was comparable to invasive electrophysiology testing. Recent studies of patients meeting MADIT II⁵⁶ or SCD-HeFT⁶⁵ criteria for ICD therapy have demonstrated that approximately one-quarter to one-third of patients with impaired LVEF will have a negative MTWA test result^{55, 57, 66} and based on the pooled analysis described above⁶¹, it can be estimated that the risk of SCD in these patients is approximately 0.9% per year. No study has ever demonstrated a benefit to primary prevention ICD therapy in patients with a SCD risk as low as $<1\%$ per year, suggesting that the excellent negative predictive value of a negative MTWA test may still have an important clinical role in identifying patients who are unlikely to benefit from ICD therapy. The ability to safely withhold device therapy from these patients represents a major opportunity to reduce unnecessary exposure to an invasive treatment with well-established short- and long-term complications⁶⁷, while at the same time improving resource allocation and reducing the cost burden to the healthcare system.

The above described clinical data reference primarily the Fast Fourier Transform (FFT)-based spectral method for estimating MTWA during a graded increase in heart rate via low-level exercise, chronotropic stimulation or atrial pacing. However, several other methods have been applied for the detection and quantification of MTWA including autocorrelation⁶⁸, complex demodulation⁶⁹, autoregression⁷⁰ and the modified moving average (MMA)^{71, 72}. To date, the FFT based method remains the most studied and best validated method for measuring RA due in large part to its ability to differentiate between true alternans and non-specific noise in the ECG. The FFT method serves as the basis for the commercially available Cambridge Heart system, while the MMA method, which can be employed during both exercise and during ambulatory (Holter) monitoring, is manufactured by GE Healthcare®. Although both methods are designed to detect the same phenomenon, head-to-head comparative data on the clinical performance of the two methods are lacking⁷³.

Emerging clinical applications of RA

Although MTWA testing has traditionally been used for predicting medium- and long-term risk of ventricular arrhythmias, the concept of MTWA may have several novel clinical applications. The pathophysiology of alternans suggests that alternation in APD may play a critical role in generating the necessary electrophysiologic substrate for arrhythmia onset. Numerous experimental^{11, 12, 74, 75} and computational⁷⁶⁻⁷⁸ studies have demonstrated that *discordant* APD alternans, where the APDs of adjacent regions of myocardium oscillate out-of-phase (Figure 2), is associated with increased DR and VT/VF (DR is greater at sites of discordant vs. concordant alternans)¹¹. In this paradigm, the presence of APD alternans may also serve as an important marker of *short-term* arrhythmia susceptibility. Several lines of clinical evidence support this idea. Analysis of ambulatory body-surface electrograms (Holter monitors) from patients with various forms of heart disease has demonstrated a sharp upsurge in repolarization alternans (measured by time-domain techniques) within the

minutes prior to spontaneous VTE⁷⁹. Similarly, analysis of body-surface electrocardiograms from patient hospitalized with decompensated heart failure has demonstrated a significant upsurge in MTWA during the 15-30 mins prior to the onset of spontaneous VTE⁸⁰.

Analysis of intra-cardiac electrograms from ICDs has also demonstrated a sharp increase in MTWA magnitude immediately prior to spontaneous ventricular arrhythmias⁸¹⁻⁸⁴. However, a similar upsurge in MTWA has not been observed prior to induced ventricular arrhythmias or preceding inappropriate ICD shocks⁸¹, suggesting that the presence of increased MTWA magnitude is not just a by-product of a ventricular arrhythmia or a consequence of an ICD shock. Simultaneous measurement of MTWA from body-surface and intracardiac electrograms by our group⁶³ and others⁸⁵ has shown a high degree of correlation suggesting that these measurements are detecting the same electrical phenomenon. Additionally, we have recently developed a novel intra-cardiac lead configuration consisting of leads in the right ventricle and the coronary sinus that provides an “optimal” sensitivity in detecting intra-cardiac MTWA⁶³ (Figure 5).

The ability to detect acute surges in RA/TWA from intra-cardiac or body-surface electrograms, respectively, immediately prior to the onset of spontaneous VTE holds significant promise for developing tools to warn patients of impending arrhythmias and possibly to deliver upstream therapy and preempt arrhythmia onset. For instance, there has been significant interest in the use of dynamic pacing protocols to control APD and suppress discordant RA. Experimental studies have demonstrated that stimulation during the absolute refractory period is capable of controlling APD, in part through modulation of cellular calcium transients^{86,87}. Based on this premise, our group has recently developed a method for *in situ* dynamic control of MTWA in a large animal model⁸⁸. In this model, the delivery of sub-threshold pacing stimuli during the absolute refractory period is capable of suppressing MTWA in a swine heart failure model, even when the pacing site (right ventricle) was located at a distance from the site of alternans genesis (left ventricle).

Extension of these findings raises the possibility of incorporating adaptive pacing protocols into implantable devices such that if the device detects an unstable myocardial substrate (as evidenced by heightened MTWA magnitude), the adaptive pacing protocol would be activated to deliver electrical therapy that is specific to the underlying electrical instability to re-stabilize the electrical substrate and prevent the onset of a spontaneous VTE. The adaptive pacing protocol could be terminated when the MTWA magnitude falls below a predetermined threshold. Beyond adaptive pacing protocols, detection of MTWA by implantable devices may also be coupled to other forms of suppressive therapy. For instance, there is significant interest in coupling micro-electromechanical systems (MEMS) to implantable devices to facilitate localized delivery of pharmacologic agents for treating various aspects of chronic heart failure (i.e. neurohormonal antagonists, diuretics, anti-arrhythmic agents)⁸⁹. It's conceivable that timely and potentially localized delivery of such agents may be capable of suppressing MTWA and re-stabilizing the electrical substrate. In an analogous manner, detection of heightened MTWA in patients hospitalized with decompensated heart failure may prompt down-titration of inotropic/chronotropic agents or temporary initiation of anti-arrhythmic therapy to quell the arrhythmogenic substrate and preempt VTE onset.

Although ventricular RA/TWA has traditionally been implicated in the pathogenesis and risk stratification of ventricular arrhythmias, another emerging application in the clinical arena involves atrial arrhythmogenesis. Alternation of atrial APD has been implicated in the transition from atrial flutter to atrial fibrillation (AF)⁹⁰ and atrial APD restitution dynamics have been implicated as a mechanism for why premature atrial depolarizations from

pulmonary vein foci may trigger AF in susceptible substrates²⁴. Additionally, alternation of atrial APD has been documented to occur at lower heart rates in patients with persistent AF versus those with paroxysmal AF or controls, thus revealing important differences in the underlying substrate among these groups⁹¹. Furthermore, the presence of atrial APD alternans preceded the transition to AF in all instances. These findings suggest that atrial alternans may play a crucial role in the genesis of AF and mechanistic insights into the pathophysiology of atrial alternans may lead to novel risk stratification tools and therapeutic options.

Conclusions

Numerous experimental and computational studies have demonstrated that APD alternans gives rise to T-wave alternans and can provide the substrate for reentrant arrhythmias. Although MTWA testing has traditionally been utilized as a clinical tool for SCD risk stratification, as highlighted in this paper, the role of MTWA testing in the context of primary prevention ICD therapy continues to evolve. However, as the pathogenesis of repolarization alternans is better elucidated, it is likely that MTWA will play a broader clinical role in both *short-term* arrhythmia prediction and management of congestive heart failure.

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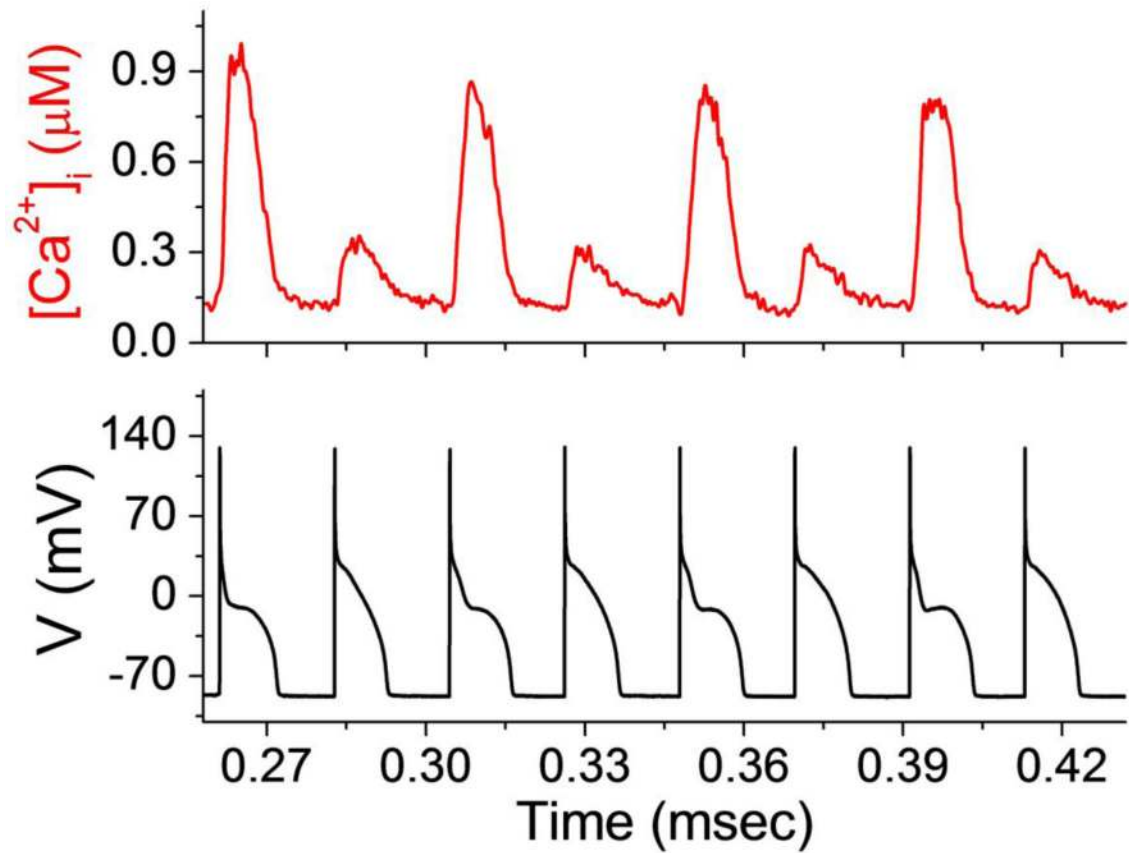


Figure 1. Illustration of $[Ca^{2+}]_i$ and AP alternans. Representative example of intracellular calcium concentration ($[Ca^{2+}]_i$) and action potential (AP) voltage alternans in a left ventricular canine myocyte.

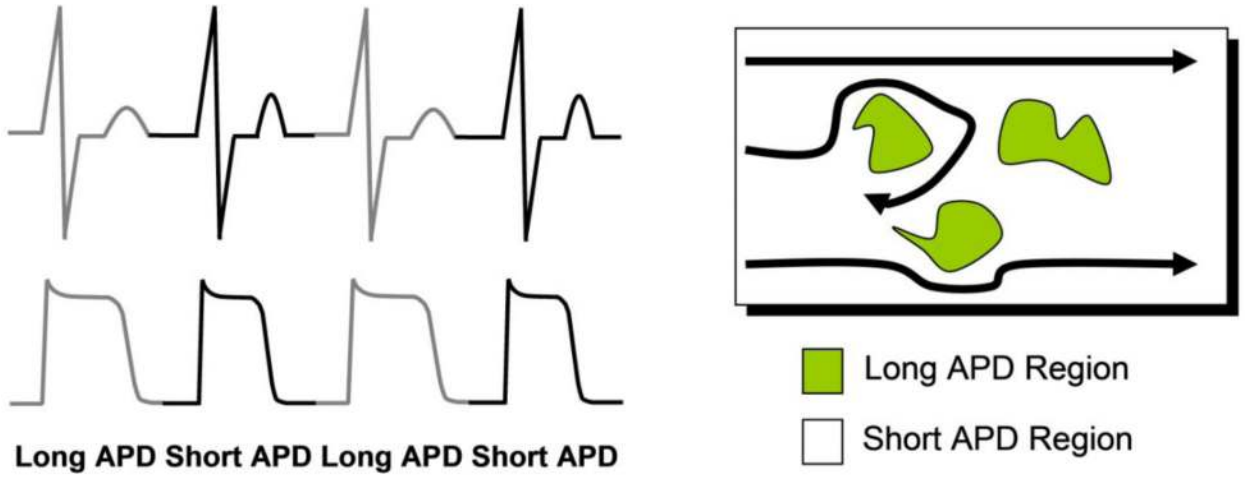


Figure 2. Functional relationship of alternans and re-entry. Localized action potential alternans is manifested as repolarization alternans on the electrocardiogram. Localized regions of tissue exhibiting action potential alternans are associated with delayed recovery on an every other beat basis. These tissue areas of delayed recovery may lead to wavebreak and the development of reentry.

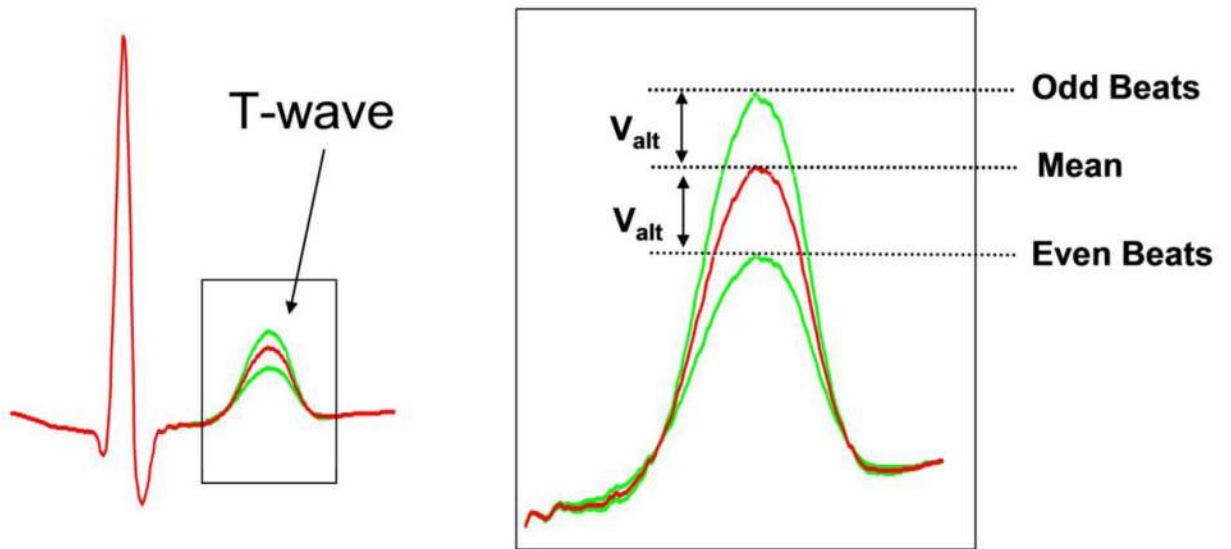
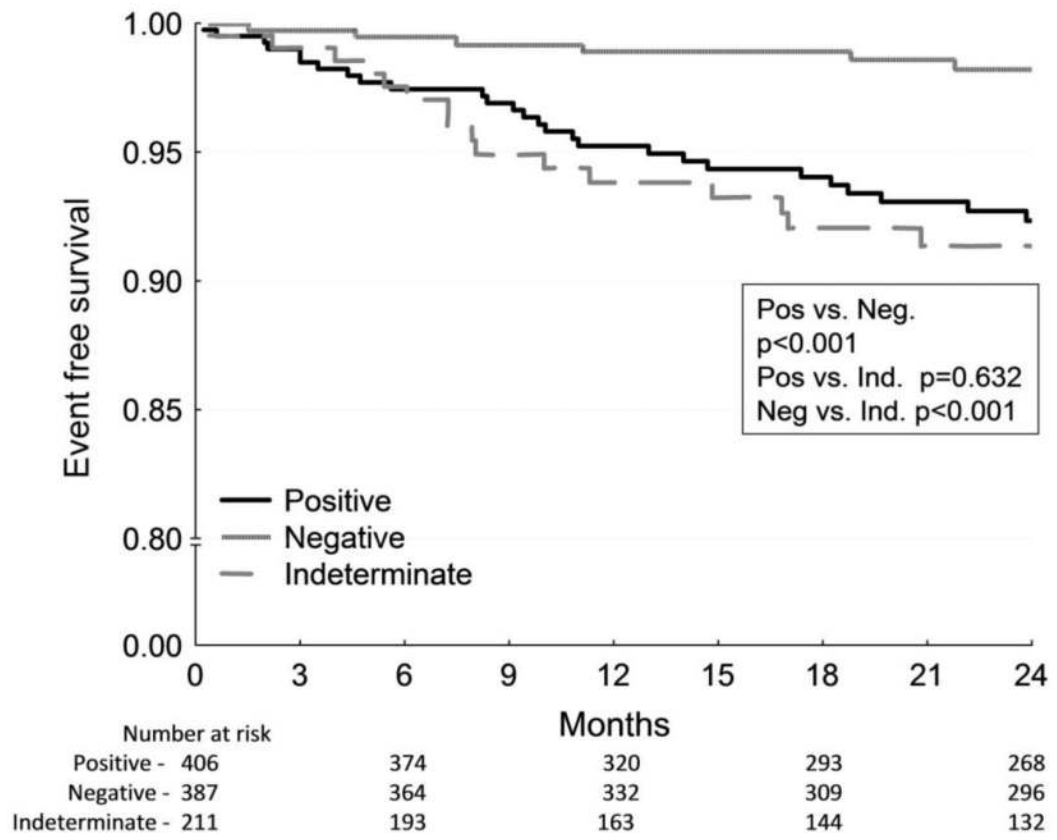


Figure 3. Beat-to-beat alternation in T-wave morphology. Illustration of microvolt level (V_{alt}) alternation in T-wave amplitude which serves as the premise of clinical microvolt T-wave alternans (MTWA) testing.



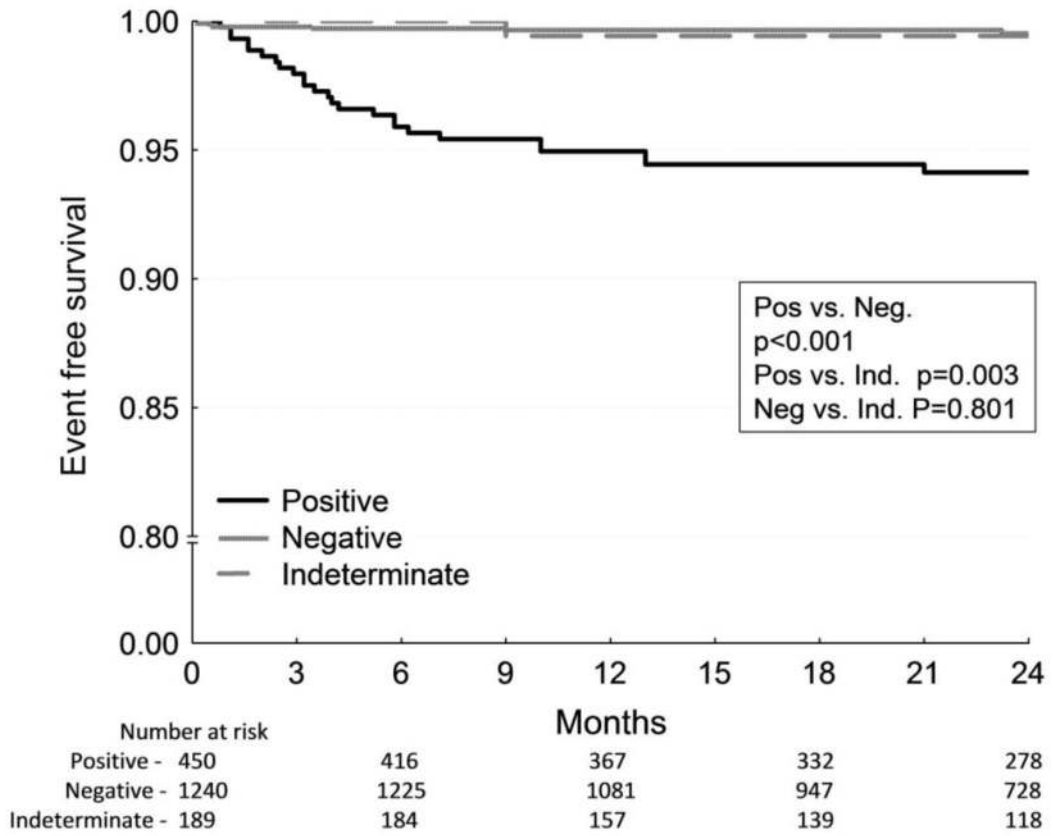


Figure 4. Kaplan-Meier event-free survival curves for arrhythmic mortality/sudden cardiac death stratified by MTWA test result. A, Among patients with left ventricle ejection fraction (LVEF) $\leq 35\%$, patients with a positive or indeterminate MTWA test result demonstrate significantly higher mortality than those with negative MTWA results. B, In contrast, among patients with LVEF $> 35\%$, only a positive MTWA test predicts increased mortality. All p values are generated by the log-rank test. (From: Merchant FM, Ikeda T, Pedretti RF, Salerno-Uriarte JA, Chow T, Chan PS, Bartone C, Hohnloser SH, Cohen RJ, Armoundas AA. Clinical utility of microvolt T-wave alternans testing in identifying patients at high or low risk of sudden cardiac death. *Heart Rhythm*. 2012;9(8):1256-1264 e1252) [61••].

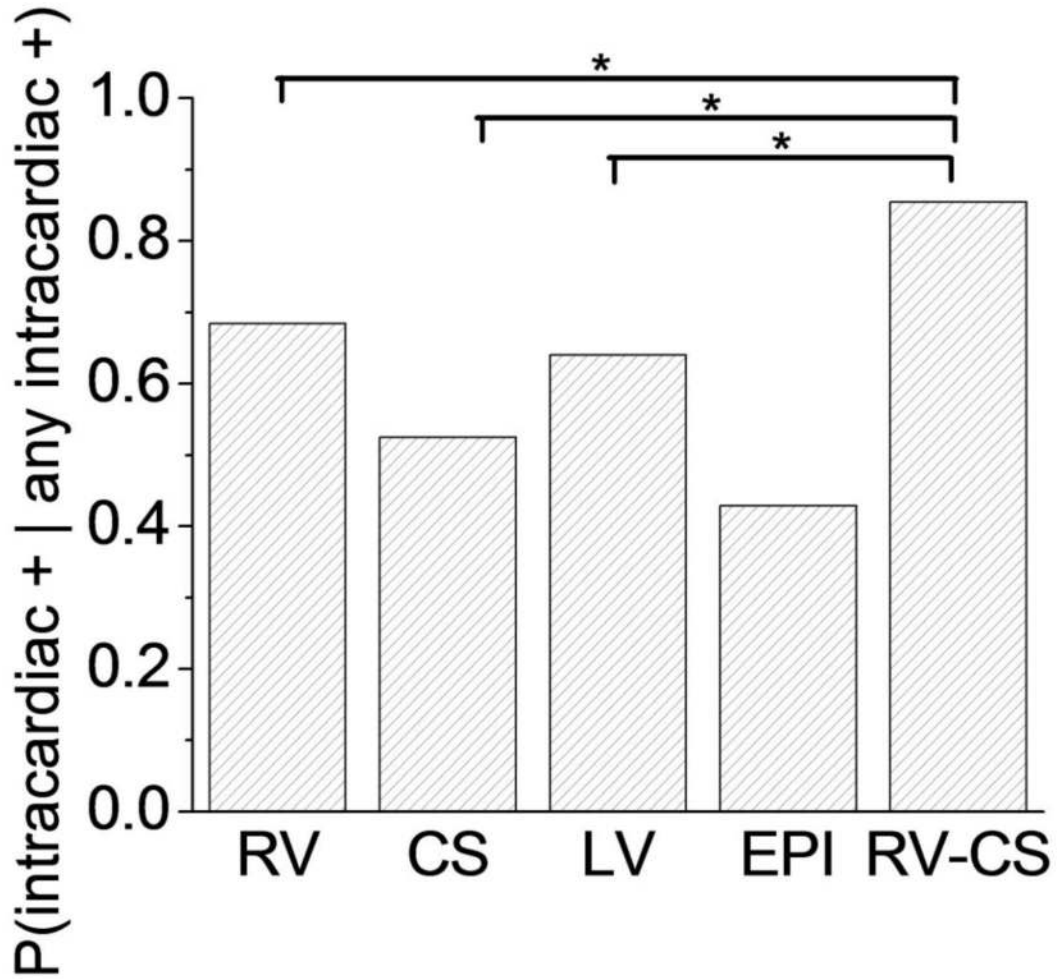


Figure 5.

Sensitivity of alternans detection in intra-cardiac leads. Probability that a far-field bipolar intra-cardiac lead is positive for repolarization alternans (RA), given that at least 1 intra-cardiac far-field lead is positive for RA, for each of the right ventricle (RV), coronary sinus (CS), left ventricle (LV), epicardial (EPI), and triangular right ventricle-coronary sinus (RV-CS) far-field intra-cardiac lead configurations. The RV-CS positive percentage was significantly larger than for the RV configuration ($P=0.040$), the CS configuration ($P=0.004$), and the LV configuration ($P=0.035$) but not for the EPI configuration ($P=0.270$). Statistically significant comparisons are marked by an asterisk. (From: Weiss EH, Merchant FM, d'Avila A, Foley L, Reddy VY, Singh JP, Mela T, Ruskin JN, Aroundas AA. A novel lead configuration for optimal spatio-temporal detection of intracardiac repolarization alternans. *Circ Arrhythm Electrophysiol.* Jun 1, 2011: 407-417) [63•].