Microvolt T-Wave Alternans: Physiologic Basis, Methods of Measurement, and Clinical Utility

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Consensus Guideline by International Society for Holter and Noninvasive Electrocardiology

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Abstract

This consensus guideline was prepared on behalf of the International Society for Holter and Noninvasive Electrocardiology (ISHNE) and is co-sponsored by the Japanese Circulation Society, the Computers in Cardiology Working Group of the European Society of Cardiology, and the European Cardiac Arrhythmia Society. It discusses the electrocardiographic phenomenon of T-wave alternans (TWA), that is, a beat-to-beat alternation in the morphology and amplitude of the ST segment or T wave. This statement focuses on its physiologic basis, measurement technologies, and its clinical utility in stratifying risk for life-threatening ventricular arrhythmias. Signal processing techniques including the frequency-domain Spectral Method and the time-domain Modified Moving Average Method have demonstrated TWA's utility in arrhythmia risk stratification. The majority of exercise-based studies using both methods reported high relative risks for cardiovascular mortality and for sudden cardiac death in patients with preserved as well as depressed left ventricular ejection fraction. Studies with ambulatory electrocardiogram-based TWA analysis using Modified Moving Average Method yielded significant predictive capacity. However, negative studies with the Spectral Method have also appeared, including two interventional studies in patients with implantable defibrillators. Meta-analyses have been performed to gain insights into this issue. Frontiers of TWA research include use in arrhythmia risk stratification of individuals with preserved ejection fraction, improvements in predictivity based on quantitative analysis, and utility in guiding medical as well as device-based therapy. Overall, while TWA appears to be a useful marker of risk for arrhythmic and cardiovascular death, there is yet no definitive evidence that it can guide therapy.

Keywords: T-wave alternans, risk stratification, sudden cardiac death, cardiovascular mortality, exercise testing, ambulatory ECG monitoring

Abbreviations:

CI = confidence interval

ECG = electrocardiogram

FFT = Fast Fourier Transform

HERG = cardiac potassium channel gene causing long QT2 type of long QT syndrome

ICD = implantable cardioverter defibrillator

ISHNE = International Society for Holter and Noninvasive Electrocardiology

LVEF = left ventricular ejection fraction

MMA = Modified Moving Average

TWA = T-wave alternans

Investigations:

ABCD = Alternans Before Cardioverter Defibrillator

ALPHA = T-Wave Alternans in Patients with Heart Failure

ATRAMI = Autonomic Tone and Reflexes after Myocardial Infarction

CARISMA = Cardiac Arrhythmias and Risk Stratification after Acute Myocardial Infarction

CHS = Cardiovascular Health Study

EPHESUS = Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study

ESVEM = Electrophysiologic Study Versus Electrocardiographic Monitoring

FINCAVAS = Finnish Cardiovascular Study

MADIT = Multicenter Automatic Defibrillator Trial

MASTER = Microvolt T Wave Alternans Testing for Risk Stratification of Post-Myocardial Infarction Patients

REFINE = Risk Estimation Following Infarction, Noninvasive Evaluation

REFINE-ICD = Risk Estimation Following Infarction, Noninvasive Evaluation of ICD Therapy

SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial

Introduction

The International Society for Holter and Noninvasive Electrophysiology (ISHNE) together with the Japanese Circulation Society, the Computers in Cardiology Working Group of European Society of Cardiology, and the European Cardiac Arrhythmia Society charged the authors with reviewing the topic of microvolt T-wave alternans (TWA) to provide a consensus guideline regarding its physiologic basis, measurement methods, and clinical utility.

Physiology of T-Wave Alternans

The TWA phenomenon, a repeating ABABAB pattern in the morphology and amplitude of the ST segment or T wave, has long been recognized and linked to arrhythmogenesis (1). This pattern distinguishes TWA from other types of ST-segment and T-wave variability (Fig. 1). TWA reflects spatiotemporal heterogeneity of repolarization, is sensitive to perturbations in intracellular calcium handling, and serves as a mechanism of arrhythmogenesis by amplifying repolarization heterogeneity. It arises from beat-to-beat alternation of action potential duration at the level of cardiac myocytes. TWA may be either spatially concordant, when action potentials in neighboring cell regions alternate in phase, or discordant, when they are out of phase (Figs. 2,3). The physiologic basis of TWA has recently been reviewed in detail (2-7).

Link to Repolarization Heterogeneity

The association of TWA with spatiotemporal heterogeneity of repolarization, *i.e.*, transient or lasting repolarization differences among neighboring myocardial regions, is supported by a number of investigations, including *in vitro* optical mapping (5-9), intact large animal experimental laboratory studies (10-13), computer simulations, and clinical studies involving programmed electrical stimulation (14,15). Higher levels of TWA indicate greater risk for arrhythmias (13,16), which becomes especially elevated when alternation in neighboring

areas is discordant, *i.e.*, out of phase (7,10). Changes in action potential duration and conduction velocity restitution, premature beats, and functional and/or anatomic gradients in action potential duration facilitate development of steep, heterogeneous repolarization gradients conducive to reentry and wavebreak. Clinically important anatomic barriers include post-infarction myocardial scar and abnormal fiber orientation and/or fibrosis in patients with hypertrophy (17).

Influence of Physiological Interventions on TWA

TWA magnitude coincides with vulnerability to lethal ventricular tachyarrhythmias. It is amplified by heart rate increases, ventricular premature beats (18), coronary artery occlusion and reperfusion (3,12,14,19-21), adrenergic stimulation (19,22) and mental stress (23). Blockade of beta-adrenergic receptors (24,25), sympathetic denervation (19), and vagus nerve and spinal cord stimulation (26), which reduce susceptibility to ventricular tachyarrhythmias, decrease TWA magnitude. Clinical studies with ambulatory ECG monitoring (27) and recordings from intracardiac leads of implanted devices (28) reveal a progressive increase in TWA preceding the onset of spontaneous ventricular arrhythmias.

Heart Rate and Autonomic Factors

Heart rate influences TWA, likely by impacting on intracellular calcium cycling (4) and engaging the steepest portions of the electrical restitution curve (5,29). Even in the normal heart, excessive heart rates of >170 beats/min in guinea pigs and >200 beats/min in canines, are capable of inducing TWA (30). During myocardial ischemia or heart failure, the onset heart rate for TWA is considerably lower (9,12) due to impaired capacity of the sarcoplasmic reticulum to reuptake calcium. Heart rate is not the sole determinant of TWA, as autonomic neurotransmitters and changes in myocardial substrate can lead to elevated levels of TWA during fixed rate pacing

(16,19). Furthermore, pacing alone does not replicate the TWA enhancement at comparable heart rates due to adrenergic stimulation or myocardial ischemia (22-25).

Myocardial Ischemia and Heart Failure

Myocardial ischemia can increase TWA magnitude, as is evidenced in animals during coronary artery occlusion (16,19,20) and in humans during angioplasty (16,21). Experimental studies with fixed heart rates indicated that myocardial ischemia and reperfusion-induced increases in TWA magnitude paralleled (r^2=0.98) incidence of ischemia-induced ventricular tachycardia and fibrillation (16). Marked changes in T-wave complexity and heterogeneity, *i.e.*, nonuniformity in T-wave morphology (12,13), occurred simultaneously with TWA magnitude surges, with transition from concordant to discordant alternans. Loss of intracellular coupling was implicated when rotigaptide decreased connexin43 dephosphorylation in parallel with ischemia-induced TWA and dispersion of repolarization (31).

Derangements in calcium cycling and conduction constitute ionic bases for TWA during myocardial ischemia and heart failure (8,9). Using luminescent dyes, Clusin (8) demonstrated ischemia-induced concordant and discordant alternation in calcium transients. Moreover, calcium channel blockade reversed ischemia-induced TWA in parallel with arrhythmia suppression in anesthetized canines (32). Experimental models of heart failure demonstrated associations of TWA with disturbances in calcium handling and development of discordant alternans, which set up proarrhythmic preconditions for conduction block and reentry. In particular, heart failure reduces sarcoplasmic reticulum Ca2+-adenosine triphosphatase expression and inhibits ryanodine receptor function, resulting in impaired reuptake and release of calcium in the sarcoplasmic reticulum, both contributing to marked derangements in intracellular Ca^{2+} handling (9). Recent studies in cardiomyopathy patients showed that TWA may be

attributable to oscillations in the action potential plateau that, in computational models, were best explained by reduced calcium uptake into the sarcoplasmic reticulum (15,29).

TWA in Nonischemic Cardiomyopathy

Sympathetic nerve activity and abnormalities in calcium handling may serve as arrhythmogenic factors in nonischemic disease patients, who experience enhanced adrenergic activity to compensate for myocardial contractility reduction. The vulnerable myocardial substrate is susceptible to transient alterations in neural activity and electrolyte imbalance, which may initiate disturbances in cardiac repolarization and ventricular arrhythmogenesis. Imaging studies (33) demonstrated the important role of increased sympathetic nerve activity in provoking TWA in idiopathic dilated cardiomyopathy. During exercise, patients with dilated or hypertrophic cardiomyopathy also experience repolarization abnormalities including TWA that are associated with ventricular tachycardia. Histopathological changes, particularly fiber disarray and/or fibrosis, are correlated with TWA occurrence and ventricular tachyarrhythmias in hypertrophic cardiomyopathy (17).

Methodology for T-Wave Alternans Assessment

Two contemporary techniques employed in sizeable clinical studies for arrhythmia risk stratification by microvolt-level TWA are the Spectral and the Modified Moving Average (MMA) Methods (Tables 1,2). Both allow detection of subtle levels of TWA in the nonvisible microvolt range as well as visible, macroscopic TWA. Experience with the Spectral Method is more extensive. Other analytical methods employed in experimental and clinical studies (19,21,28,34,35) have been reviewed (34).

Spectral Method

Analysis approach. The concept of analyzing morphology fluctuations in the T wave by computerized spectral techniques dates from experimental studies (30) employing the Fast Fourier Transform (FFT) (Fig. 4) (36). In detail, sequential ECG cycles are aligned to their QRS complex and the amplitude of the ST segments and T waves at a predefined point *t* (relative to the JT interval) is measured. Subsequently, this beat-to-beat series of amplitude fluctuations is divided into 128 segments and processed with FFT to generate a separate spectrum for each point *t*. The spectra corresponding to different time points along the JT interval are averaged, producing a composite spectrum. The alternans voltage in microvolts represents the square root of the alternans power and the voltage difference between the overall mean beat and the even or odd numbered mean beats. The significance of TWA is expressed by the alternans ratio (K score), calculated as the ratio of alternans power at 0.5 cycle/beat divided by the standard deviation of spectral noise (37) . The greater the power, the higher is the alternans voltage. ECG fluctuations occurring at other frequencies are not included in TWA assessment. Use of this technique in clinical practice is evidenced by substantial sales of commercial equipment and consumables as publicly reported by Cambridge Heart, Inc.

Test methodology. Since the Spectral Method involves a graded increase in heart rate, the TWA test is usually conducted during bicycle or treadmill exercise to an optimum heart rate (38). Some investigators infused chronotropic agents (22,25) or employed atrial pacing to elevate and stabilize heart rate (24,39-41). TWA can occur in normal individuals at heart rates >120 beats/min. Consequently, a target heart rate range of 105-110 beats/min was determined for pathologic alternans in adults (37,42). Practice has varied regarding withholding beta-adrenergic blockade to allow patients to reach this heart rate (43). The current recommendation is to maintain chronic medications during the test (24).

TWA is determined from standard precordial and orthogonal X,Y,Z leads. Special high-resolution electrodes can minimize noise. TWA is not measured in ECG portions in which ectopic or premature beats constitute >10% of beats (37), since the readings can be influenced by excessive numbers of premature beats or by attendant phase changes of alternans (e.g., from "ABAB" to "BABA").

Classification of test results. TWA level >1.9-μV cutpoint with alternans signal-to-noise ratio K>3 sustained for >2 minutes is defined as a positive test result based on outcome data of clinical studies (37,44). Test results below this level are considered negative.

Because of a relatively high incidence (20-40% of all cases) of indeterminate test results, a test classification of "abnormal due to patient factors" was introduced (45). This classification is employed when the test is associated with excessive ectopy (~32%), lack of capacity to reach a target rate of 105-110 beats/min (~51%), or nonsustained TWA (~10%). Abnormal test results due to patient factors carry greater risk than positive test results. In contrast, the occurrence of muscle, respiration, or other movement artifacts or electrode noise accounts for 6.4% of indeterminate test results in experienced centers and is referred to as "technically indeterminate." Those tests have no prognostic value *per se*.

Modified Moving Average Method

Analysis approach. The MMA Method employs the noise-rejection principle of recursive averaging (34). The algorithm continuously streams odd and even beats into separate bins and creates median complexes for each bin (Fig. 5) (20). These complexes are then superimposed, and the maximum difference between the odd and even median complexes at any point within the JT segment is averaged for every 10-15 seconds and reported as the TWA value. The moving average allows control of the influence of new incoming beats on the median templates with an adjustable update factor, *i.e.*, the fraction of morphology change that an incoming beat can

contribute. The recommended, rapid update factor of 1/8 provides greater sensitivity and capacity to detect transient but clinically important surges in TWA than 1/16 or 1/32 (46). Noise measurements are in part derived from mismatch of the even or odd median complexes outside the JT segment. The algorithm excludes extrasystoles, noisy beats, and the beats preceding them and filters effects of noise, movement, and respiration.

Test methodology. MMA allows microvolt TWA analysis during routine, symptom-limited exercise stress testing (46-49) and during post-exercise recovery (48,50,51) as well as during ambulatory ECG monitoring (52-56) in the flow of clinical evaluation (Table 2). The cutpoint employed is the peak TWA value throughout the 24-hour ambulatory ECG recording or the symptom-limited exercise test.

MMA-based TWA is calculated from standard precordial ECG leads using standard electrodes (46-56). Because limb leads are prone to motion artifact (47), TWA in these leads should be interpreted with caution. The MMA Method generates high-resolution templates of superimposed QRS-aligned complexes showing the alternation pattern, permitting visual examination to verify TWA's presence and magnitude (Fig. 1) (47,53). TWA values should be overread for verification down to 20 μV.

Classification of test results. MMA-based TWA studies with ambulatory ECG recordings and exercise support the concept that TWA represents a continuum of risk with higher TWA levels indicating greater risk (46,47,49,51). Using the recommended update factor of 1/8, TWA ≥60 μV during routine exercise testing (46-48,51) and ambulatory ECG monitoring (54,56) indicates severely elevated risk for sudden cardiac death and/or cardiovascular mortality. In patients during the early post-MI phase with or without heart failure, a cutpoint of ≥47 μV also predicted sudden cardiac death (52,53). Leino et al (49) demonstrated a 55% and 58% increase in risk of cardiovascular and sudden cardiac death, respectively, per 20 μV of TWA.

Short-term and Long-term Repeatability of TWA Testing

Immediate repeatability of Spectral Method test results was verified with bicycle ergometry with 15 minutes and 4 hours between the tests (57), as well as during atrial pacing (24). Data on long-term stability of TWA results using the Spectral Method are sparse (58). Repeatability has not been reported with the MMA Method.

Comparison of TWA Values Obtained using the Spectral and MMA Methods

The methods are analytically comparable although they differ in noise processing. The 4- to 10-fold differences in TWA voltages reported by MMA and Spectral Method tests can be accounted for by the update factor. Briefly, the Spectral Method reports one half of the average TWA magnitude across the entire JT interval for 128 beats, whereas the MMA Method reports the peak TWA level at any point within the JT interval for each 10- to 15-second interval.

Clinical Utility

Spectral Method

Significant predictivity of TWA analysis by the Spectral Method has been prospectively demonstrated in >7, 800 patients with various types of cardiovascular disease, including myocardial infarction, congestive heart failure, ischemic cardiomyopathy, and nonischemic dilated cardiomyopathy (Table 1) (Fig. 6A,B,C) (48,50,59). Lack of significant predictivity in a few observational studies has been attributed to short periods after myocardial infarction during ongoing remodeling (60,61), washout of beta-blocking agents prior to the test (24,43,59), and use of ICD firing as a surrogate endpoint for arrhythmic death (62-64).

A focus of most TWA studies with the Spectral Method has been on identifying patients who would not benefit from ICD implantation, particularly those fulfilling the Multicenter Automatic Defibrillator Trial II (MADIT II) criteria, namely, prior myocardial infarction and left

ventricular ejection fraction (LVEF) ≤30% (64,65). The need for accurate identification of patients who would not benefit from ICD implantation is unmet, since one third of ICD patients receive an inappropriate shock within 1 to 3 years of implantation (66,67) and ICD shock is associated with a 2- to 5-fold increase in mortality, most commonly due to progressive heart failure (67). Event-free survival from all-cause or cardiac mortality and/or ventricular tachyarrhythmias averaged 97-98% in patients with negative TWA test results, pointing to a potential to improve exclusion of patients who may not benefit from primary prophylactic ICD implantation, despite meeting evidence-based criterion of LVEF <35% (65,68).

TWA in Interventional ICD Trials. TWA stratified total mortality in the Microvolt T Wave Alternans Testing for Risk Stratification of Post-Myocardial Infarction Patients (MASTER) trial of MADIT II-type patients but did not predict sudden cardiac death or appropriate ICD discharge in MASTER (64) or sudden cardiac death, sustained ventricular tachycardia or fibrillation, or appropriate ICD discharge in Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) TWA substudy (Fig. 6D) (63). A recent meta-analysis addressing lack of predictivity of ICD discharge in these trials indicated that predictive accuracy was strong in the TWA studies enrolling relatively few patients with ICDs, with a composite hazard ratio for prediction by abnormal vs. negative TWA of 13.6 [95% confidence interval (CI), 8.5-30.4], and that predictive accuracy in studies with high ICD use was low at 1.6 (95% CI, 1.2-2.1) (62). Thus, ICD firing, employed as a surrogate endpoint for sudden cardiac death, may have underrepresented the utility of the test. An alternative explanation implicates withholding beta-adrenergic blocking agents to explain the inconsistent results (Fig. 7) (43).

Guiding ICD Implantation. Data to support use of TWA to withhold or delay ICD implantation are insufficient at present. To date, only the Alternans Before Cardioverter Defibrillator (ABCD) trial (69) has tested TWA's capacity to guide prophylactic ICD implantation. Event rates were higher in patients with either a positive TWA (hazard ratio 2.1,

p=0.03) or a positive electrophysiologic study (hazard ratio 2.4, p=0.007) than in those whose TWA and electrophysiologic tests were either negative or indeterminate at the pre-specified primary time point of one year. Moreover, the event rate in patients with both negative TWA and electrophysiologic study test results was lower than in patients with two positive tests (2% vs. 12%; p=0.017), suggesting synergy between the tests. But, TWA did not predict endpoint events at two years, suggesting potential time dependence.

In their meta-analysis, Hohnloser et al (62) proposed a clinical algorithm to identify patients who would not benefit from ICD implantation for primary prevention. (See their Fig. 2.) Their analysis revealed that the mortality rate of TWA negative patients with LVEF ≤35% but no history of ventricular arrhythmias and no prior implantation was 4-fold lower than that of MADIT II or SCD-HeFT trial patients randomized to ICD therapy. Accordingly, the negative predictive value derived for this group is >99%. This algorithm will require testing in a prospective trial.

TWA in Hereditary Channelopathies. Although intracardiac repolarization alternans plays a pivotal pathogenetic role in the genesis of malignant arrhythmias, particularly torsades de pointes, in channelopathies (70), prospective studies have not demonstrated that TWA identifies patients with long QT (71,72) or Brugada syndromes (73,74) who will experience episodes of torsades de pointes. The disappearance of TWA during atrial pacing at 110 beats/min may provide clues regarding difficulties in sensing TWA during target heart-rate exercise in Brugada patients (75).

Modified Moving Average Method

Predictivity of TWA analysis by the MMA Method has been demonstrated in >4,200 patients, including those with coronary artery disease, recent or old myocardial infarction, congestive heart failure, or cardiomyopathy (Table 2). In the Finnish Cardiovascular Study

(FINCAVAS), the largest investigation of TWA to date, TWA predicted sudden cardiac death and cardiovascular and total mortality in a general population of >3,500 low-risk patients referred for routine, symptom-limited exercise testing (46,47,49). MMA-based TWA is also predictive when monitored during immediate post-exercise recovery (48,50,51) or from ambulatory ECG records (52-56) (Fig. 6B). Sudden cardiac death was witnessed (54) or adjudicated (55,76-78). TWA detected with continuous 24-hour ECG monitoring reflects the influences of daily activity, mental stress (23), sleep states (79), and sleep apnea (80). Results of these investigations support MMA analysis of TWA during the flow of routine clinical assessment.

Comparison of TWA's Predictivity using the Spectral and MMA Methods

Hazard ratios for prediction by the Spectral and MMA Methods are similar, whether in the same population (50) or in studies overall (Tables 1,2). Exner et al (50) determined that TWA assessed by the Spectral Method during exercise and by the MMA Method during the post-exercise recovery phase yielded significant odds ratios of 2.75 and 2.94, respectively, in 322 post-myocardial infarction patients with better-preserved LVEF (mean 47% measured at 8 weeks after myocardial infarction) but without an ICD who were enrolled in the REFINE study (Fig. 6C). The concordance of the two methods measured simultaneously during exercise has not been systematically investigated. In a study using atrial pacing (N=41), Cox et al (40) found that the Spectral Method was predictive ($p<0.02$) and that with their customized software and using 1/16 rather than the recommended 1/8 update factor, MMA was nearly significant ($p<0.06$) in the same patients. TWA analyzed by both the Spectral Method and MMA was significantly elevated at 8-15 minutes prior to the onset of spontaneous ventricular tachyarrhythmias in ambulatory ECGs in the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) trial (27).

Risk Stratification in Patients with Preserved Ejection Fraction

An important frontier in arrhythmia risk stratification concerns patients with preserved LVEF, in whom the majority of sudden cardiac deaths occur albeit with low incidence (81). Ikeda et al (82) using the Spectral Method and the FINCAVAS investigators (46-49) using the MMA Method showed that TWA can identify individuals with preserved LVEF but heightened risk for sudden cardiac death. Positive predictivity in this population is relatively low, in the 8-10% range, typical for prognostic markers applied to low-risk groups.

Combinations of Noninvasive Parameters to Improve Risk Stratification

Improved risk stratification in patients with preserved LVEF may be attained by a combination of noninvasive markers, since the capacity to detect risk increases markedly when more than one factor is analyzed (83). Hazard or odds ratios were more than doubled and positive predictive value was improved by 40% to 78% when cardiac electrical instability quantified by TWA (48,84) was combined with signal averaged ECG or heart rate recovery, which are independent markers of risk of cardiovascular death and may disclose the pathologic basis for TWA. Use of combinations of noninvasive parameters, specifically including TWA, was recently recommended in a National Heart, Lung, and Blood Institute and Heart Rhythm Society Workshop report on sudden cardiac death prediction and prevention (85), citing complexities of myocardial substrates underlying sudden cardiac death risk. However, high levels of TWA even in the absence of additional risk markers should be noted.

Quantitative Analysis of TWA Voltage

Graded Assessment of Risk. To date, most TWA studies have employed a binary approach to classify test results as either normal or abnormal based on a cutpoint. However, as

TWA reflects a continuum of cardiac electrical instability, its quantification offers the potential for diagnosing levels of risk and for improving prognostics. Treating a continuous variable as binary may reduce predictive power by one third to one half (86).

Clinical studies using either the Spectral (27,87) or MMA Methods (27,47,49,51) reveal that higher TWA magnitudes indicate increased risk for ventricular tachyarrhythmias. Klingenheben et al (87) found in patients with infarct-related or nonischemic cardiomyopathy that TWA magnitude, not merely its presence, was associated with tachyarrhythmic complications. In the FINCAVAS database, Minkkinen (47), Slawnych (51), and Leino et al (49) reported that sudden cardiac death incidence and cardiovascular and total mortality rose with elevated TWA values (Fig. 7) (51). Leino et al (49) determined that risk for cardiovascular death and sudden cardiac death increased by 55% and 58%, respectively, for each 20 μV of TWA. A crescendo in TWA magnitude consistently occurred prior to onset of life-threatening ventricular tachyarrhythmias in ambulatory subjects with ischemic heart disease enrolled in the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) trial (27). During the arrhythmia-free period, TWA was significantly lower than during the 15 minutes immediately preceding ventricular tachycardia onset.

Quantitative TWA analysis may allow tracking changes in risk over time, as patients recover and the myocardium remodels, as cardiac disease or heart failure status are altered, or in response to medical therapy. TWA quantification may also permit comparison of risk levels across different populations and disease states. For example, it was recently shown that TWA is markedly elevated (≥60 μV) in dialysis patients in the absence of an acute cardiovascular event, consistent with their established heightened risk for sudden cardiac death (88).

Guiding Medical Therapy. Clinical studies and reports suggest that the magnitude of TWA reflects the effects of pharmacologic therapy without reducing the phenomenon's predictive capacity (89). Beta-adrenergic (24,25,43) and sodium channel blocking agents (90)

diminish TWA magnitude, reflecting these agents' capacity to reduce sudden cardiac death and cardiovascular mortality (91). In the Brugada syndrome, sodium channel blockade provokes the diagnostic ECG changes as well as macroscopic TWA and arrhythmias (92). The proarrhythmic effects associated with cardiovascular and non-cardiovascular agents may also be disclosed by elevated levels of TWA

Because antiadrenergic and antiarrhythmic drugs influence TWA, the decision to withhold these agents at the time of TWA testing is a matter of debate. Some investigators withheld beta-blocker therapy to avoid drug-induced chronotropic incompetence (59,63,64,69,93-95), whereas others performed the test with full cardioprotective medication (96-99). In a meta-analysis, Chan et al (43) determined that TWA's predictive capacity for ventricular arrhythmic events was significantly weaker in studies withholding beta-blockade therapy (relative risk=1.40; 95% CI, 1.06-1.84; p=0.02) than in studies performed with discharge medications (relative risk=5.39; 95% CI, 2.68-10.84; p<0.001) (Fig. 8). An important corollary of these findings is that the effects of medications on TWA may represent not a disruption in measurement but an indication of therapeutic efficacy (89).

Summary and Recommendations for Clinical Practice

An extensive body of evidence from prospective studies in patients with depressed or preserved LVEF supports the use of TWA analysis in assessing risk for cardiovascular mortality and sudden cardiac death (Tables 1,2) (100). Hazard ratios generated by the Spectral and MMA Methods are similar, whether in the same population (50) or in studies overall. Multivariate analyses confirm that TWA provides information beyond standard clinical variables for cardiovascular disease, including demographic factors (e.g., age, sex, and race) and traditional cardiovascular risk markers (e.g., smoking, blood pressure, history, and medications). Currently, the only established risk marker for sudden cardiac death and the only parameter approved to

identify high-risk patients for ICD implantation is depressed LVEF (101). This parameter has significant limitations, as underscored by the fact that the majority of individuals who die suddenly have preserved LVEF (81). TWA is being assessed along with candidate genes as arrhythmia markers in a large cohort of patients with ICDs for ICD shock risk and mortality in the "EU TrigTreat Clinical Study: An Arrhythmia Risk Stratification and Genetic Trial" (EUTrigTreat) (Clinical Trials.gov identifier #NCT01209494) and in the Medtronic Genetic Arrhythmia Markers for Early Detection (GAME Study) (Clinical Trials.gov identifier #NCT00664807).

Accordingly, we concur with the recommendations of guidelines committees of the American Heart Association, American College of Cardiology, European Society of Cardiology, and/or Heart Rhythm Society by Zipes et al (102), who assigned Class I Level of Evidence A and Class IIa Level of Evidence A indications to TWA testing for arrhythmia risk, and by Goldberger et al (103), that TWA provides valuable information regarding risk for cardiovascular mortality and sudden cardiac death. Additional applications recommended by task force or consensus statement authors are in neonates, in whom the appearance of TWA signals the highest level of risk (104), and in hospital settings to warn of the development of torsade de pointes (105).

Interventional trials, which have been performed to date only with the Spectral Method, have not demonstrated that a negative TWA test result can sufficiently guide decision-making regarding ICD implantation (63,64,69). Thus, TWA should not be used as a sole parameter either to rule in or to rule out ICD implantation. A clinical algorithm that incorporates LVEF and electrophysiologic study in the decision-making process seems promising based on a meta-analysis (62). However, this proposal will require prospective testing. Also, use of more advanced statistical approaches and criteria for evaluation of novel markers of cardiovascular risk is recommended (106).

Acknowledging the complexities of myocardial substrates underlying sudden cardiac death risk, a recent National Heart, Lung, and Blood Institute and Heart Rhythm Society Workshop report on prediction and prevention proposed combinations of risk markers specifically including TWA (85). The utility of ambulatory TWA combined with heart rate turbulence, an indicator of baroreceptor sensitivity (107), to identify post-myocardial infarction patients with preserved LVEF who would benefit from ICD implantation is the subject of an ongoing clinical trial, Risk Estimation Following Infarction, Noninvasive Evaluation of ICD Therapy (REFINE-ICD) (108) (Clinical trials.gov identifier #NCT00673842).

The time period for optimum predictive accuracy of TWA for arrhythmic events, cardiovascular mortality, and total mortality in patients with acute myocardial infarction is under investigation in a clinical trial, "T-Wave Alternans in Acute Myocardial Infarction: An Evaluation of the Time of Testing on Its Prognostic Accuracy" (Clinical trials.gov identifier #NCT00589849). Exner et al determined that for long-term prediction, TWA testing should be performed at 10-14 weeks following myocardial infarction (50). However, there is a rationale for considering earlier TWA testing, as 1.4% of patients (~17,500 in the United States) experience sudden cardiac death in the first month after myocardial infarction during the acute remodeling period (109).

Evidence supports the value of quantitative TWA analysis for both the Spectral and MMA Methods. Quantification offers inherent advantages with respect to gauging level of risk across time following cardiovascular events and in evaluation of the potential anti- and proarrhythmic effects of medical therapy by conventional and nonconventional agents (89). These applications merit exploration in interventional trials.

It is recommended that TWA testing be performed on discharge medications, particularly with respect to beta-blockade therapy (24,43), to ensure that the test results reflect the effects of chronic drug therapy.

Overall, our assessment is that it is reasonable to consider TWA evaluation whenever there is suspicion of vulnerability to lethal cardiac arrhythmias. However, there is as yet no definitive evidence from interventional trials that it can guide therapy.

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FIGURE LEGENDS:

Fig. 1: TWA and Non-Alternating Fluctuations. (**A**) Precordial (V4) ECG rhythm strip (left) and high-resolution template of QRS-aligned complexes (right) during routine exercise testing from a patient with coronary artery disease. The template illustrates TWA as a separation between ST-T segments in A and B beats. TWA magnitude =106μV. mV = millivolt; sec = second. (**B**) Non-alternating fluctuations in T-wave amplitude following ajmaline administration in a Brugada syndrome patient.

Fig. 2: Discordant alternans leading to VF. Action potential propagation between two ventricular sites (*A* to *B*) is shown. *L* indicates long and *S* short action potential durations. Shaded bars show dispersion of repolarization between sites. Transition from concordant to discordant alternans and development of ventricular fibrillation (VF) are shown. Premature beats are represented by asterisks (6) (Adapted with permission from Springer.)

Fig. 3: Interlead discordant alternans. Mid-myocardial/epicardial recordings following an abrupt decrease in pacing cycle length from 1,000 to 500 msec. Marked discordant alternans is associated with the onset of ventricular tachyarrhythmia following a premature beat (asterisk). Ventricular tachycardia was initiated by a premature focal discharge from a left ventricular endocardial site, which induced areas of functional conduction block and reentrant excitation. Numbers above tracing are calculated activation-recovery intervals (ARI). Numbers below tracing are dispersion of ARI between mid-myocardial and epicardial sites (7). (Reprinted with permission from John Wiley & Sons.)

Fig. 4: Spectral TWA method. Schematic representation of T-wave alternans (TWA) assessment of the electrocardiogram (ECG) using the Spectral Method (36). See text for details. (Adapted with permission from Saunders.)

Fig. 5: MMA TWA method. Flow chart of the major components of the Modified Moving Average (MMA) Method of T-wave alternans (TWA) analysis (20). See text for details. (Adapted with permission from American Physiological Society.)

Fig. 6: (**A**) ALPHA TWA study: Kaplan-Meier cumulative event-free (cardiac death/life-threatening arrhythmias) survival according to T-wave alternans (TWA) Spectral Method testing (99). Patients at risk are shown at selected time points.

(**B**) Ambulatory ECG TWA study. Event-free (cardiac mortality in ischemic (A) and nonischemic (B) subgroups) based on maximum T-wave alternans (TWA) voltage by the Modified Moving Average (MMA) Method (54). (Adapted with permission from Lippincott, Williams & Wilkins.)

(**C**) REFINE TWA study. Risk of cardiac death or resuscitated cardiac arrest (primary outcome) among patients with impaired autonomic tone, measured using heart rate turbulence + abnormal repolarization alternans + ejection fraction <50% versus remaining patients. Left panel indicates TWA results with the Spectral Method during exercise; right panel indicates results of Modified Moving Average (MMA) analysis during recovery from exercise. Patients at risk are shown at selected time points. TWA=T-wave alternans; LVEF = left ventricular ejection fraction (50).

(**D**) TWA substudy of SCD-HeFT trial. Comparison of primary event rates for microvolt T-wave alternans (MTWA) in non-negative (broken line) and negative (solid line)

patients (n=490). No significant difference between event rates was found for the 2 groups (63). (Reprinted with permission from Lippincott, Williams & Wilkins.)

Fig. 7: Beta-blocker TWA meta-analysis. Association between microvolt T-wave alternans (MTWA) analyzed by the Spectral Method and ventricular arrhythmic events, stratified by screening protocol discontinuation of beta-blocker therapy (43). Washout of beta-adrenergic blockade impaired predictivity. *Study estimates for meta-analysis were hazard or risk ratios; **No events in MTWA negative group (p=0.04). RR=12.44 reflects 0.5 correction factor; therefore, no 95% confidence interval is depicted; ***Test for heterogeneity: p=0.025. (Reprinted with permission from John Wiley & Sons.)

Fig. 8: REFINE/FINCAVAS TWA study. Rates of cardiovascular death (orange) and total mortality (blue) at 4 years, by quintile of TWA magnitude using the Modified Moving Average (MMA) Method (51).

Table 1: Clinical Studies with the Spectral Method Enrolling >100 Patients

	PATIENT POPULATION (ENROLLMENT, DISEASE)	*MEAN LEFT VENTRICULAR EJECTION FRACTION*	*HAZARD RATIOS FOR TWA*
Predictive Studies			
Cardiomyopathy			
Kitamura et al 2002 (110)	104 patients with DCM	37%	11.9 (1.53-92.59) for SCD, VF, or sustained VT at 21±14 months
Hohnloser et al 2003a (97)	137 patients with DCM, LVEF ≤35%	29±11%	3.44 for ventricular tachyarrhythmic events at 14±6 months
Chow et al 2006 (93)	514 patients with ischemic cardiomyopathy, LVEF ≤35%, no previous sustained ventricular arrhythmia and positive or indeterminate TWA test results [patients included in Chow et al 2007b (113)]	26-29%	2.24 (1.34-3.75) for all-cause mortality; 2.29 (1.00-5.24) for arrhythmic mortality; NS for nonarrhythmic mortality
Salerno-Uriarte et al 2007 (ALPHA) (99)	446 patients with DCM, LVEF ≤40%	29.5%	4.0 (1.4-11.4) for cardiac death and life-threatening arrhythmias at 18 months
Chow et al 2007b (94)	768 patients with ischemic	26-29%	2.27 (1.22-4.24) for all-cause mortality in

	cardiomyopathy, LVEF ≤35%, no previous sustained ventricular arrhythmia		patients without an ICD; 2.42 (1.07-5.41) for all-cause mortality or appropriate ICD discharge in patients with an ICD
Chan et al 2008 (111)	768 patients with ischemic cardiomyopathy, LVEF ≤35%, no previous sustained ventricular arrhythmia [same patients as Chow 2007b (113)]	26-29%	2.19 (1.1-4.34) for all-cause mortality and appropriate ICD shocks at 1 year; 3.36 (1.28-8.83) at 2 years
Costantini et al 2009 (ABCD) (69)	566 patients with ischemic cardiomyopathy, LVEF ≤40%, and NSVT	28±8%	2.1 for SCD or appropriate ICD discharge at 1 year
Congenital Heart Disease			
Alexander et al 2006 (112)	304 consecutive pediatric patients with congenital heart disease, myopathy, syncope or history of cardiac arrest	Not stated	7.9 (95% CI, 2.2-28.1) for ventricular arrhythmia; 6.7 (1.6-28.1) for cardiac arrest at <3 years
Depressed LVEF			
Rashba et al 2002b (113)	108 consecutive patients with CAD and LVEF ≤40%	28±7%	2.2 (1.1– 4.7) for death, sustained ventricular arrhythmias, appropriate ICD discharge at 18±13 months in patients with normal QRS segment; NS in patients with prolonged QRS segment

Rashba et al 2004 (114)	144 patients with CAD and LVEF ≤40%	28±7%	2.2 (1.1-4.7) for death, sustained ventricular arrhythmia, or appropriate ICD discharge at 17±13 months; NS in patients with LVEF <30%; ∞ in patients with LVEF >30%
Bloomfield et al 2006 (98)	549 patients with LVEF ≤40%, no history of sustained ventricular arrhythmias	25%	6.5 (2.4-18.1) for all-cause mortality or nonfatal sustained ventricular arrhythmia at 2 years
Cantillon et al 2006 (115)	286 patients with LVEF ≤35%, NSVT or syncope	26±7%	2.33 (1.44–3.67) for arrhythmia-free survival at 38±11 months
Morin et al 2007 (116)	386 patients with CAD, NSVT, LVEF ≤40%	26-30%	1.64 for ventricular tachyarrhythmia or death in patients with narrow QRS segment at 40±19 months; NS in patients with wide QRS segment
Heart Failure			
Klingenheben et al 2000 (96)	107 consecutive patients with congestive heart failure, LVEF ≤45%, no history of arrhythmia, and no recent MI	28±7%	∞ for SCD, arrhythmias, sustained VT at 14.6 months
Gorodeski et al 2009 (117)	303 consecutive patients with heart failure and LVEF ≤40%	24%	1.89 (1.05-3.39) for total mortality or cardiac transplantation; NS after adjustment for metabolic measures at 2.8 years. Concordance

			index for time-to-event outcomes = 0.75. C statistic for propensity score = 0.79.
Post-Myocardial Infarction			
Ikeda et al 2000 (84)	102 post-MI patients	20-40%	16.8 (2.2–127.8) for arrhythmic events
Ikeda et al 2002 (118)	850 post-MI patients [some patients included in Ikeda 2006 (94)]	51±13%	5.9 (1.6-21.4) for SCD or resuscitated VF at 25±13 months; 82% were monitored at 2 to 10 weeks after MI
Bloomfield et al 2004 (65)	177 MADIT-II like post-MI patients with LVEF ≤30	23±6%	4.8 for all-cause mortality at 2 years
Ikeda et al 2006 (82)	1,041 post-MI patients with LVEF >40%	55±10%	23.5 monitored at 48±66 days for SCD or life-threatening arrhythmia at 32±14 months
Exner et al 2007 (REFINE) (50)	322 post-MI patients with LVEF <50	40% within 1 week and 47% at 8 weeks after MI	2.75 (1.08–7.02) monitored at 10 to 14 weeks after MI for cardiovascular death or resuscitated cardiac arrest (primary endpoint) at 47 months; NS if monitored at 2-4 weeks after MI. Area under ROC curve for primary endpoint = 0.62; for combination of TWA + HRT, area under ROC = 0.70.
Referred for Electrophysiologic Study			

Gold et al 2000 (44)	313 patients	44±18%	10.9 for SCD, sustained VT, VF, or appropriate ICD discharge at 400 days
Rashba et al 2002c (39)	251 patients with CAD and LVEF	27±8%	2.2 (1.1-4.7) for arrhythmic events (arrhythmic death, VT, aborted VF) at 499±395 days; NS for TWA during atrial pacing at 100-120 beats/min
Non-Predictive Studies			
Schwab et al 2001 (60)	140 post-MI patients	56±14%	NS if monitored at 15±6 days after MI for SCD or sustained VT at 451±210 days
Tapanainen et al 2001 (61)	379 consecutive post-MI patients	45±10%	NS for TWA monitored at ~8 days after MI for all-cause mortality or cardiac death at 14.8 months
Grimm et al 2003 (59)	343 patients with DCM, LVEF ≤45%	31±10%	NS for SCD, VF, or sustained VT at 52 months
Ikeda et al 2005 (74)	124 consecutive subjects with Brugada-type ECG	[not stated]	NS for SCD or VT at 40±19 months
Gold et al 2008 (SCD-HeFT TWA substudy) (63)	490 patients with congestive heart failure	24±7%	NS for SCD, sustained VT/VF, or appropriate ICD discharge at 2.5 years
Chow et al 2008	575 post-MI patients with LVEF ≤30%	24±5%	2.04 (1.10 to 3.78) for total mortality at

(MASTER) (64)			2.1±0.9 years; NS for ventricular tachyarrhythmic events
Huikuri et al 2009 (CARISMA) (119)	312 post-MI patients	31±6%	NS for TWA monitored at 6 weeks after MI for VF or symptomatic, sustained VT at 2 years

Note: See text for discussion of nonsignificant prediction among studies with high or low ICD use, continuance or withdrawal of beta-adrenergic blockade for test, or test time after MI. This table was developed from searches of the medical literature on the terms alternans and alternation in PubMed (National Library of Medicine, Bethesda MD) and Paperchase (Bedford MA) databases. Reference lists from these studies, from meta-analyses (48,62,100), and from recent reviews (2-6, 34) were also scanned. Only clinical studies that enrolled over 100 patients and reported hazard ratios were included.

Key: ABCD = Alternans Before Cardioverter Defibrillator; ALPHA = T-Wave Alternans in Patients With Heart Failure; CAD = coronary artery disease; CARISMA = Cardiac Arrhythmias and Risk Stratification after Acute Myocardial Infarction; DCM = dilated cardiomyopathy; EP = electrophysiologic; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MADIT = Multicenter Automatic Defibrillator Trial; MASTER = Microvolt T Wave Alternans Testing for Risk Stratification of Post-Myocardial Infarction Patients; NS = nonsignificant; NSVT = nonsustained ventricular tachycardia; REFINE = Risk Estimation Following Infarction, Noninvasive Evaluation; ROC = receiver-operator characteristic curve; SCD = sudden cardiac death; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial; TWA = T-wave alternans; VF = ventricular fibrillation; VT = ventricular tachycardia

Table 2. Clinical Studies with the Modified Moving Average Method

TEST SETTING	*PATIENT POPULATION (DISEASE, ENROLLMENT CRITERIA, MEAN AGE)*	*MEAN LEFT VENTRICULAR EJECTION FRACTION*	*HAZARD RATIOS FOR TWA; NEGATIVE AND POSITIVE PREDICTIVE VALUES*
Routine Exercise Testing			
Nieminen et al 2007 (FINCAVAS) (46)	1037 consecutive patients referred for routine exercise testing; 58+13 years [patients included in Leino et al 2011 (61)]	Mostly preserved	6.0 (95% CI: 2.8-12.8) for CV death at 44+7 months for 65-μV TWA cutpoint; NPV = 97.6; PPV = 12.6
Minkkinen et al 2009b (FINCAVAS) (47)	2119 consecutive patients referred for routine exercise testing; 57±13 years [patients included in Leino et al 2011 (61)]	Mostly preserved (60-66%)	6.4 (95% CI: 2.0–21.2) for CV death, 4.6 (1.7–12.3) for SCD at 47 months for 60-μV cutpoint; NPV for CV death = 97.4; PPV = 10.2
Leino et al 2011 (FINCAVAS) (49)	3,598 consecutive patients referred for routine exercise testing; 56±13 years	Mostly preserved	1.55 (95% CI: 1.150–2.108, p< 0.004) for CV death; 1.58 (95% CI: 1.041–2.412; p<0.033) for SCD at 55 months per 20 μV TWA in lead V_5.
Exercise Recovery			
Exner et al 2007 (REFINE) (50)	322 post-MI patients; 62 (interquartile range 53-70) years	Moderately depressed (38-48%)	2.94 (1.10–7.87) monitored at 10-14 weeks after event for CV death or resuscitated cardiac arrest (primary endpoint) at 47 months; NS when monitored at 2-4 weeks after MI. For primary

			endpoint for TWA, area under ROC curve = 0.62; for combination of TWA + HRT, area under ROC = 0.71.
Slawnych et al 2009 (REFINE/FINCAVAS) (51)	322 post-MI patients (from REFINE) and 681 CAD patients (from FINCAVAS); 69 (interquartile range 57-76) years	Moderately depressed (38-48%) and preserved (56-63%) groups	2.5 (1.1–6.0) for CV death at 48 months for 60-µV cutpoint; NPV = 96%; PPV= 13%. Area under ROC curve for CV mortality = 0.69.
Leino et al 2009 (FINCAVAS) (48)	1972 consecutive patients referred for routine exercise testing; 57±13 years [patients included in Leino et al 2011 (61)]	Mostly preserved (60-66%)	3.5 (1.6-7.9) for CV death at 48 months for 60-µV cutpoint. For CV death, C-statistic = 0.550-0.606; for combination of TWA + HRR, C-statistic = 0.671-0.691.
Ambulatory ECG monitoring			
Verrier et al 2003 (ATRAMI) (52)	Acute post-MI; Case: control analysis (15 cases: 29 controls) from 1284 ATRAMI patients, monitored at 15±10 days post-MI; 60-62 years	Moderately depressed (42±3%)	7.9 (1.9–33.1) for cardiac arrest or arrhythmic death at 21 months for *a priori* 75^{th} %ile cutpoint (47 µV); patients were monitored at 15±10 days post-MI
Stein et al 2008 (EPHESUS) (52)	Acute post-MI, LVEF ≤40%, and heart failure; Case: control analysis (46 cases: 92 controls)	Depressed (34±5 %)	5.5 (2.2–13.8) for SCD at 16.4 months for 47-µV cutpoint; patients were monitored at 2-10 days post-MI. For SCD, area under ROC curve

	from 6632 EPHESUS patients, monitored at 2-10 days post-MI; 68±11 years		= 0.73 for lead V1 and = 0.70 for lead V3 (P < 0.001).
Sakaki et al 2009 (54)	295 consecutive cardiomyopathy patients with ischemic or nonischemic left ventricular dysfunction; 66±16 years	Depressed (34±6%)	17.1 (6.3–46.6) for CV death, 22.6 (2.6 –193.7) for witnessed SCD at 1 year for 65-μV cutpoint; NPV for CV death = 97%; PPV = 37%
Maeda et al 2009 (56)	63 consecutive patients including 21 controls, 21 post-MI patients without VT, and 21 post-MI patients with VT; 65±11 years	Depressed (36-43%) for post-MI group	6.1 (1.1–34.0) for sustained VT or VF at 6 years for 65-μV cutpoint
Stein et al 2010 (CHS) (55)	General population patients ≥65 years old; case: control analysis (49 cases: 98 controls) from 1649 CHS patients	Not tested, assumed preserved	4.8 (1.48-15.81) for SCD at 14 years

Note: This table is based on searches of the medical literature on the terms alternans and alternation for all clinical studies that reported hazard ratios in PubMed (National Library of Medicine, National Institutes of Health, Bethesda MD) and Paperchase (Bedford MA) databases. Reference lists from these studies and from recent reviews (2-5, 34) were also scanned.

Key: ATRAMI = Autonomic Tone and Reflexes after Myocardial Infarction; CAD = coronary artery disease; CI = confidence interval; CHS = Cardiovascular Health Study ; CV = cardiovascular; EPHESUS = Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; FINCAVAS = Finnish Cardiovascular Study; HRR = heart rate recovery; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NPV = negative predictive value; PPV = positive predictive value; REFINE = Risk Estimation Following Infarction, Noninvasive Evaluation; ROC = receiver-operator characteristic curve; SCD = sudden cardiac death; NS = nonsignificant; VF = ventricular fibrillation; VT = ventricular tachycardia

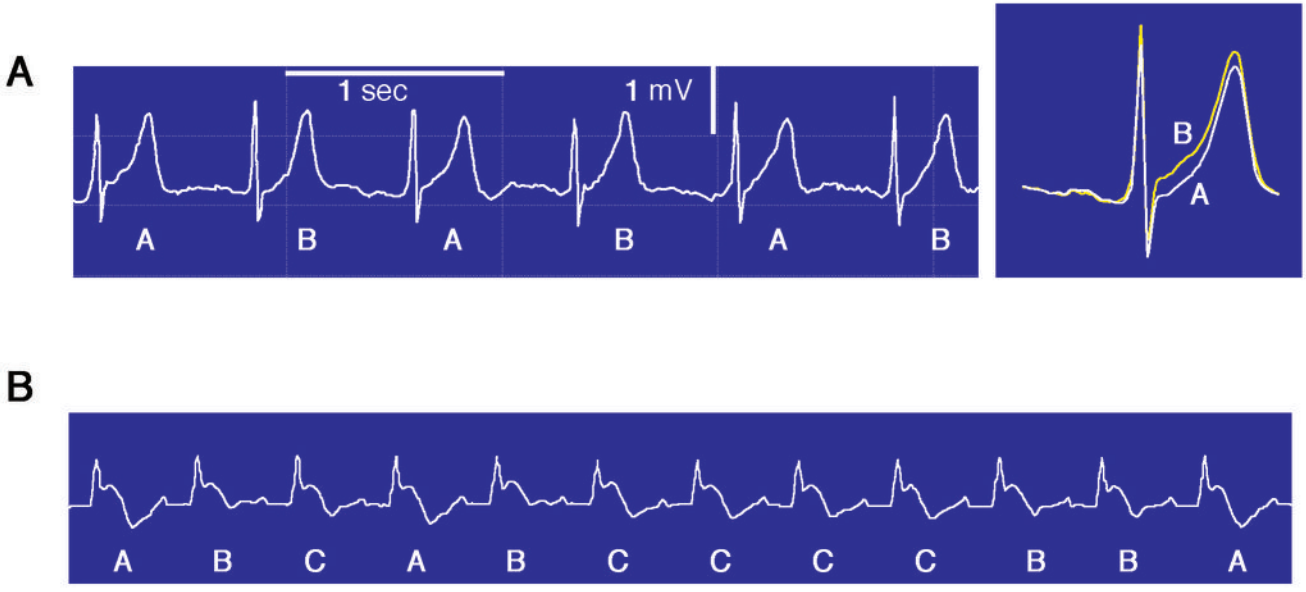

Figure 1

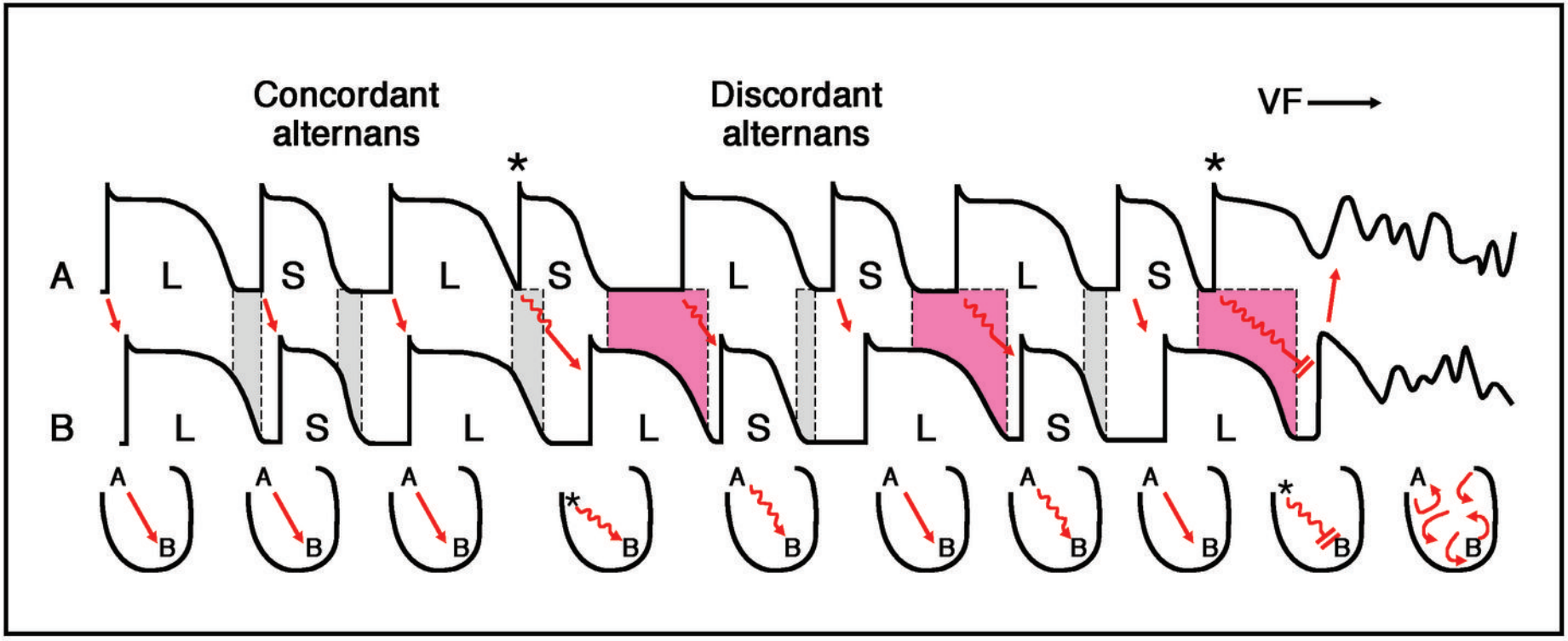

Figure 2

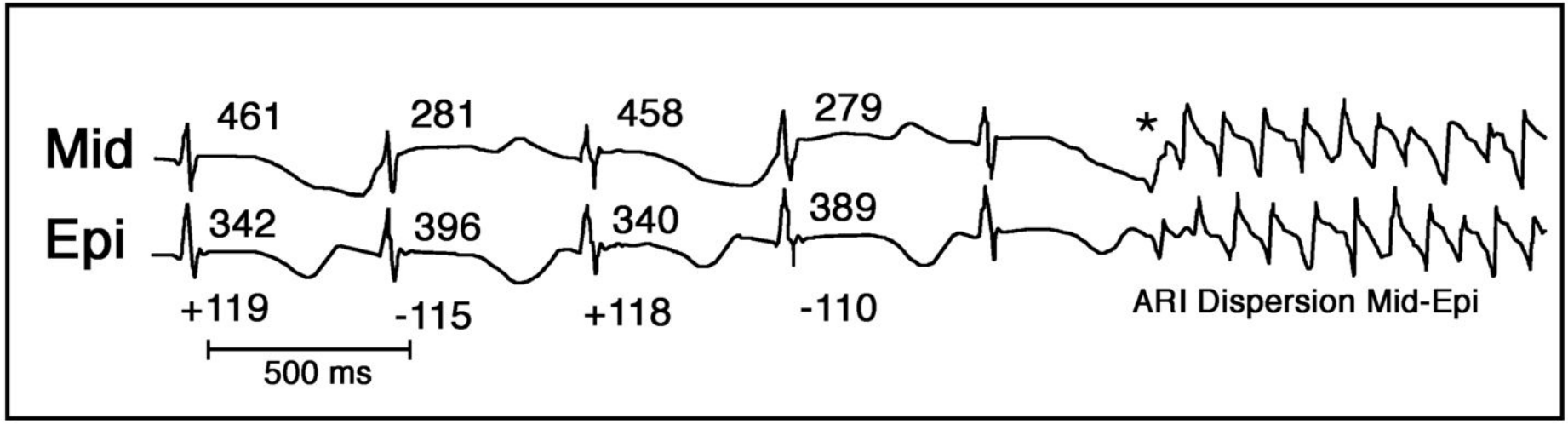
Mid
Epi
461
281
458
279
342
396
340
389
*
+119
-115
+118
-110
500 ms
ARI Dispersion Mid-Epi

Figure 3

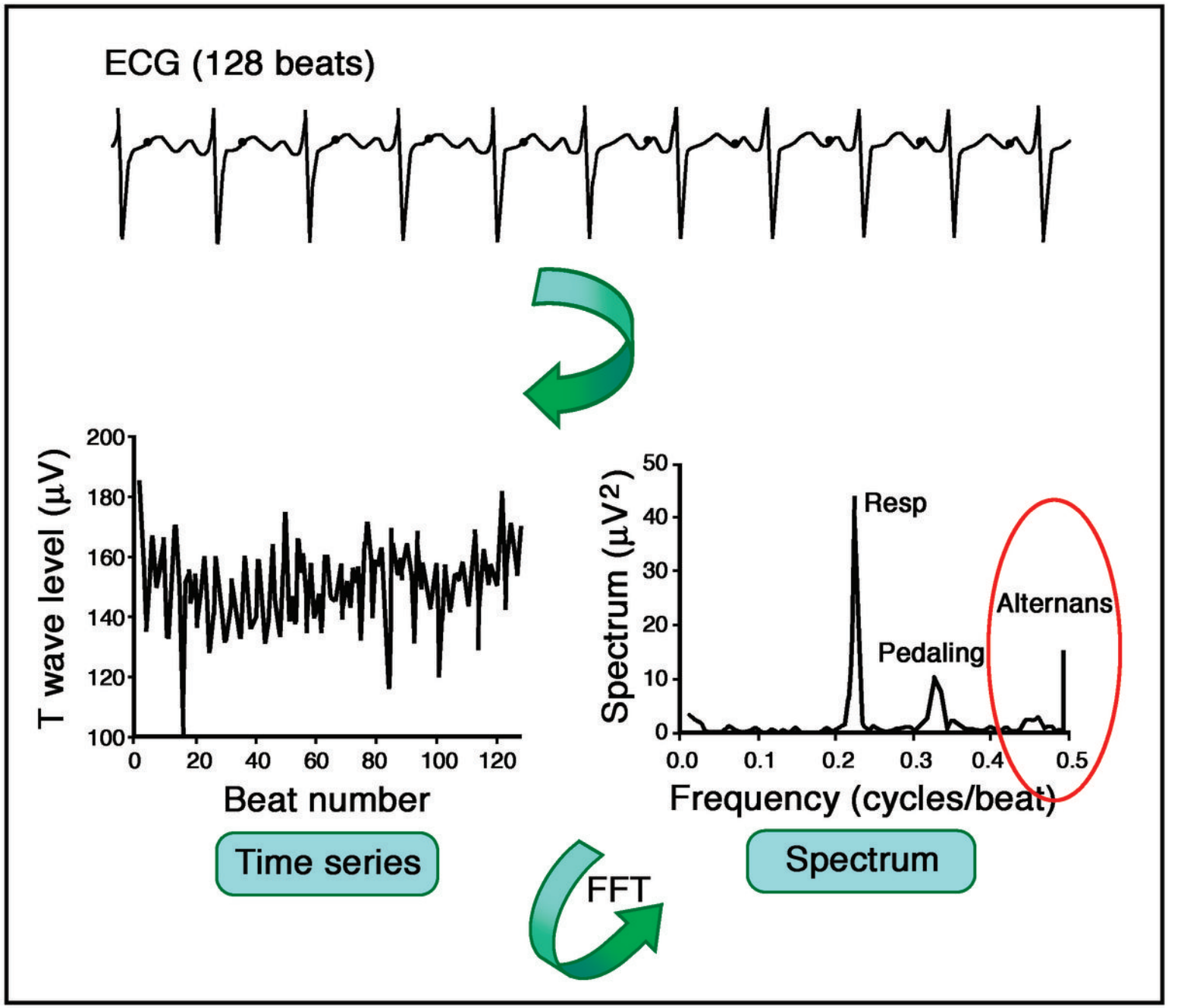
ECG (128 beats)
T wave level (μV)
200
180
160
140
120
100
0
20
40
60
80
100
120
Beat number
Time series
FFT
Spectrum (μV²)
50
40
30
20
10
0
Resp
Pedaling
Alternans
0.0
0.1
0.2
0.3
0.4
0.5
Frequency (cycles/beat)
Spectrum

Figure 4

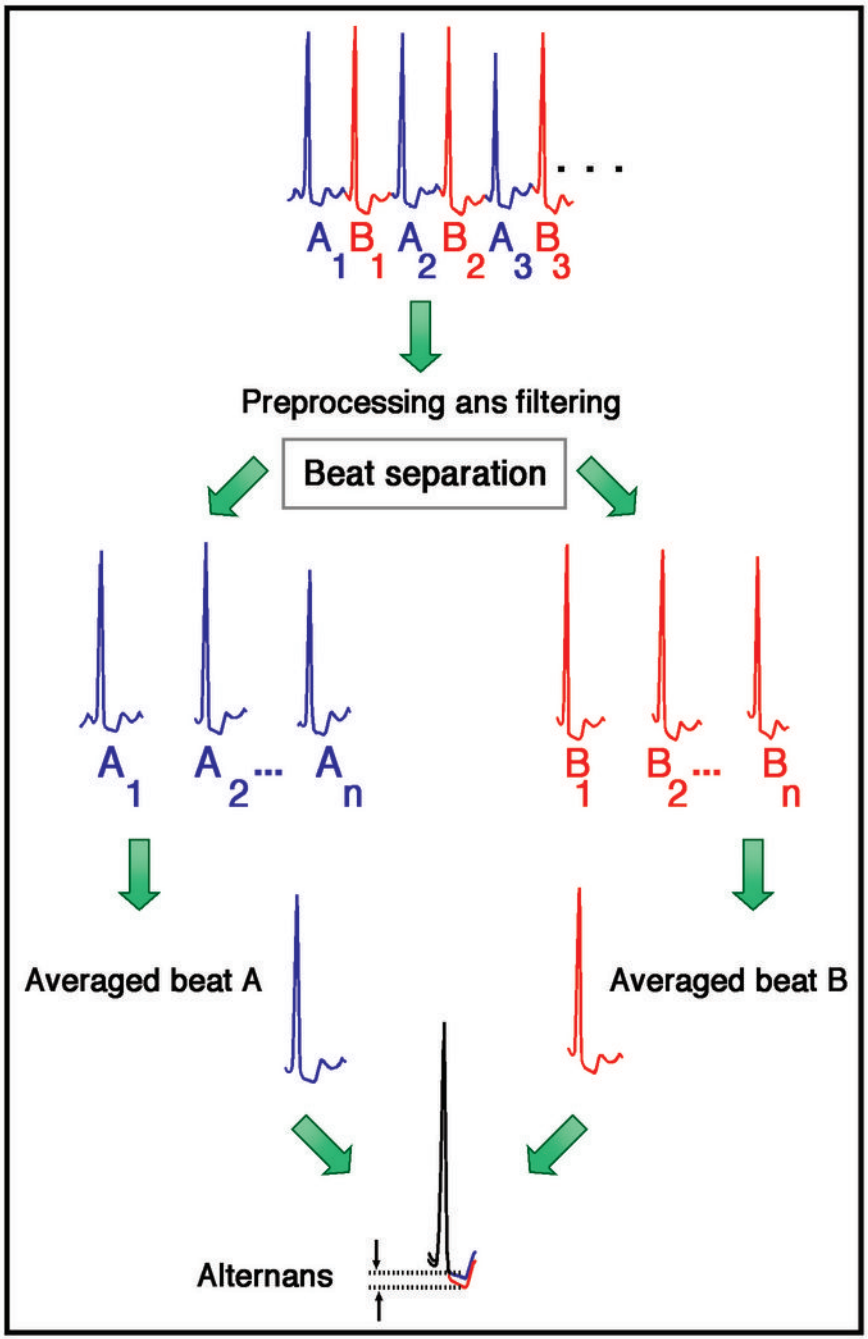
A1 B1 A2 B2 A3 B3 . . .
Preprocessing ans filtering
Beat separation
A1 A2 ... An
B1 B2 ... Bn
Averaged beat A
Averaged beat B
Alternans

Figure 5

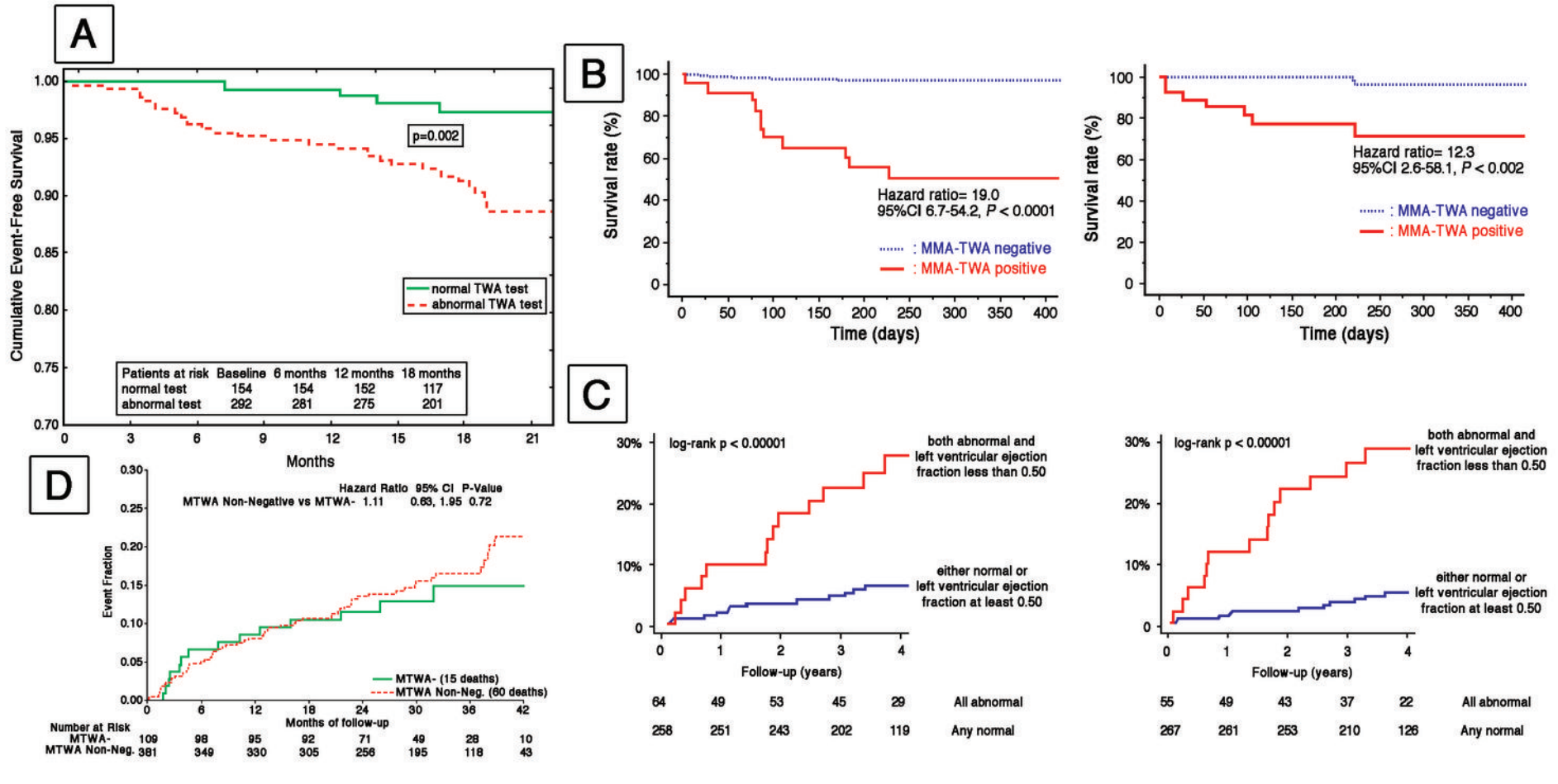
A
Cumulative Event-Free Survival
1.00
0.95
0.90
0.85
0.80
0.75
0.70
p=0.002
normal TWA test
abnormal TWA test
Patients at risk Baseline 6 months 12 months 18 months
normal test 154 154 152 117
abnormal test 292 281 275 201
0 3 6 9 12 15 18 21
Months
B
Survival rate (%)
100 80 60 40 20 0
Hazard ratio= 19.0
95%CI 6.7-54.2, P < 0.0001
: MMA-TWA negative
: MMA-TWA positive
0 50 100 150 200 250 300 350 400
Time (days)
Survival rate (%)
100 80 60 40 20 0
Hazard ratio= 12.3
95%CI 2.6-58.1, P < 0.002
: MMA-TWA negative
: MMA-TWA positive
0 50 100 150 200 250 300 350 400
Time (days)
C
30%
20%
10%
0
log-rank p < 0.00001
both abnormal and left ventricular ejection fraction less than 0.50
either normal or left ventricular ejection fraction at least 0.50
0 1 2 3 4
Follow-up (years)
64 49 53 45 29 All abnormal
258 251 243 202 119 Any normal
30%
20%
10%
0
log-rank p < 0.00001
both abnormal and left ventricular ejection fraction less than 0.50
either normal or left ventricular ejection fraction at least 0.50
0 1 2 3 4
Follow-up (years)
55 49 43 37 22 All abnormal
267 261 253 210 126 Any normal
D
Event Fraction
0.30 0.25 0.20 0.15 0.10 0.05 0.00
Hazard Ratio 95% CI P-Value
MTWA Non-Negative vs MTWA- 1.11 0.63, 1.95 0.72
MTWA- (15 deaths)
MTWA Non-Neg. (60 deaths)
0 6 12 18 24 30 36 42
Months of follow-up
Number at Risk
MTWA- 109 98 95 92 71 49 28 10
MTWA Non-Neg. 381 349 330 305 256 195 118 43

Figure 6

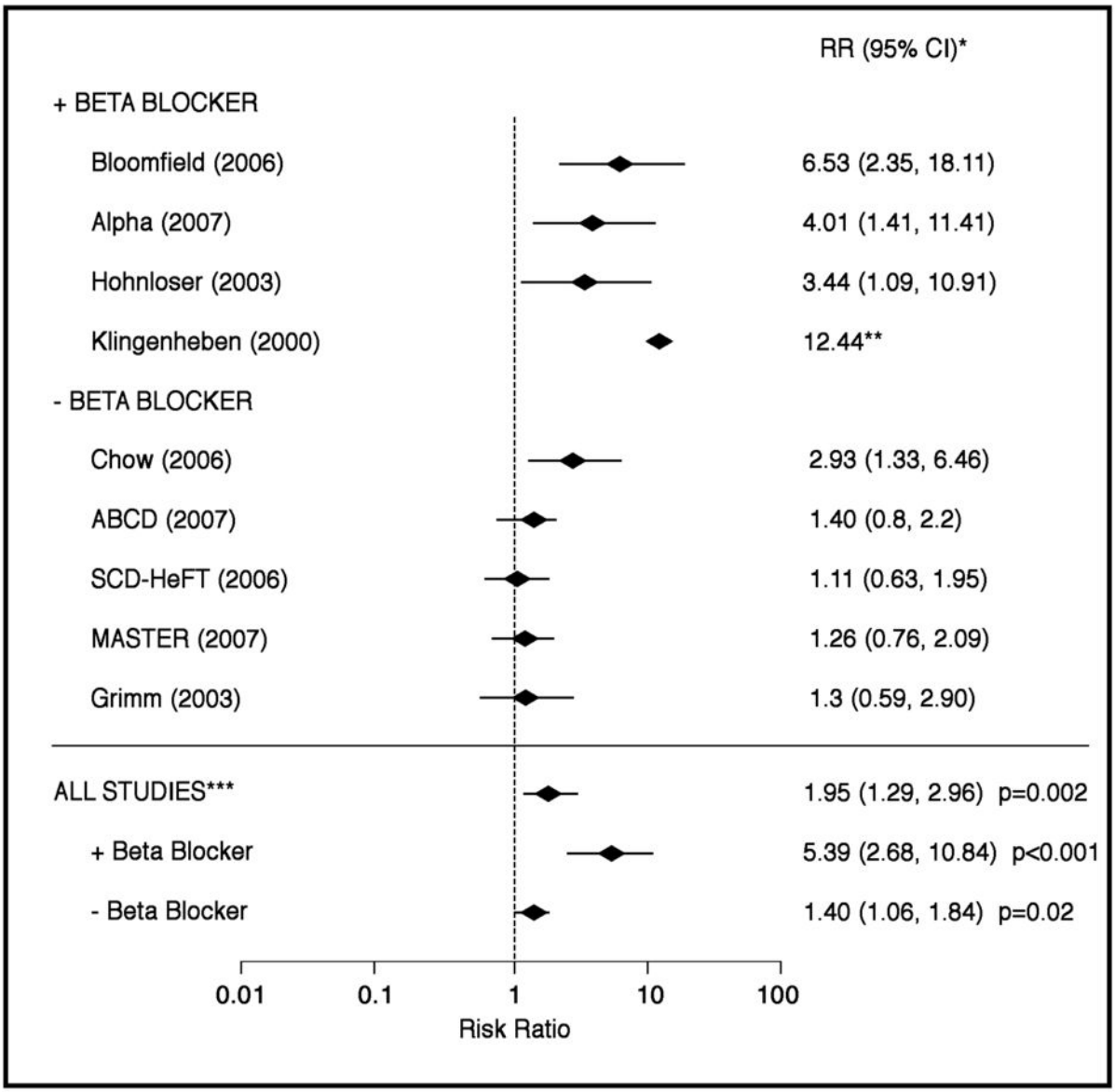
RR (95% CI)*
+ BETA BLOCKER
Bloomfield (2006)
6.53 (2.35, 18.11)
Alpha (2007)
4.01 (1.41, 11.41)
Hohnloser (2003)
3.44 (1.09, 10.91)
Klingenheben (2000)
12.44**
- BETA BLOCKER
Chow (2006)
2.93 (1.33, 6.46)
ABCD (2007)
1.40 (0.8, 2.2)
SCD-HeFT (2006)
1.11 (0.63, 1.95)
MASTER (2007)
1.26 (0.76, 2.09)
Grimm (2003)
1.3 (0.59, 2.90)
ALL STUDIES***
1.95 (1.29, 2.96) p=0.002
+ Beta Blocker
5.39 (2.68, 10.84) p<0.001
- Beta Blocker
1.40 (1.06, 1.84) p=0.02
0.01
0.1
1
10
100
Risk Ratio

Figure 7

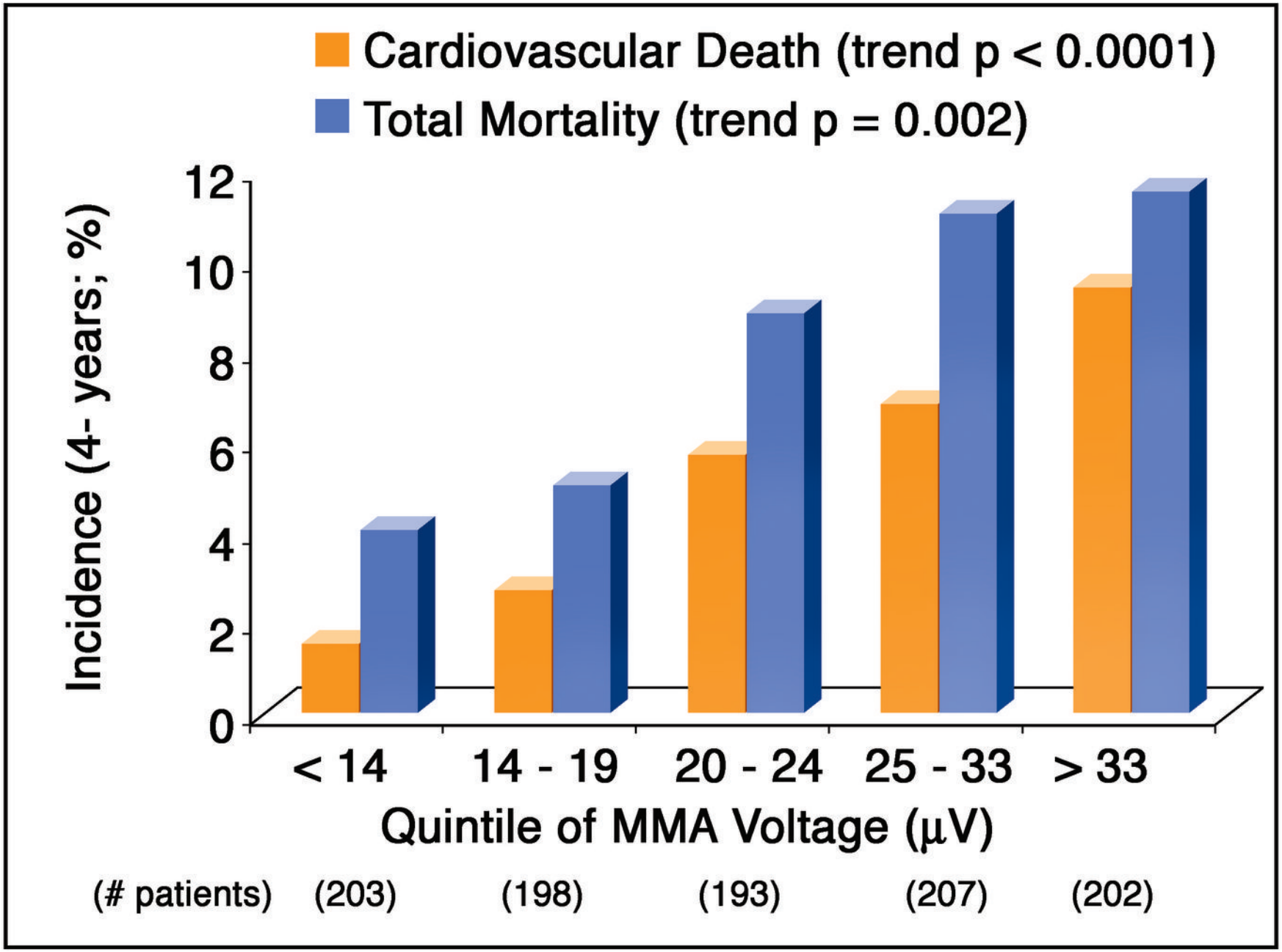
Cardiovascular Death (trend p < 0.0001)
Total Mortality (trend p = 0.002)
Incidence (4- years; %)
0
2
4
6
8
10
12
< 14
14 - 19
20 - 24
25 - 33
> 33
Quintile of MMA Voltage (µV)
(# patients)
(203)
(198)
(193)
(207)
(202)

Figure 8