MicroT-Wave Alternans & Signal Average Electrocardiogram

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Noninvasive Approaches

(1) Slowed conduction (QRS duration, signal-averaged electrocardiogram [SAECG])

(2) Heterogeneities in ventricular repolarization (QT interval, QT dispersion, T-wave alternans)

(3) Imbalance in autonomic tone (heart rate variability [HRV], heart rate turbulence, heart rate recovery after exercise, baroreceptor sensitivity),

(4) Extent of myocardial damage and scar formation (left ventricular ejection fraction [LVEF], 6-minute walk)

(5) Ventricular ectopy (longterm ambulatory monitoring)

Background

- The only established risk marker for sudden cardiac death (SCD) and the only parameter approved to identify high-risk patients for ICD implantation:

"Depressed LVEF"

Circulation 2010;122:1265–71

Background

"Identifying patients who would not benefit from ICD implantation, particularly those fulfilling the MADIT II (Multicenter Automatic Defibrillator Trial II) criteria."

- One-third of ICD patients receives an inappropriate shock within 1 to 3 years of implantation

Circulation 2006;113:776–82

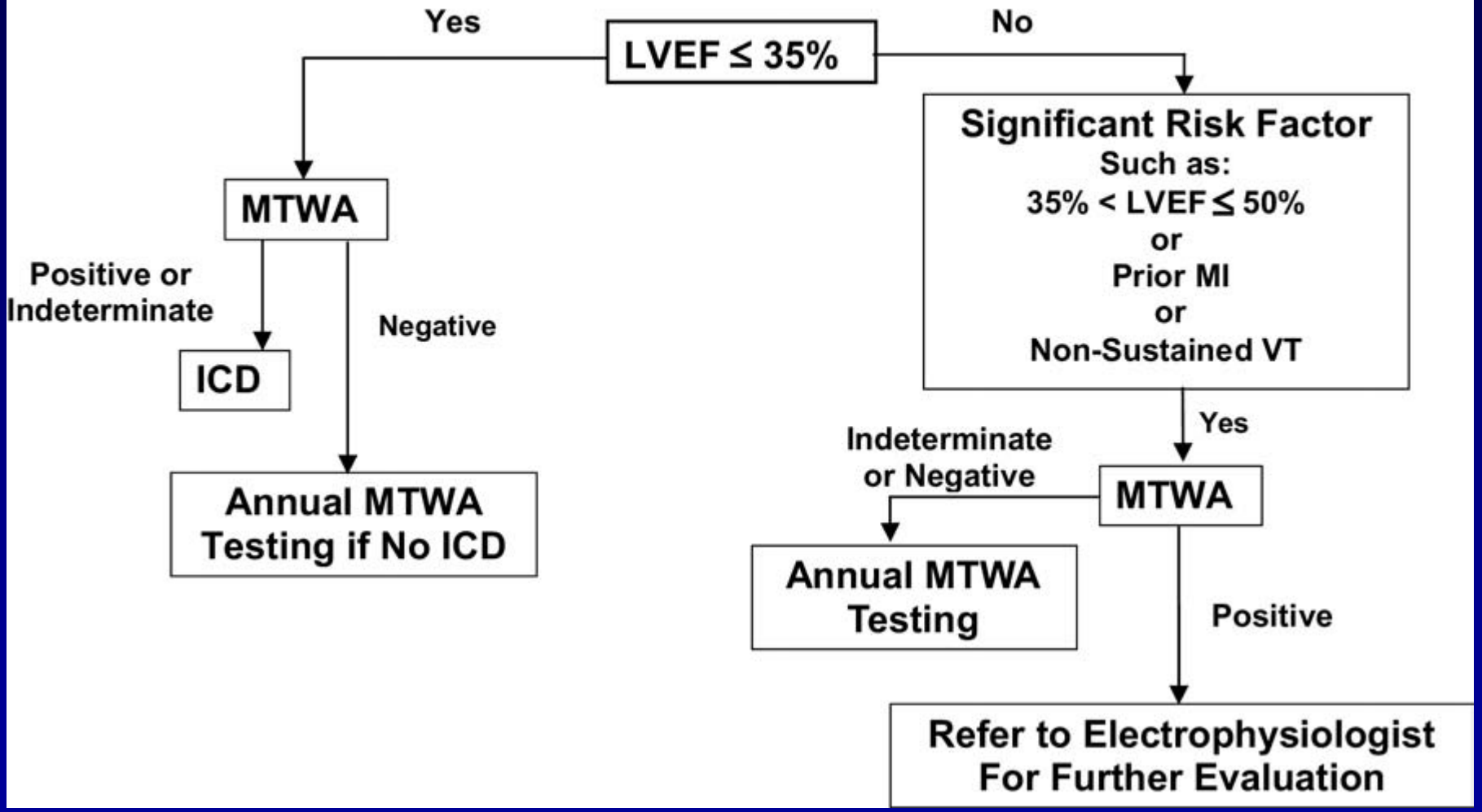
- ICD shock is associated with a 2- to 5-fold increase in mortality, most commonly due to progressive heart failure

J Am Coll Cardiol 2009;54:1993–2000

- Event-free survival from all-cause or cardiac mortality and/or ventricular tachyarrhythmias averaged 97% to 98% in patients with negative micro T wave alternans (mTWA) test results

Lancet 2003;362:125– 6

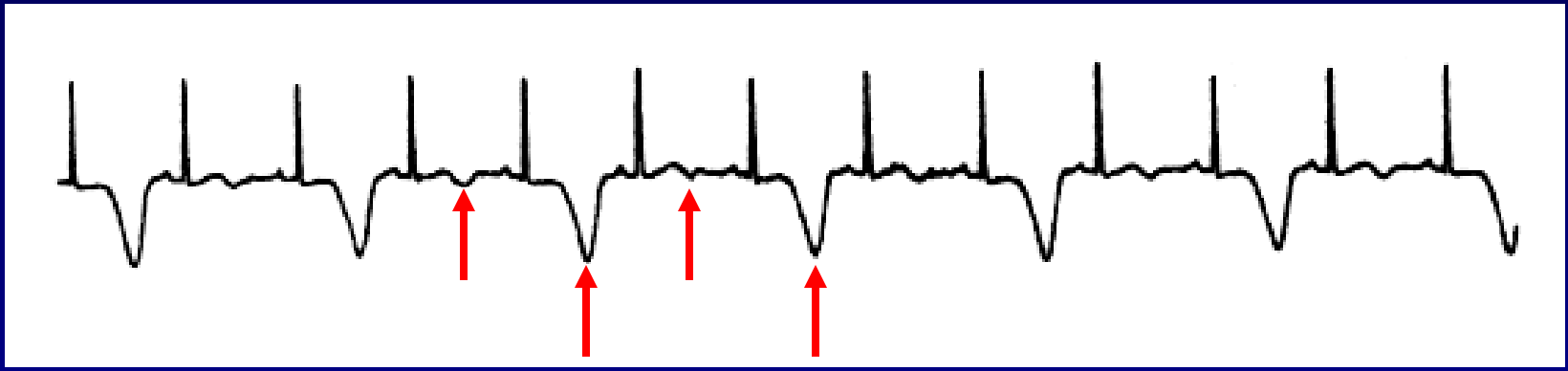
Clinical Algorithm for MTWA Based Management of Primary Prevention Patients



Heart Rhythm 2009;6:S36–44

Background

- T wave alternans (TWA)



- 1st Electrocardiographic alternans in 1908 by Hering

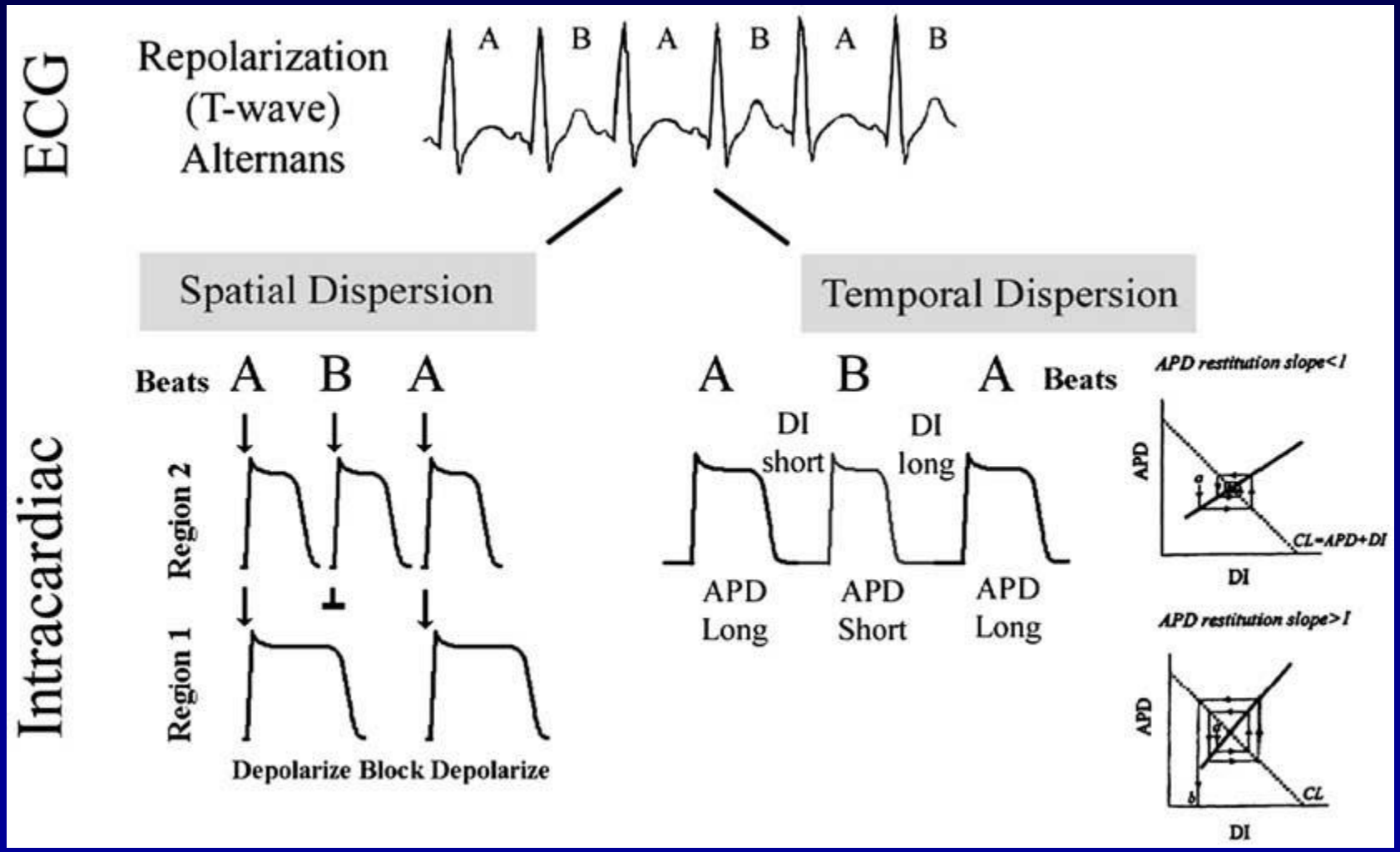
- A harbinger of malignant ventricular arrhythmia

NEJM 1992;326:271-272

Background

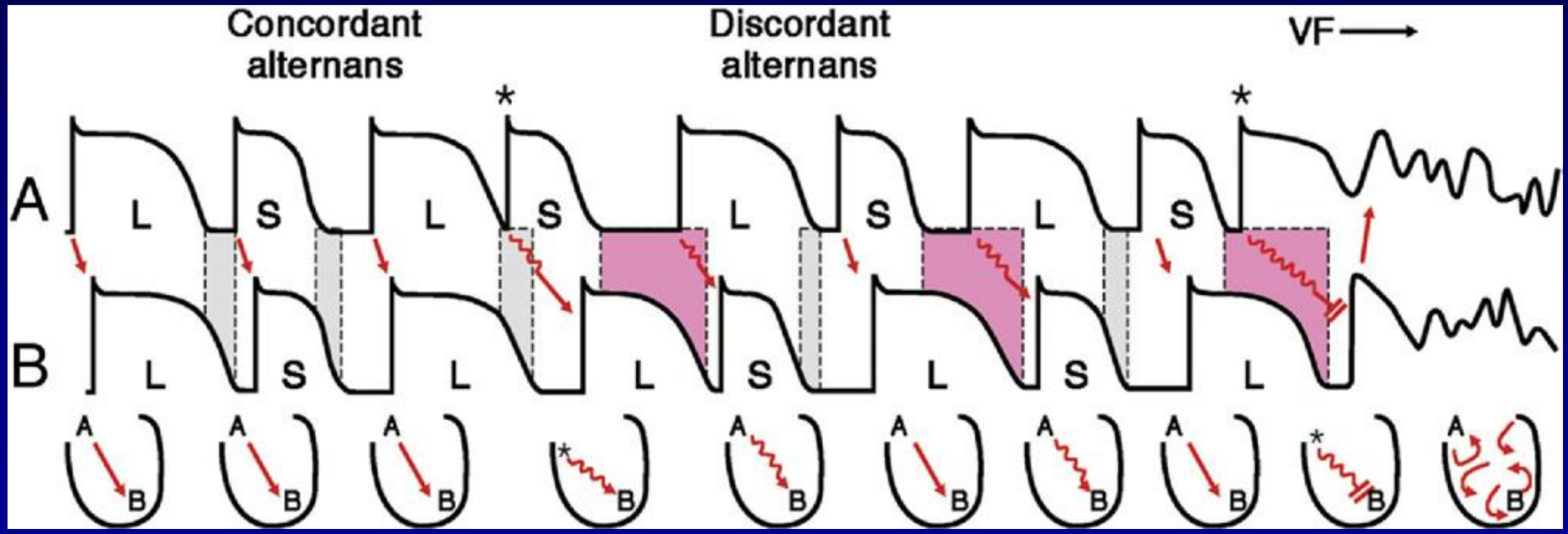
TWA : spatiotemporal heterogeneity of repolarization, is sensitive to perturbations in intracellular calcium handling, and serves as a mechanism of arrhythmogenesis by amplifying repolarization heterogeneity

Mechanisms Underlying TWA



Progress in Cardiovascular Diseases, Vol. 51, No. 2 , 2008: pp 118-127

Discordant Alternans Leading to VF



Verrier RL. et al. JACC 2011

Influence of Physiological Interventions on TWA

Amplified by

- increased heart rates (Cardiovasc Res 1994)
- ventricular premature beats (Circulation 1999)
- coronary artery occlusion and reperfusion (Circ Res 2002)
- adrenergic stimulation (Science 1991)
- mental stress (J Am Coll Cardiol 2009)

Heart Rate and Autonomic Factors on TWA

- Heart rate influences TWA
  - impacting on intracellular calcium cycling

J Am Coll Cardiol 2006;47:269–81

  - engaging the steepest portions of the electrical restitution curve

Circ Res 2011;108:98 –112

- During myocardial ischemia or heart failure, the onset heart rate for TWA is considerably lower due to impaired capacity of the sarcoplasmic reticulum (SR) to reuptake calcium

Heart Rhythm 2009;6:251–9
Circ Res 2002;91:727–32

- Autonomic neurotransmitters and changes in myocardial substrate can lead to elevated levels of TWA during fixed rate pacing

Science 1991;252:437– 40

Myocardial ischemia and TWA

- Myocardial ischemia can increase TWA magnitude

Science 1991;252:437– 40
Cardiovasc Res 1994;28:1440 –9

- Experimental studies with fixed heart rates indicated that myocardial ischemia- and reperfusion-induced increases in TWA magnitude paralleled ($r^2 = 0.98$) incidence of ventricular tachycardia and fibrillation

Cardiovasc Res 1994;28:1440 –9

- Loss of intercellular coupling by ischemia was implicated when rotigaptide decreased connexin43 dephosphorylation in parallel with ischemia-induced TWA and dispersion of repolarization

Am J Physiol Heart Circ Physiol 2008;294:H41–9

Calcium Cycling and TWA in Myocardial Ischemia and Heart Failure

"Derangements in calcium cycling and conduction: ionic bases for TWA during myocardial ischemia and heart failure"

- Ischemia induce concordant and discordant alternation in calcium transients

  Am J Physiol Heart Circ Physiol 2008

- Heart failure reduced SR Ca^{2+}-adenosine triphosphatase expression and inhibited ryanodine receptor function, resulting in impaired reuptake and release of calcium in the SR

  Am J Physiol Heart Circ Physiol 2008
  Heart Rhythm 2009

- TWA may be attributable to oscillations in the action potential plateau that, in computational models, were best explained by reduced calcium uptake into the SR in cardiomyopathy patients

  J Am Coll Cardiol 2008

TWA in Nonischemic Cardiomyopathy

- Sympathetic nerve activity and abnormalities in calcium handling may serve as arrhythmogenic factors in nonischemic disease patients

Am J Cardiol 2003;92:998 –1001

- During exercise, patients with dilated or hypertrophic cardiomyopathy also experience repolarization abnormalities including TWA

Am J Cardiol 2003

- Histopathological changes, particularly fiber disarray and/or fibrosis, are correlated with TWA occurrence and ventricular tachyarrhythmias in hypertrophic cardiomyopathy

J Cardiovasc Electrophysiol 2001

Methodology for TWA Assessment

- Micro-level T wave alternans (mTWA)

  - 1st reported in 1982

IEEE Comput Cardiol 1982:241-4

  - Strong relationship between the presence of mTWA and vulnerability to ventricular arrhythmia

NEJM 1994;330:235-41

Methodology for mTWA Assessment

- Spectral Method (Cambridge Heart, Bedford, MA)

- Modified Moving Average (MMA) Methods
  (GE Medical Systems, Milwaukee, WI)

Spectral TWA Method

Spectral Method

1) Exercise protocol

Increase heart rate to 105-110 beats/min by bicycle ergometer

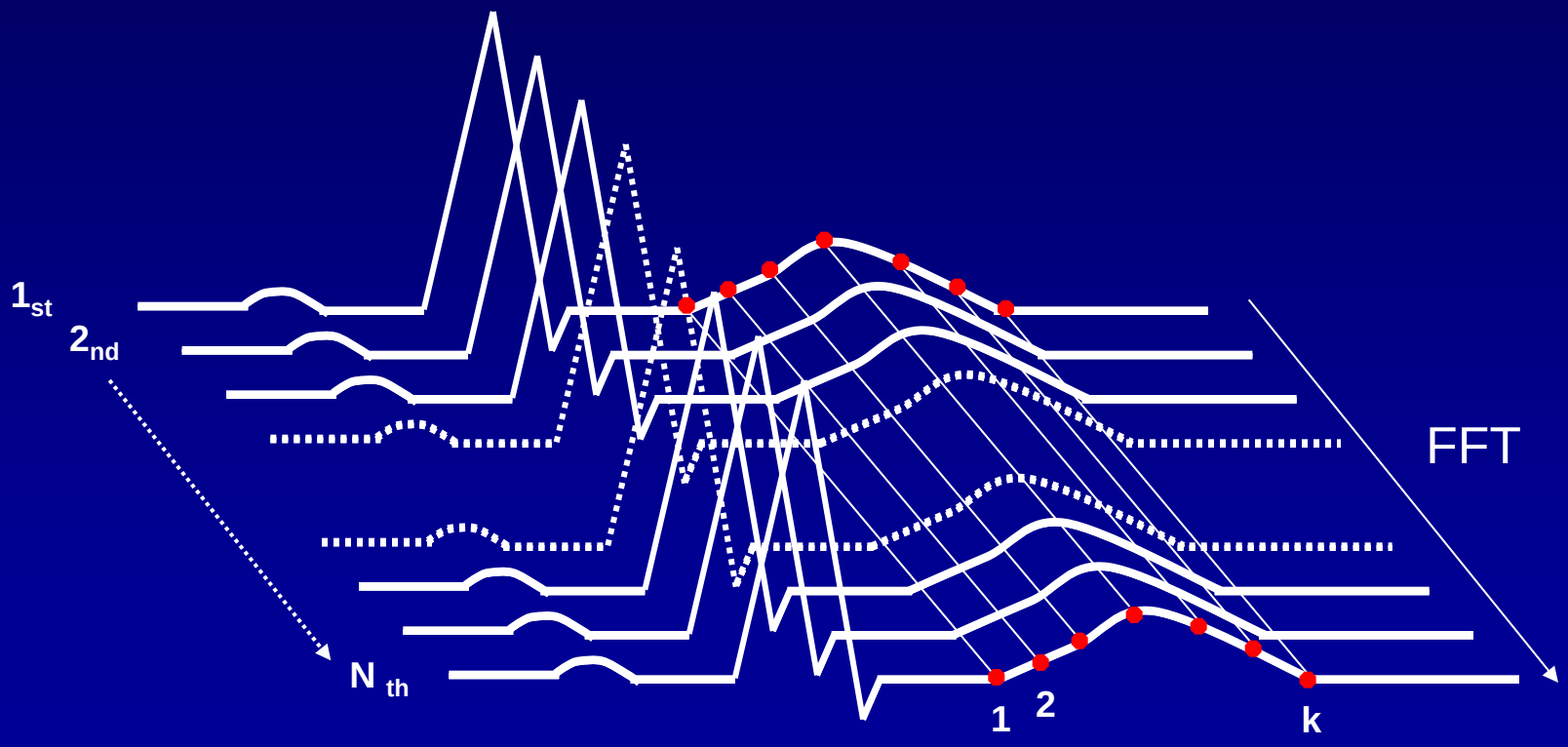
2) Fast Fourier transformation (FFT)

Beat-to-beat fluctuations in the amplitudes of T waves from 128 consecutive beats

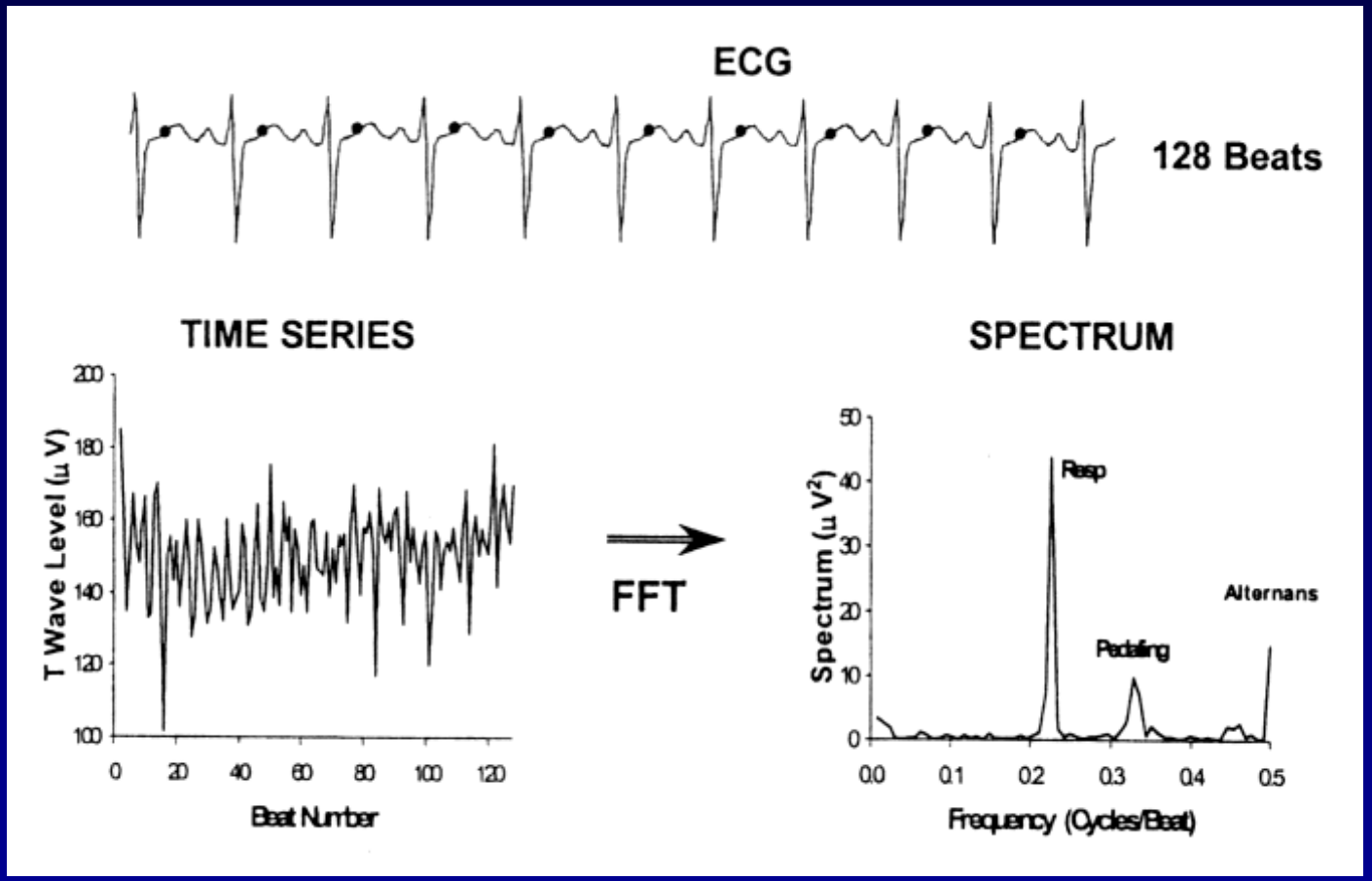
→ Power spectra

Spectral TWA Method

Arrangement of QRS and ST-T segment according to continuous sequence



Spectral TWA Method



J Cardiovasc Electrophysiol 2002;13:502-512

* Alternans ratio (R_{alt}) = alternans power $(\sum T\text{-}\mu_{noise})/\sigma_{noise}$
* Alternans voltage (V_{alt}) = $\sqrt{\sum T\text{-}\mu_{noise}}$/ST-T duration

Spectral TWA Method

3) Definitions

- Positive:
  - V_{alt} ≥1.9 µV
  - R_{alt} ≥3.0
  - Duration >2 min with HR ≤110 BPM
- Negative:
  - Test results below this level
- Indeterminate

Indeterminate test results

20% to 40% of all cases

"Abnormal due to patient factors"

- excessive ectopy (approximately 32%)
- lack of capacity to reach a target rate of 105 to 110 beats/min (approximately 51%)
- non sustained TWA (approximately 10%)

carry greater risk than positive test results

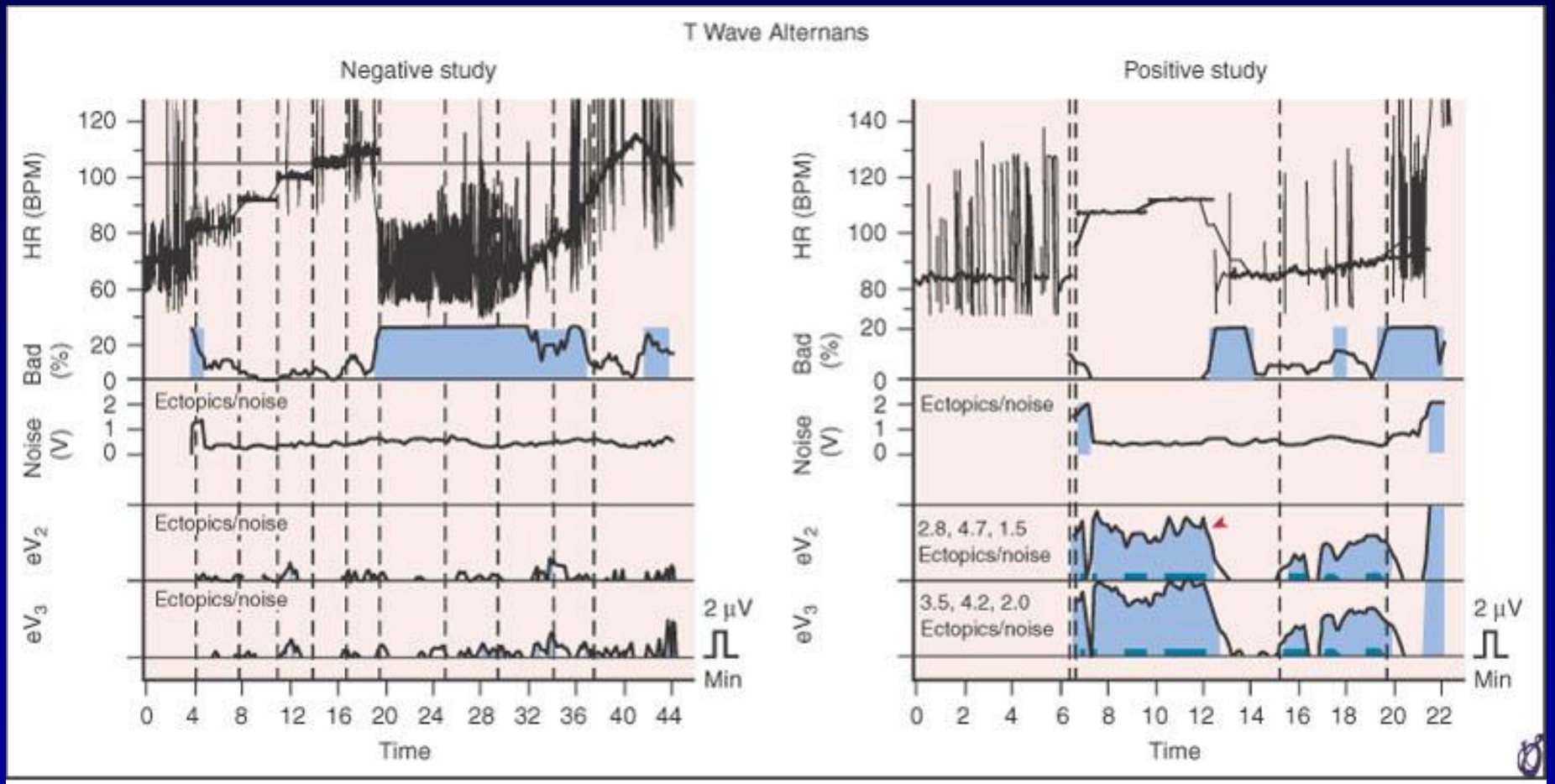
"Technically indeterminate (6.4%)"

- the occurrence of muscle, respiration or other movement artifacts or electrode noise

no prognostic value per se

J Am Coll Cardiol 2006;48:1399–404

mTWA



Braunwald's Heart Disease 8th edition

Spectral TWA Method

Clinical Utility

- Significant predictivity of TWA analysis by the Spectral Method
  : Prospectively demonstrated in >7,200 patients with various types of cardiovascular disease, including myocardial infarction, CHF, ischemic CMP, and nonischemic DCMP

J Am Coll Cardiol 2007;50:1896 –904
J Am Coll Cardiol 2007;50:2275– 84

- Event-free survival from all-cause or cardiac mortality and/or ventricular tachyarrhythmias averaged 97% to 98% in patients with negative TWA test results

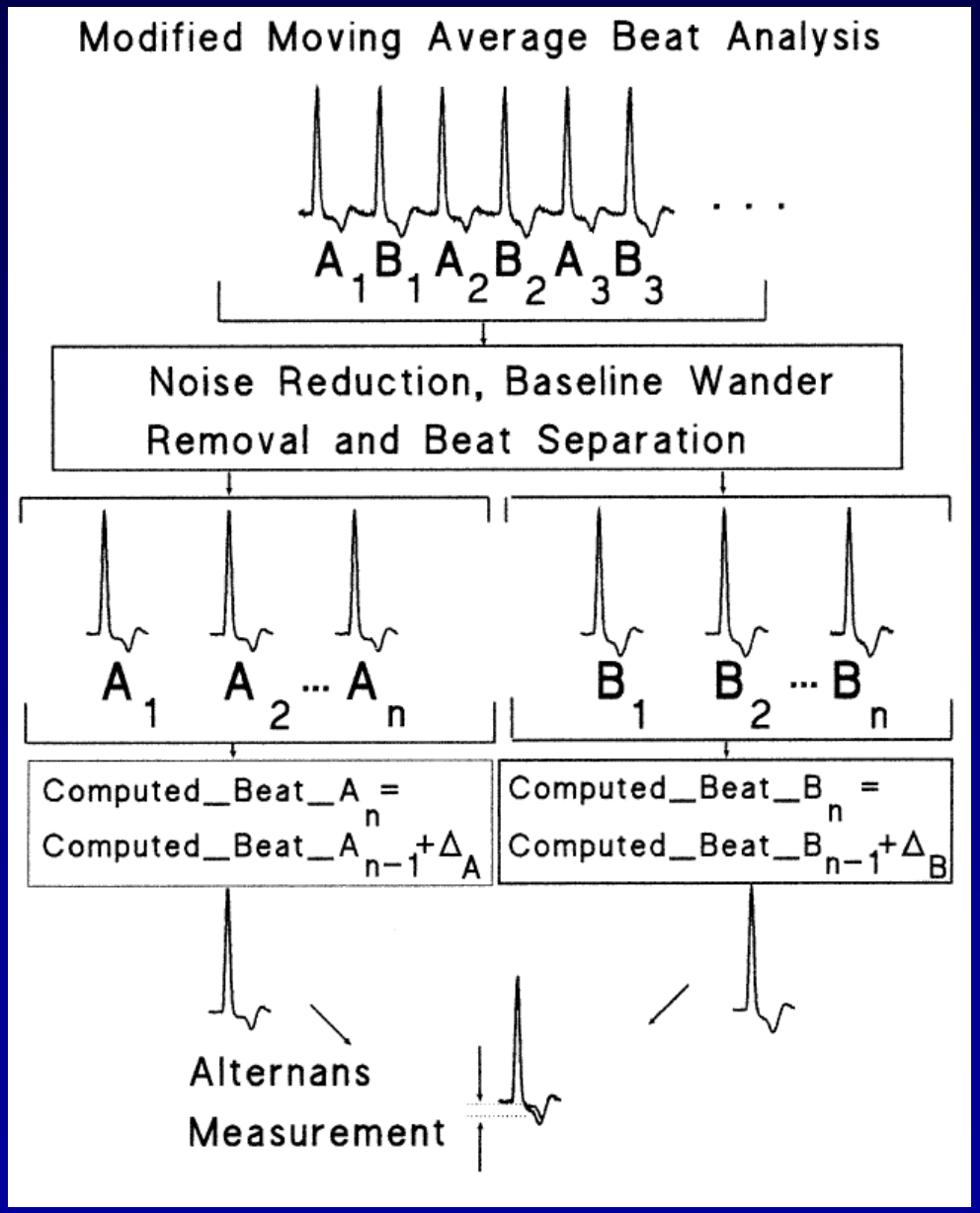
MADIT II. Circulation 2004;110:1885–9
Lancet 2003;362:125– 6

- TWA stratified total mortality did not predict sudden cardiac death or appropriate ICD discharge in the MASTER (Microvolt T Wave Alternans Testing for Risk Stratification of Post-Myocardial Infarction Patients) trial of MADIT II-type patients and the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) TWA substudy

J Am Coll Cardiol 2008;52:1607–15
Circulation 2008;118:2022– 8

MMA TWA Method

MMA TWA Method



During
- routine, symptom-limited exercise stress testing

- post-exercise recovery

- ambulatory ECG monitoring

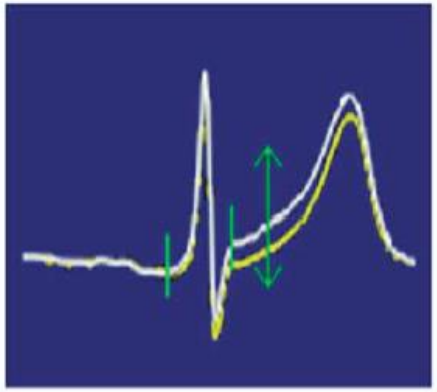
"Calculated from standard precordial ECG leads with standard electrodes"

J Cardiovasc Electrophysiol 14:70S, 2003

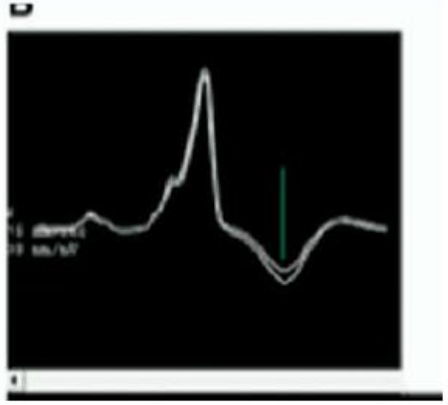
MMA TWA Method

Exercise Stress Test for TWA with MMA Method

QRS-Aligned
TWA Templates



Ambulatory ECG Monitoring for TWA with MMA Method



Heart Rhythm 2009;6:416–422

MMA TWA Method

- TWA ≥ 60 μV during routine exercise testing and ambulatory ECG monitoring
  : severely elevated risk for sudden cardiac death

  J Am Coll Cardiol 2009;53:1130 –7

- During the early post-MI phase with or without heart failure, a cutpoint of 47 μV also predicted sudden cardiac death

  J Cardiovasc Electrophysiol 2008;19:1037– 42

- A 55% and 58% increase in risk of cardiovascular and sudden cardiac death, respectively, per 20 μV of TWA

  Heart Rhythm 2011;8:385–90

MMA TWA Method

Clinical Utility

- Predictivity of TWA analysis by the MMA method
  : demonstrated in > 4,800 patients, including those with coronary artery disease, recent or old MI, CHF, or cardiomyopathy

Eur Heart J 2007;28:2332–7
J Cardiovasc Electrophysiol 2009;20:408 –15
Heart Rhythm 2011;8:385–90
Heart Rhythm 2009;6:1765–71

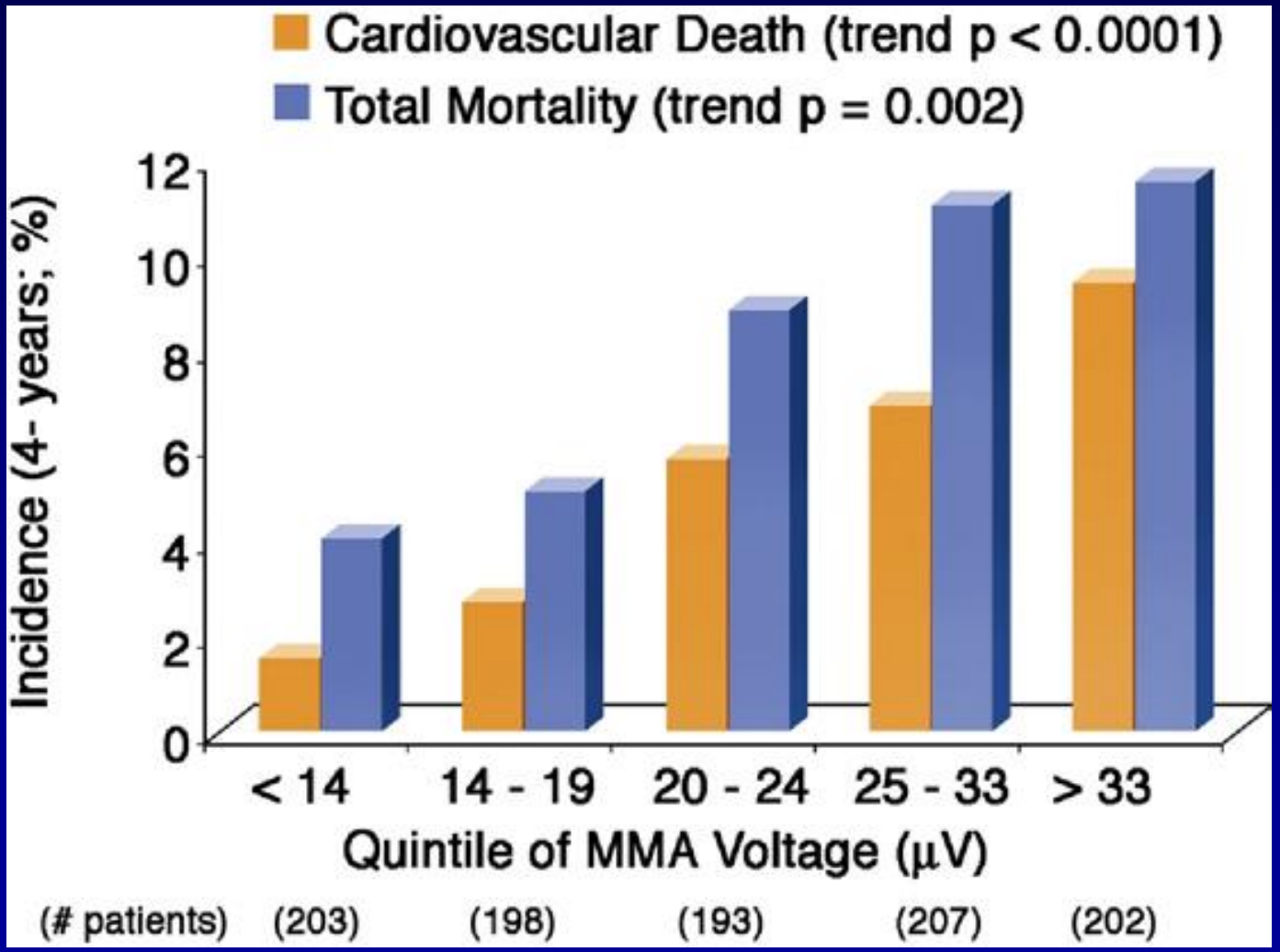
- MMA-based TWA is predictive
  - immediate post-exercise recovery

J Am Coll Cardiol 2007;50:2275– 84
J Am Coll Cardiol 2009;53:1130 –7
Heart Rhythm 2009;6:1765–71

  - From ambulatory ECG records

J Cardiovasc Electrophysiol 2003;14:705–11
J Cardiovasc Electrophysiol 2008;19:1037– 42
Heart Rhythm 2009;6:332–7
Circ J 2009;73:2223– 8
J Electrocardiol 2010;43:251–9

Quantitative Analysis of TWA Voltage MMA method



J Am Coll Cardiol 2009;53:1130 –7

Comparison of the Predictivity of TWA With the Spectral and MMA Methods

- Spectral Method: one-half of the average TWA magnitude across the entire JT interval for 128 beats
- MMA method: the peak TWA level at any point within the JT interval for each 10 to 15-s interval

- Hazard ratios for prediction by the Spectral and MMA methods are similar, whether in the same population or in studies overall

- 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 postmyocardial infarction patients with better-preserved LVEF

J Am Coll Cardiol 2007;50:2275– 84

Comparison of the Predictivity of TWA With the Spectral and MMA Methods

- In a study using atrial pacing (n= 41)
  - Spectral Method: predictive (p= 0.02)
  - MMA: nearly significant (p= 0.06) in the same patients
  - MMA significantly amplified TWA and was less specific for SCA than spectral TWA

Pacing Clin Electrophysiol 2007;30:352– 8

- TWA analyzed by both the Spectral Method and MMA was significantly elevated at 8 to 15 min before the onset of spontaneous ventricular tachyarrhythmias in ambulatory ECGs

Circulation 2006;113:2880 –7

Guiding Medical Therapy

- Beta-adrenergic and sodium channel blocking agents diminish TWA magnitude, reflecting the capacity of these agents to reduce sudden cardiac death and cardiovascular mortality

J Am Coll Cardiol 2001;38:2013–9
Heart Rhythm 2011;8:608 –14

- In the Brugada syndrome, sodium channel blockade provokes the diagnostic ECG changes as well as macroscopic TWA and arrhythmias

J Cardiovasc Electrophysiol 2008;19:56–61

Signal Average Electrocardiogram (SAECG)

- Signal averaging: a method that improves signal to noise ratio when signals are recurrent and the noise is random

- Late potentials: low-amplitude signals that occur after the end of the QRS complex

- Late potential (LP):
  - i) filtered QRS duration >114-120 ms
  - ii) less than 20 mV of root mean square signal amplitude in the last 40 ms of the filtered QRS complex
  - iii) terminal filtered QRS complex remains below 40 mV for longer than 39 ms

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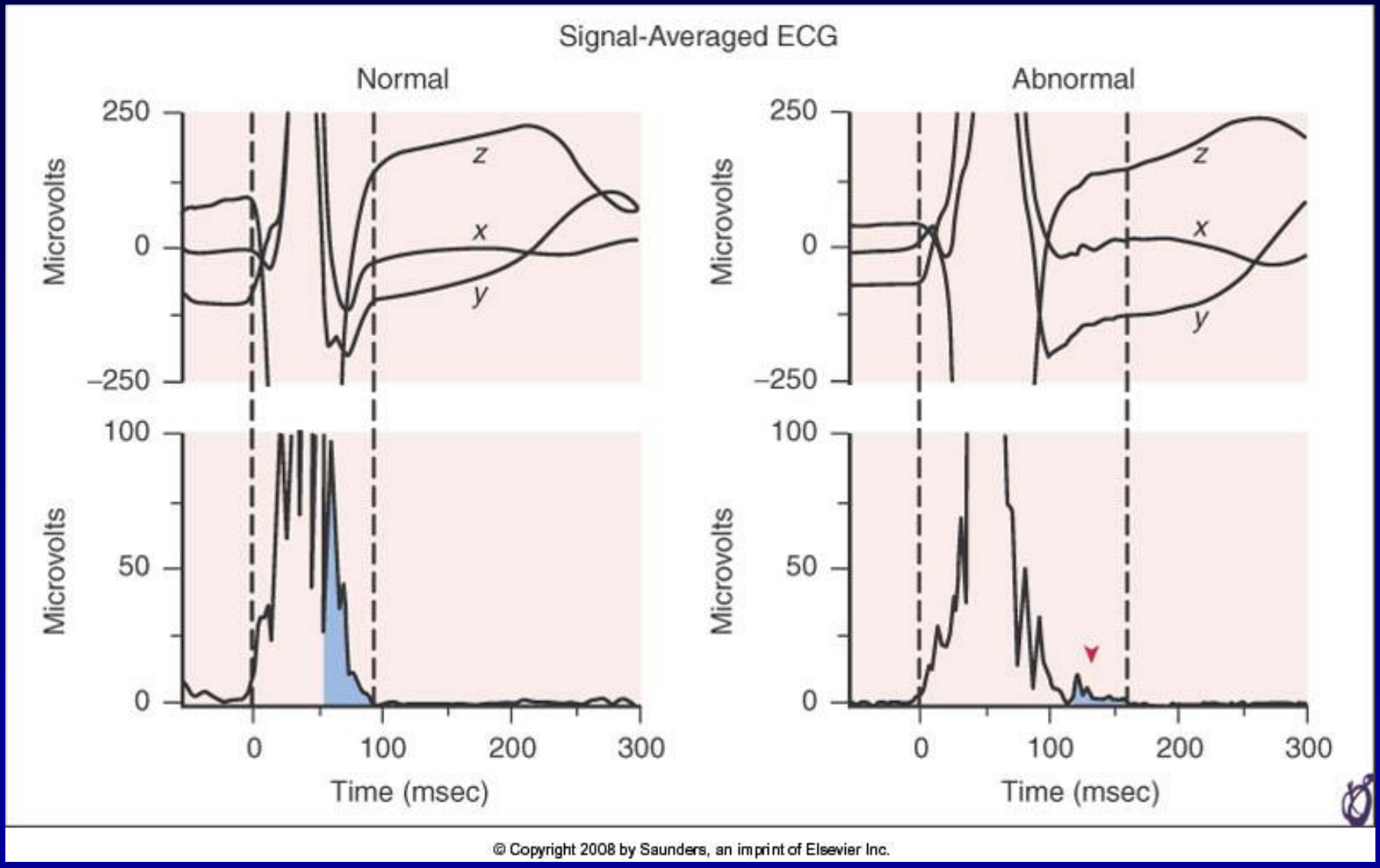
SAECG



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SAECG

- SAECG performed early after MI is abnormal in 15% to 35% of patients. SCD or cardiac arrest occurs in 3.3% to 9% of these patients over the following 1 to 3 year

- For the prediction of SCD or arrhythmic events, the sensitivity of an abnormal SAECG has been reported to vary from 30% to 76% and the specificity from 63% to 96%

J Am Coll Cardiol. 1993;21:1419–1427
J Am Coll Cardiol. 2001;38:1902–1911
Circulation. 1997;96:202–213
J Am Coll Cardiol. 1996;27:53–59

Conclusions

- TWA is a promising ECG index of arrhythmic susceptibility that has been shown to provide a high negative predictive value for ventricular arrhythmias and thus identify individuals who may not benefit from ICD implantation

- Overall, although TWA appears to be a useful marker of risk for arrhythmic and cardiovascular death, there is as yet no definitive evidence that it can guide therapy

- Given the high negative predictive value of SAECG, it may be useful for the identification of patients at low risk: prognostic use at high risk for SCD is limited