

T-Wave Alternans and Drug Safety: Importance of Quantitative TWA Analysis

Richard L. Verrier, Ph.D., F.A.C.C.

Associate Professor of Medicine, Harvard Medical School
Cardiology Division, Beth Israel Deaconess Medical Center



Disclosures

- Co-inventor with Dr. Bruce Nearing of the Modified Moving Average Method for T-wave alternans analysis, which has been licensed by GE Healthcare
- Research grants from Medtronic, Inc., Gilead Palo Alto, Inc., Center for Integration of Medicine and Innovative Technology (CIMIT), and NIH

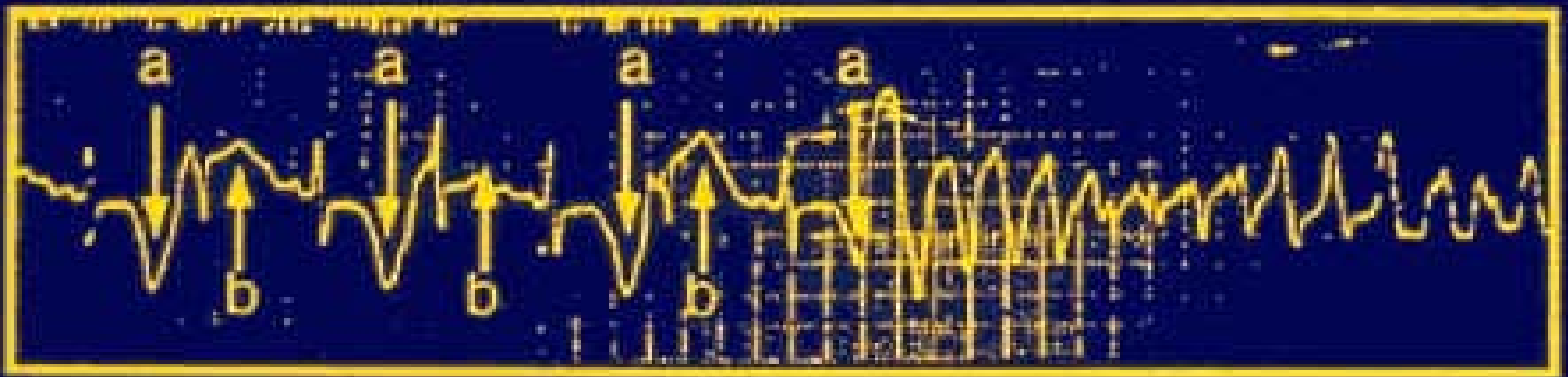
Objectives

- Rationale for TWA in evaluating drug safety
- Methodology for Holter-based quantitative TWA analysis
- Clinical evidence of TWA's estimation of cardiovascular risk
- Experience with contemporary drugs

TWA Definition and Rationale

- Repeating ABAB pattern in amplitude and shape of T wave
- Phenomenon frequently associated with heightened risk for life-threatening arrhythmias

Progression from TWA to Polymorphic Ventricular Tachycardia



TWA Rationale

- Reflects a quantifiable, fundamental electrophysiologic property linked to VF, the arrhythmia responsible for sudden death.
- Measures temporal-spatial heterogeneity of repolarization
 - Can complement QT interval length assessment
- Compatible with ambulatory ECG monitoring
 - Attendant physical and mental stimuli can expose latent electrical instability

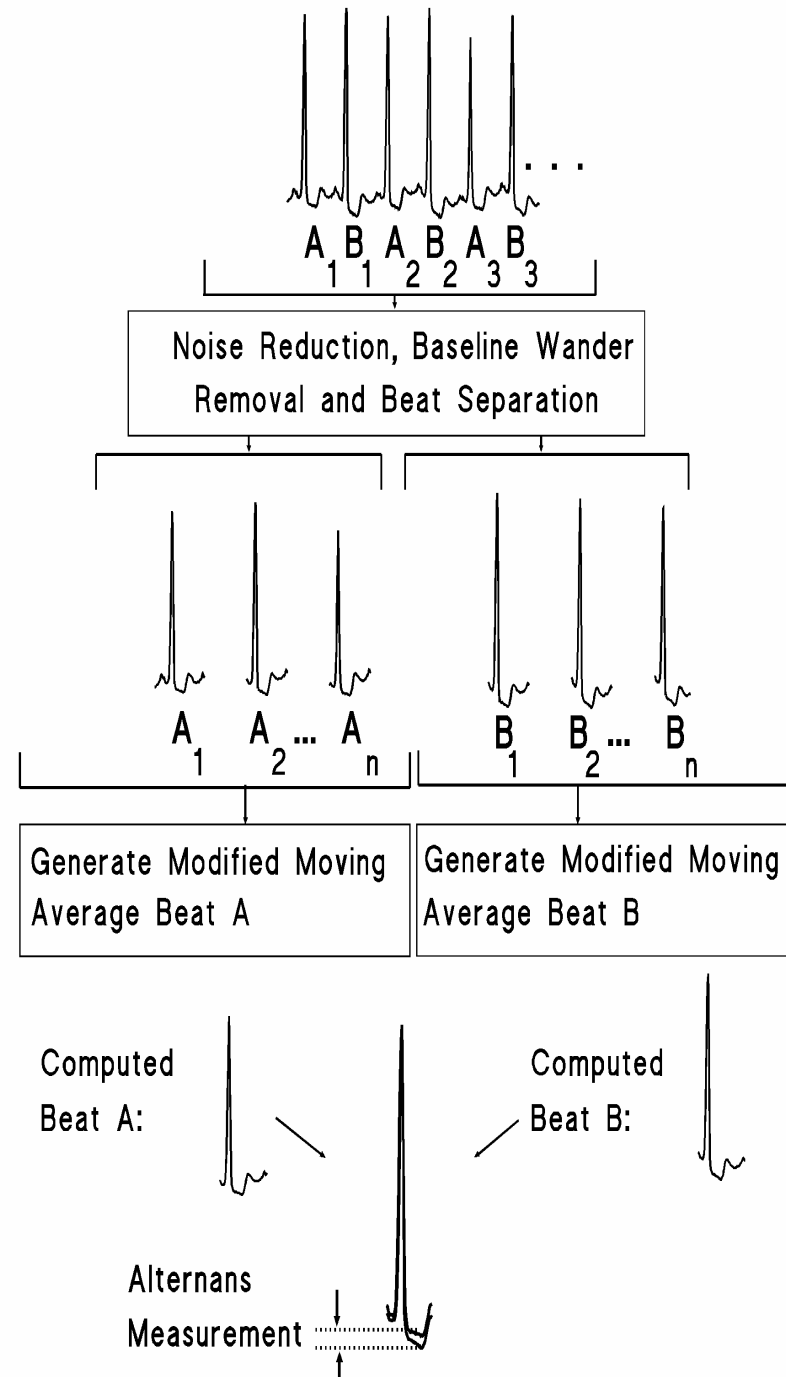
Pathologic States with Association between TWA and SCD

- Myocardial Ischemia and Infarction
- Prinzmetal's Angina
- Heart Failure
- Cardiomyopathies
- Implantable Cardioverter/Defibrillator Patients
- Sudden Infant Death Syndrome
- Channelopathies-- Long QT and Brugada Syndromes
- Drug-Induced Torsade de Pointes

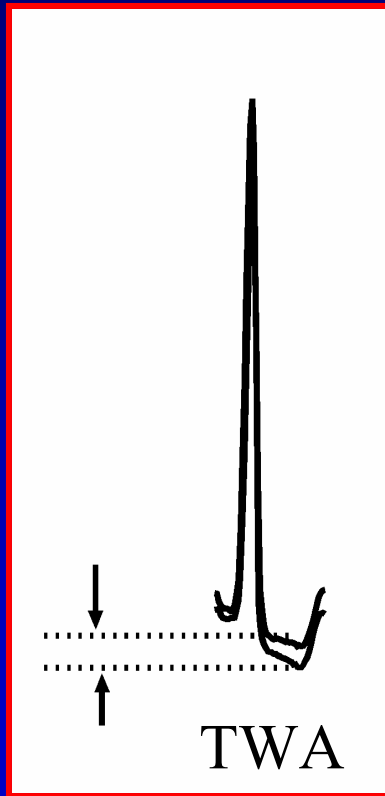
Modified Moving Average Method

- Analyzes TWA in time domain
 - Continuous stream of A and B forms
 - **Maximum** alternation between consecutive beats per 15 seconds
- Does not require data stationarity
- Standard electrodes
- 1-microvolt resolution
- TWA template for computer-aided waveform inspection

Modified Moving Average Analysis of T-Wave Alternans



Analytical Features of TWA Median Template

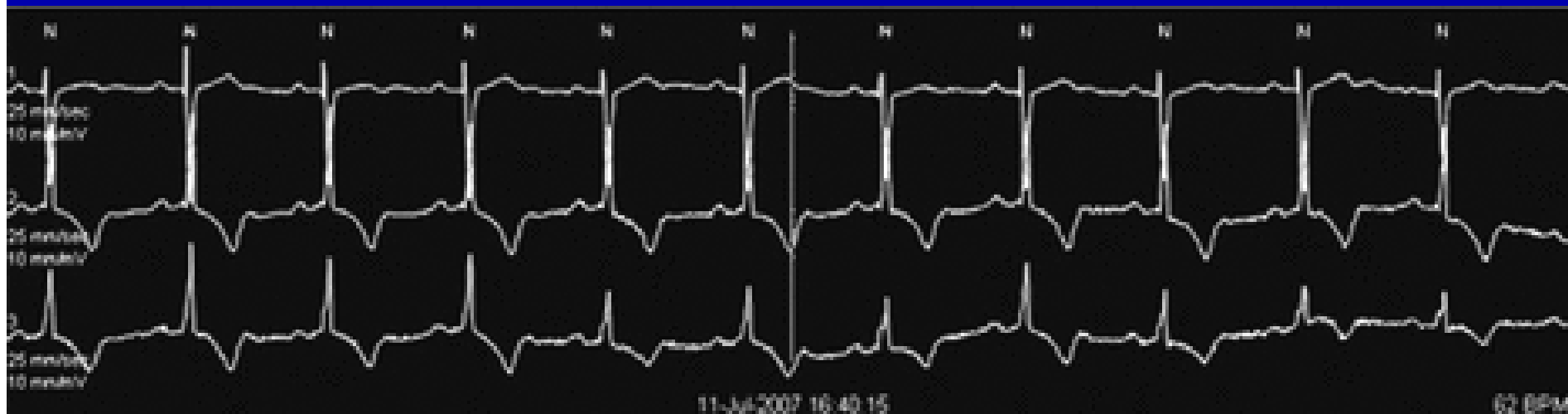
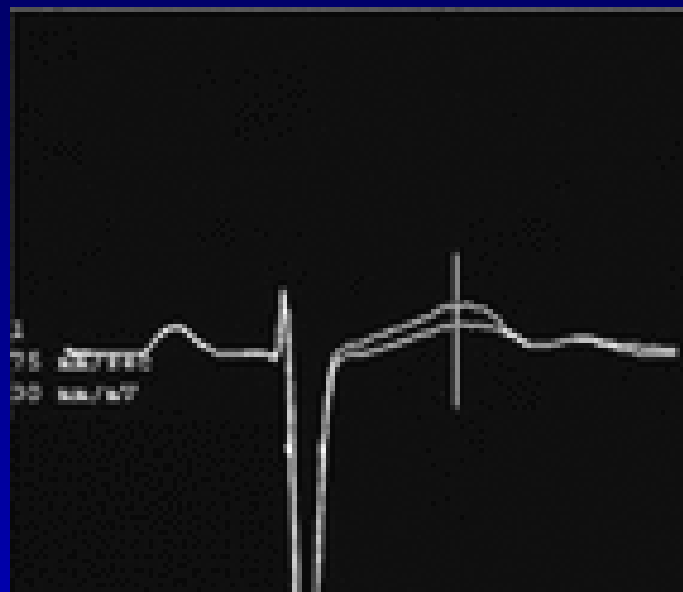


- High-resolution superimposed ECGs for visual inspection
 - To rule out false TWA
 - To evaluate QRS changes
 - To confirm TWA visually down to $20\mu\text{V}$
 - To determine component of T-wave that alternates
 - Potential mechanistic insights

TWA Predicts Sudden Cardiac Death in EPHEBUS Substudy

- 493 hospitalized high-risk post-MI patients
 - 46 cardiovascular deaths including 18 SCD
- Odds ratios for SCD = ≥ 5.2 for patients with TWA $\geq 47\mu\text{V}$
- Optimum cutpoints identified 11 of the 18 patients with LV dysfunction who died suddenly

Superimposed Waveforms Indicate Maximum TWA of 75 μ V with Associated Lead V1 ECG Strip for EPHESUS Patient



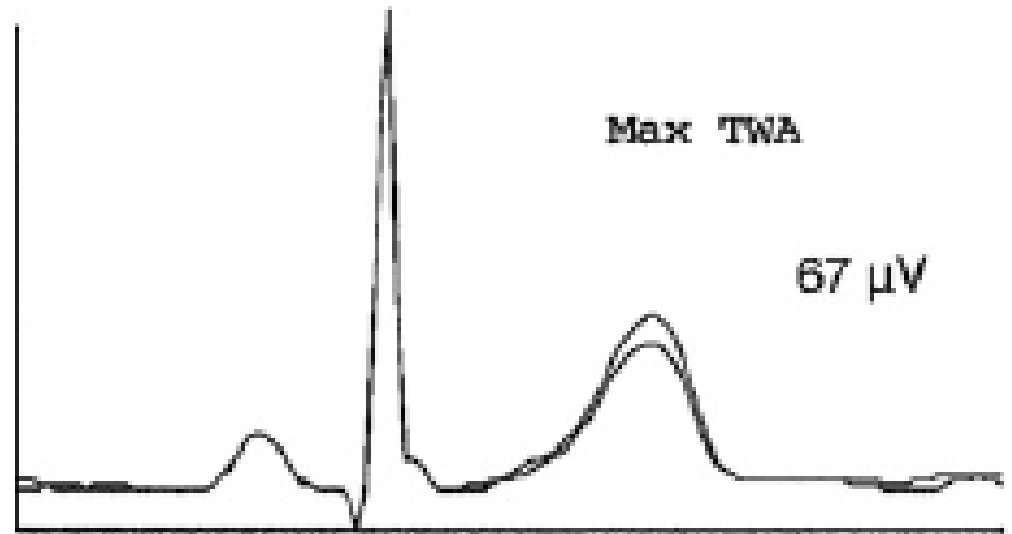
TWA in Japanese Full-Cohort AECG Study

- 295 consecutive high-risk patients
 - 27 cardiac deaths, 5 witnessed SCD
- Odds ratio for cardiac death = 17.1
 - 95% CI = 6.3-46.6, $p < 0.0001$
 - Significant in both ischemic and nonischemic subgroups
- Odds ratio for sudden death = 22.6
 - 95% CI = 2.6-193.7, $p < 0.005$
- TWA indeterminate in 40 patients (9%)
 - AF, extrasystoles

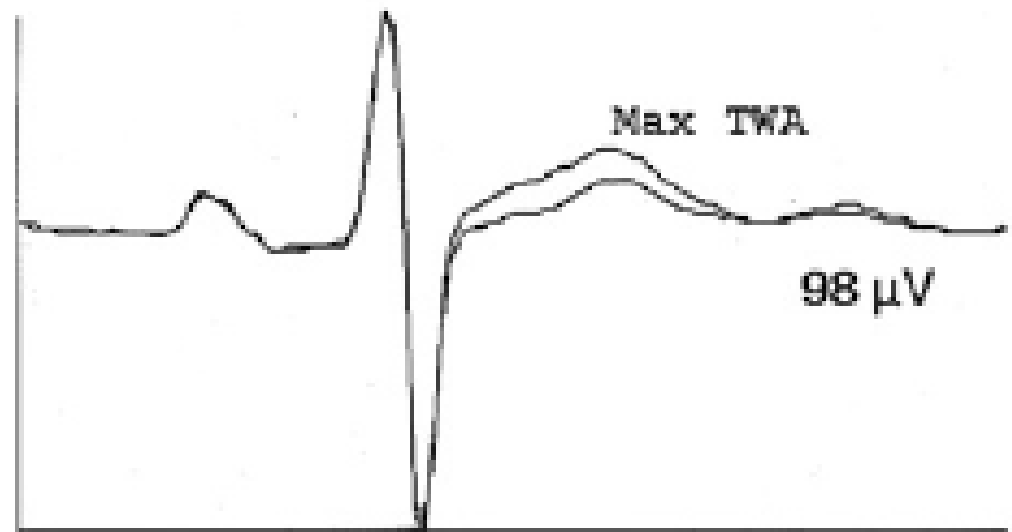
Superimposed
ECG
Complexes
Indicating
Maximum
TWA

Sakaki *Heart Rhythm* 2009

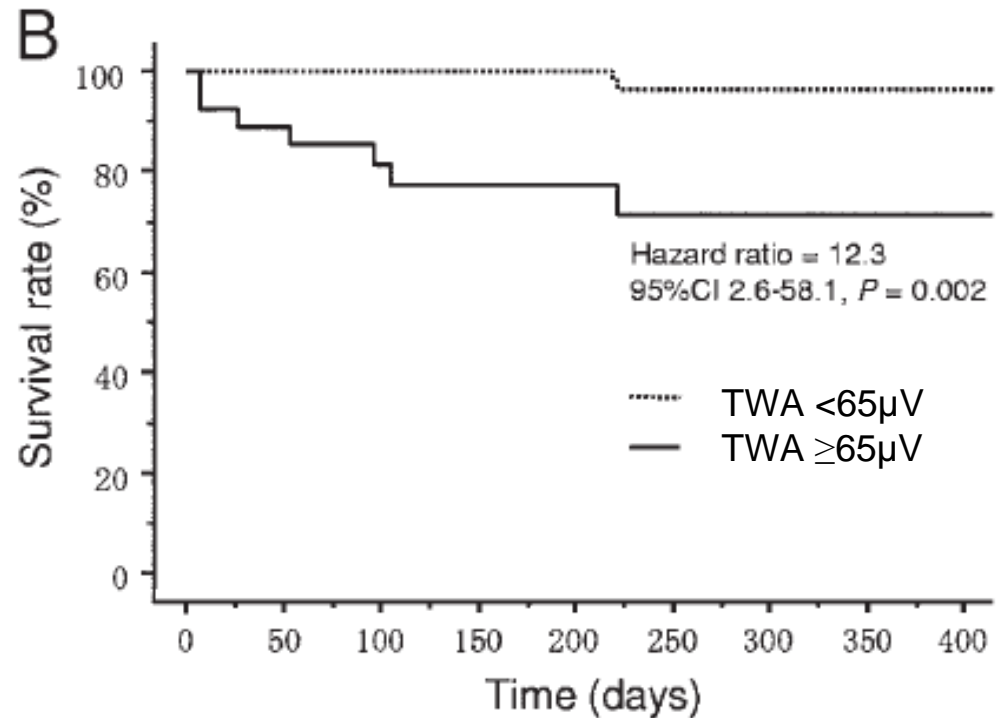
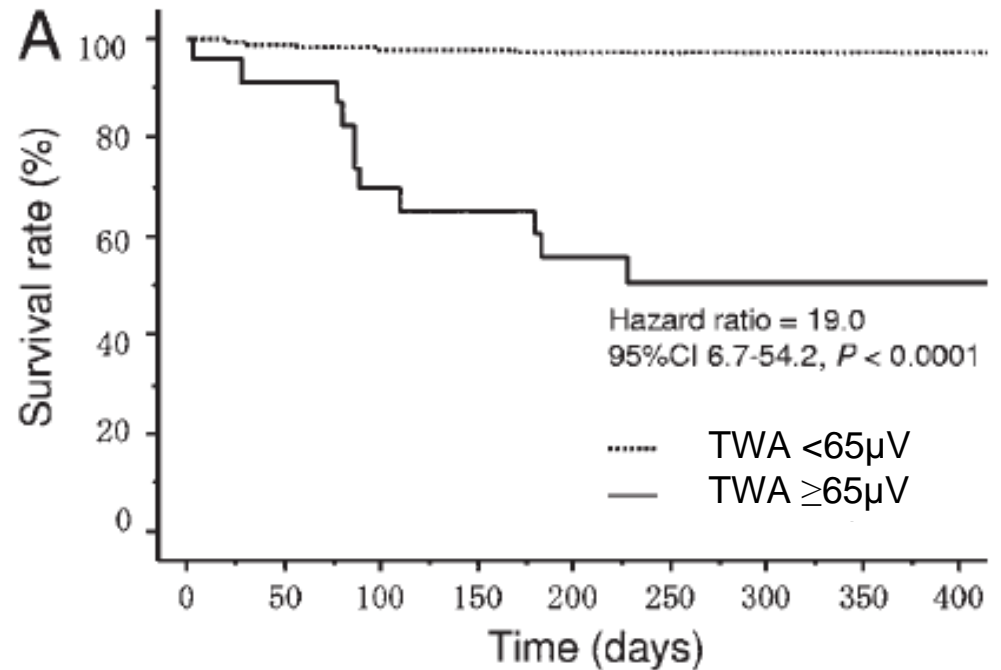
V₅ (CM₅)



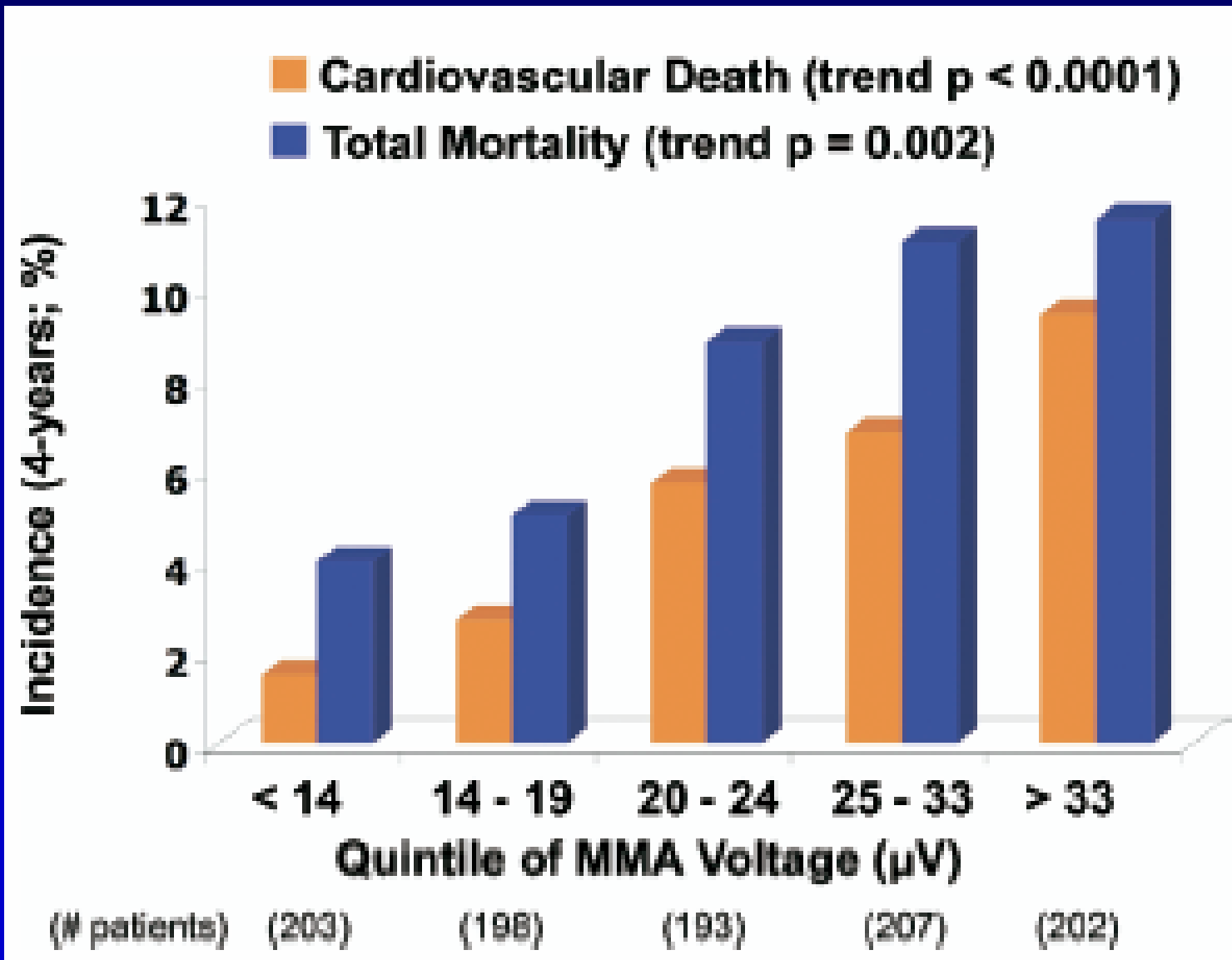
V₁ (NASA)



Cardiac
Mortality Risk
in Ischemic
(A) and
Nonischemic
(B) Subgroups



Linear Relationship of TWA Magnitude with Cardiovascular Death and Total Mortality



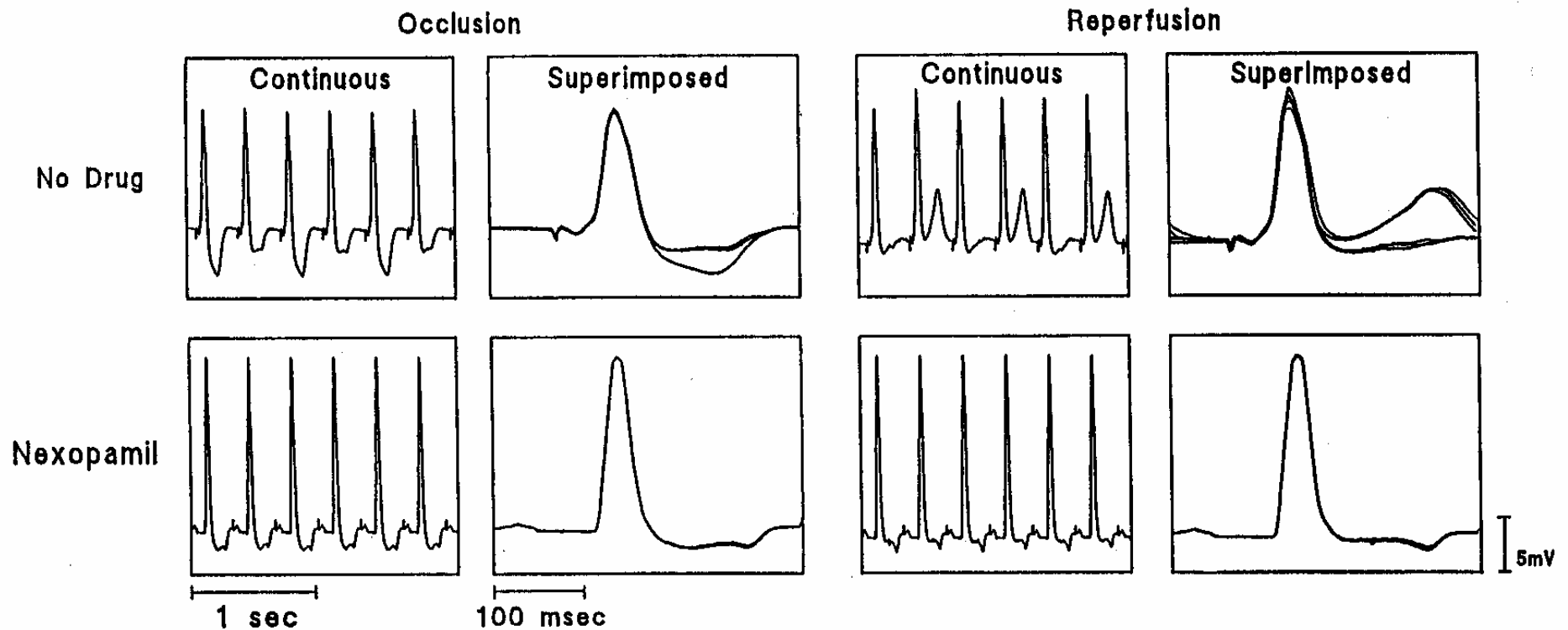
Summary of TWA Clinical Evidence

- Prospective trial evidence supports predictive utility of MMA-based TWA analysis on Holter
- TWA magnitude parallels level of arrhythmia risk
- Thus, the influence of drugs on TWA magnitude should be useful in evaluating both anti- and proarrhythmic actions

Drugs that Affect TWA Magnitude

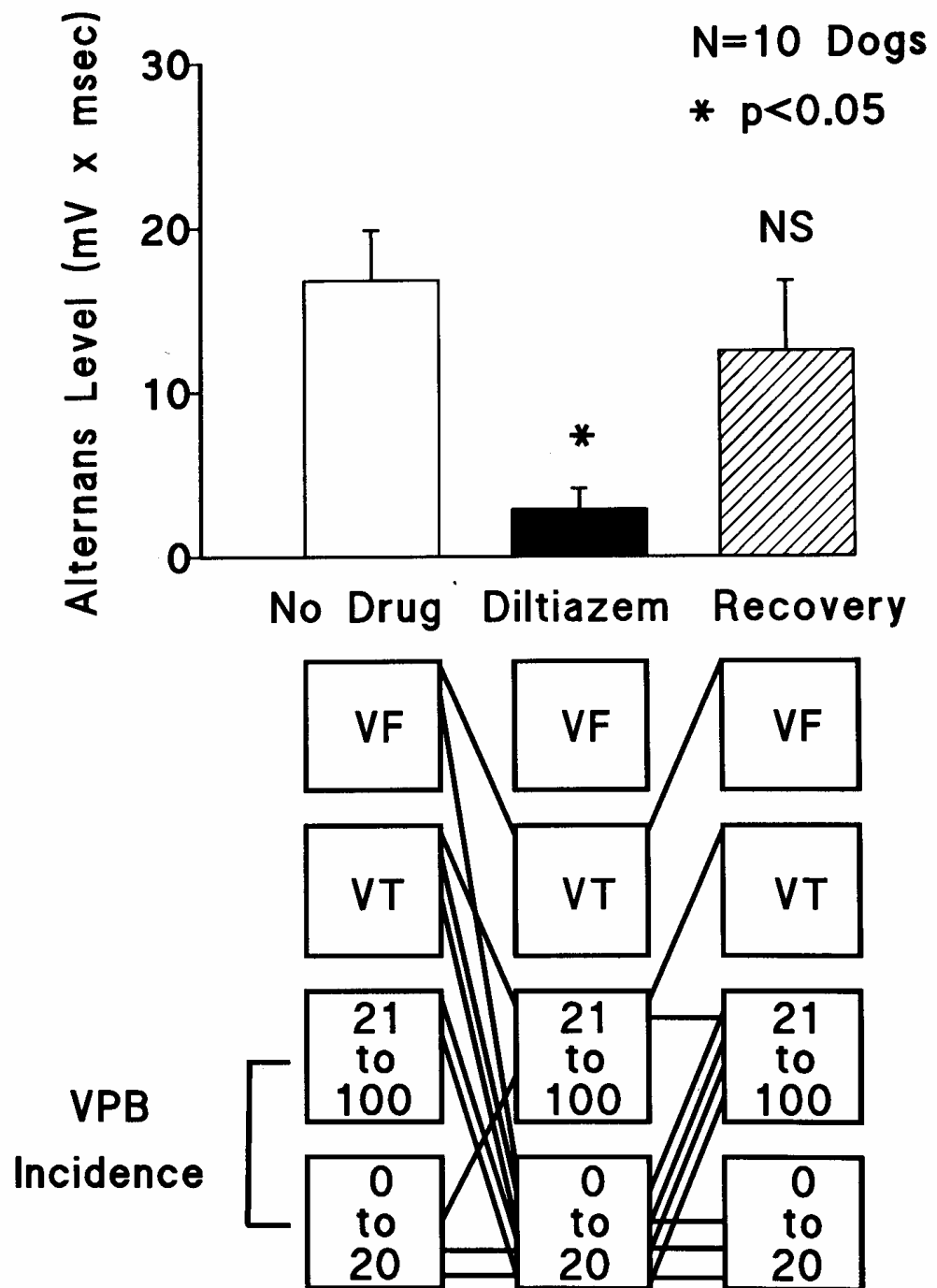
- Decrease TWA
 - Beta-adrenergic blockade (metoprolol)
 - Calcium channel blockade (diltiazem)
 - Amiodarone
 - Ranolazine
- Increase TWA
 - Amiodarone prior to Torsades de Pointes onset
 - Pentamidine for HIV

Calcium Channel Blockade and Ischemia-Induced TWA

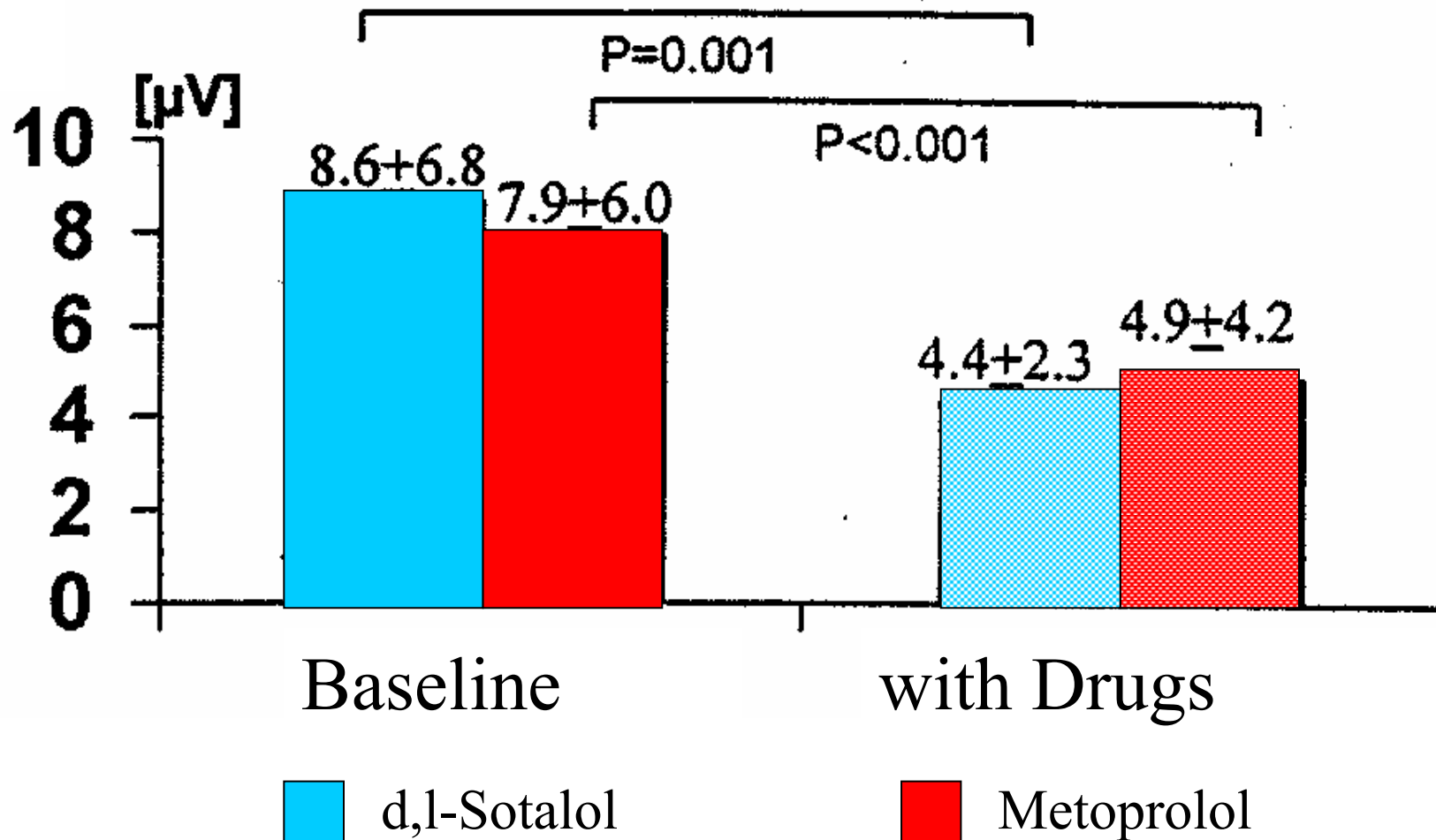


Parallel Effects of Diltiazem on TWA and Arrhythmia during Coronary Artery Occlusion

Nearing, Hutter, Verrier
J CV Pharmacol 1996



Beta-Blocking Agents Decrease TWA



TWA for Detection of Proarrhythmia

- Congenital
- Acquired, drug-induced

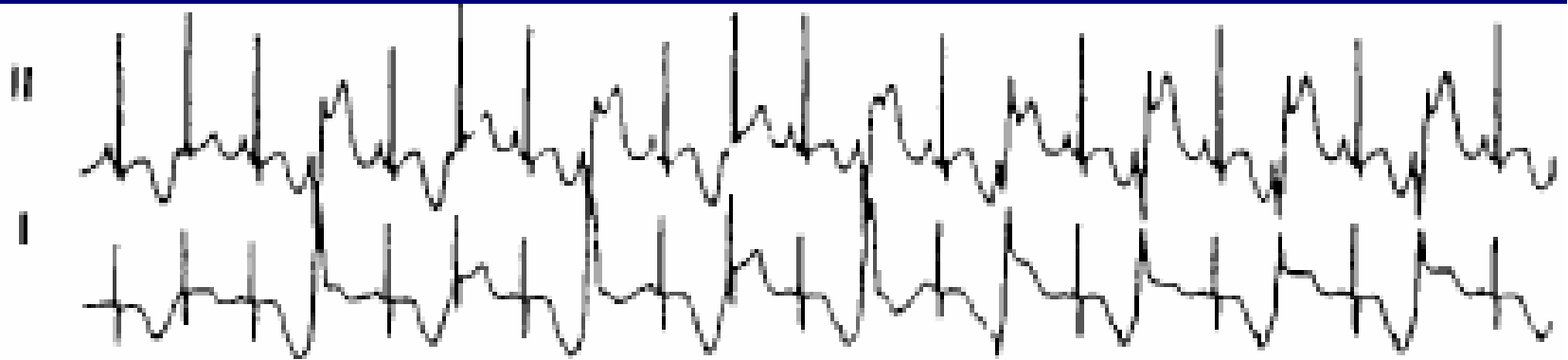
TWA Heralds Amiodarone-Induced Proarrhythmia on In-Hospital Monitoring



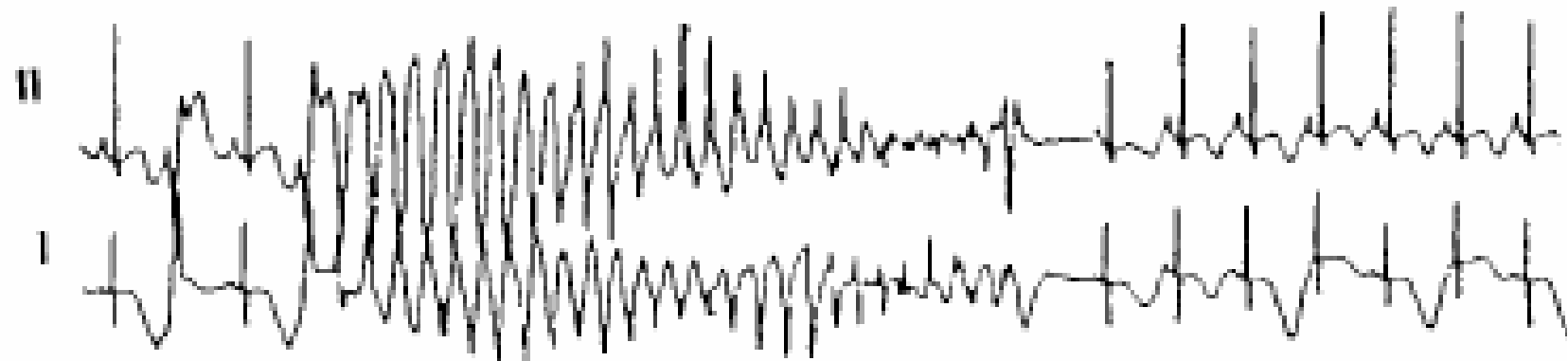
Hohnloser *JCE* 1999

Pentamidine-Induced TWA and Torsades de Pointes in HIV Patient

05:15:01



05:17:31



TWA: A Quantifiable Index of the Link between Prolonged QT and Torsades de Pointes

- Both congenital and acquired QT prolongation
- Mechanism: 2:1 conduction of EADs leading to ABAB T-wave pattern
- Readily quantifiable on Holter recordings

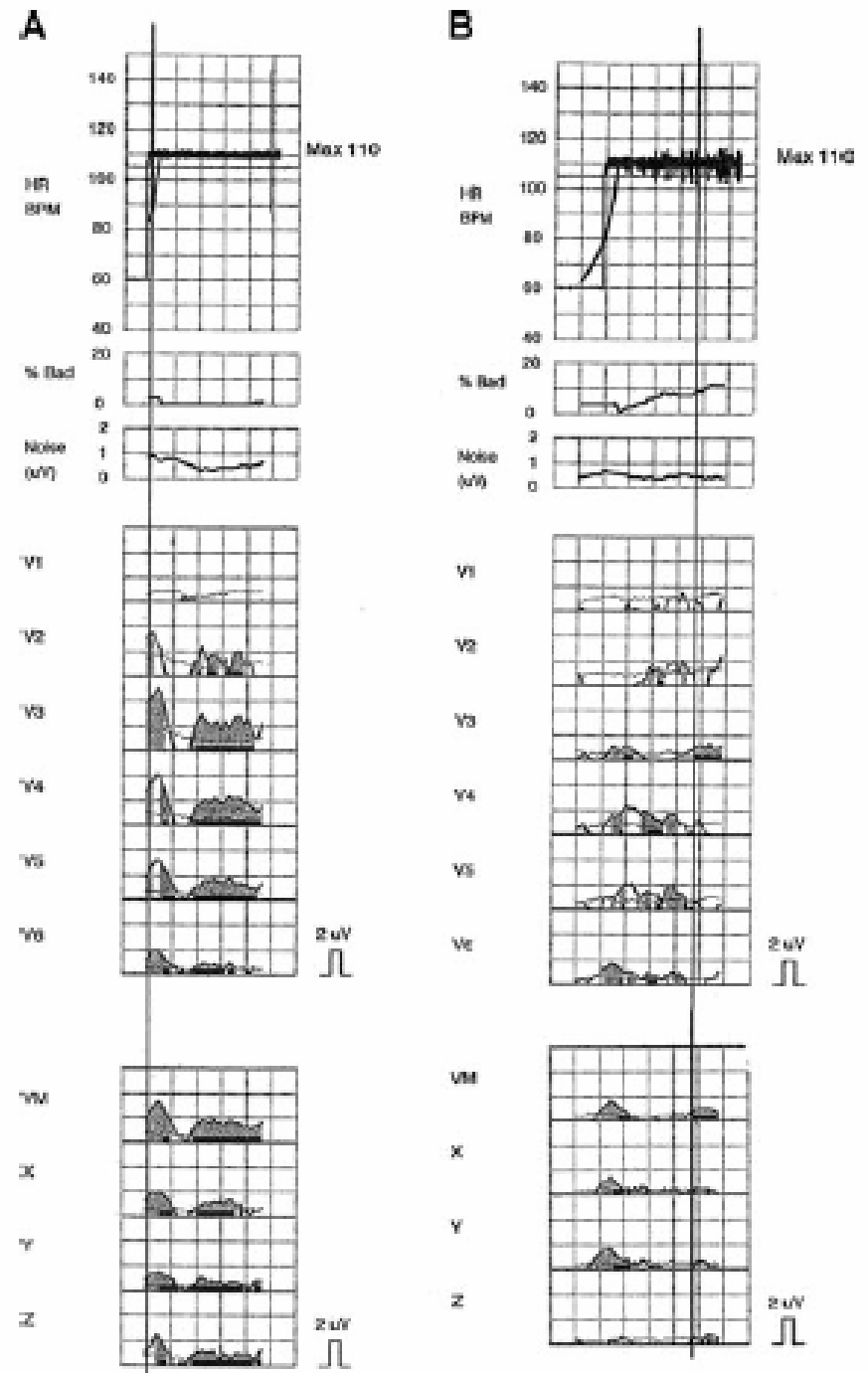
Conclusions

- TWA permits assessment of fundamental electrophysiological properties associated with arrhythmia risk
 - Can complement QT interval length assessment
- Time-domain modified moving average (MMA) analysis permits quantitative assessment of TWA on Holter
- Trial evidence supports predictive accuracy of MMA-based TWA
- TWA on Holter can detect the antiarrhythmic and proarrhythmic effects of drugs



Ranolazine Results in Parallel Suppression of Arrhythmia and TWA

Murdock *PACE* 2008



Suppression of
VT by
Ranolazine [C]
and its
Recurrence
Following Drug
Cessation [D]

