T-Wave Alternans and Risk Stratification for Sudden Cardiac Death

Richard L. Verrier, Ph.D., F.A.C.C.
Associate Professor of Medicine
Harvard Medical School
Cardiology Division
Beth Israel Deaconess Medical Center

Disclosure: Inventor with Dr. Bruce Nearing
of the Modified Moving Average method for TWA analysis
licensed by GE Healthcare

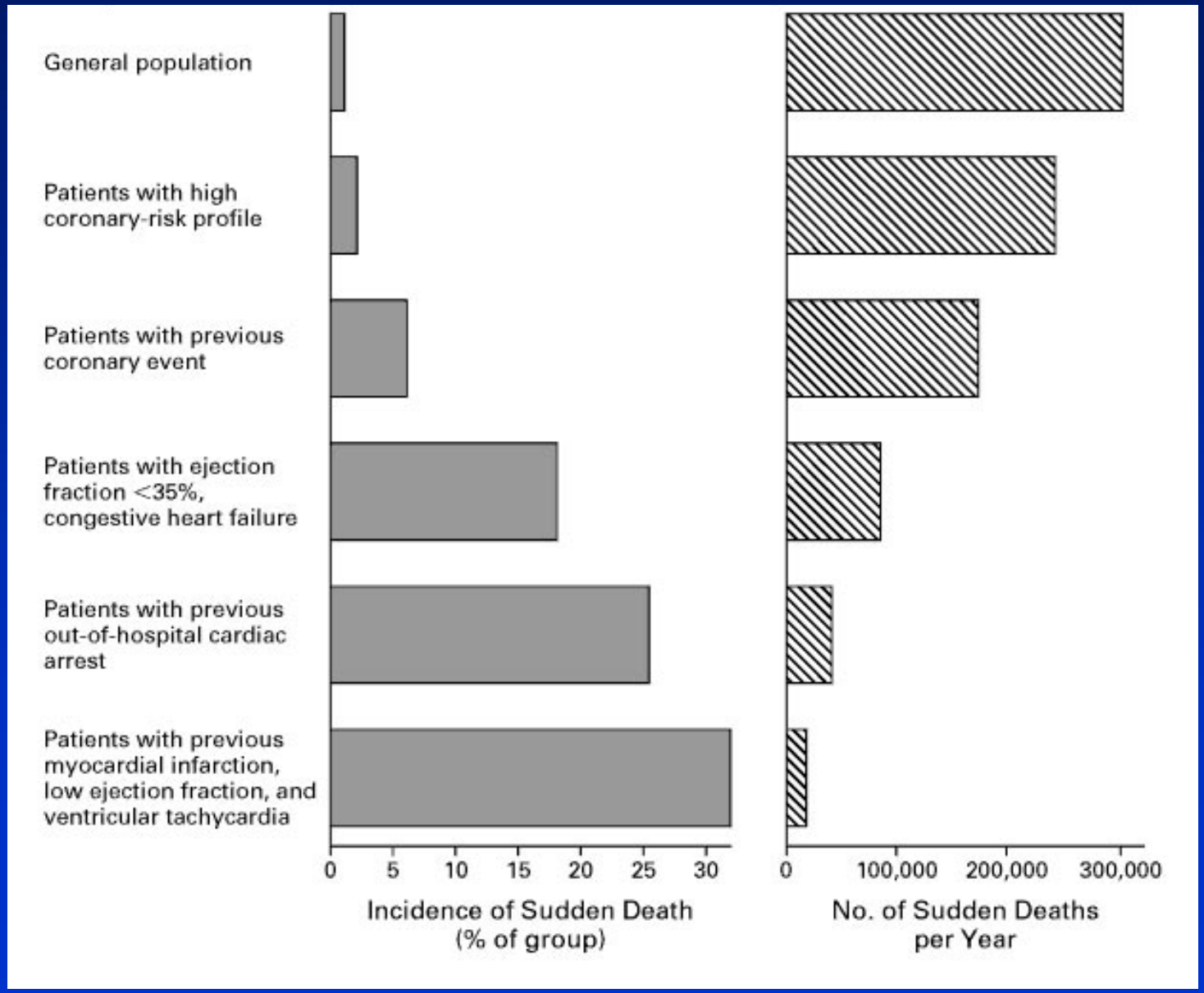
Objectives

- Sudden cardiac death: scope and risk stratification challenge
- TWA: definition and clinical presentation
- Scientific underpinnings of TWA testing
- Methodologies for TWA assessment
- Clinical evidence of TWA's utility
- Future directions

Scope and Characteristics of Sudden Death Problem

- 350,000 deaths/year
- In 20-30%, SCD is first manifestation
- Electrical event, VF in 85% of cases
- Due to interaction between trigger (e.g., exercise stress, circadian factors) and vulnerable myocardial substrate (MI, myopathy, heart failure)

Sudden Death in Specific Populations



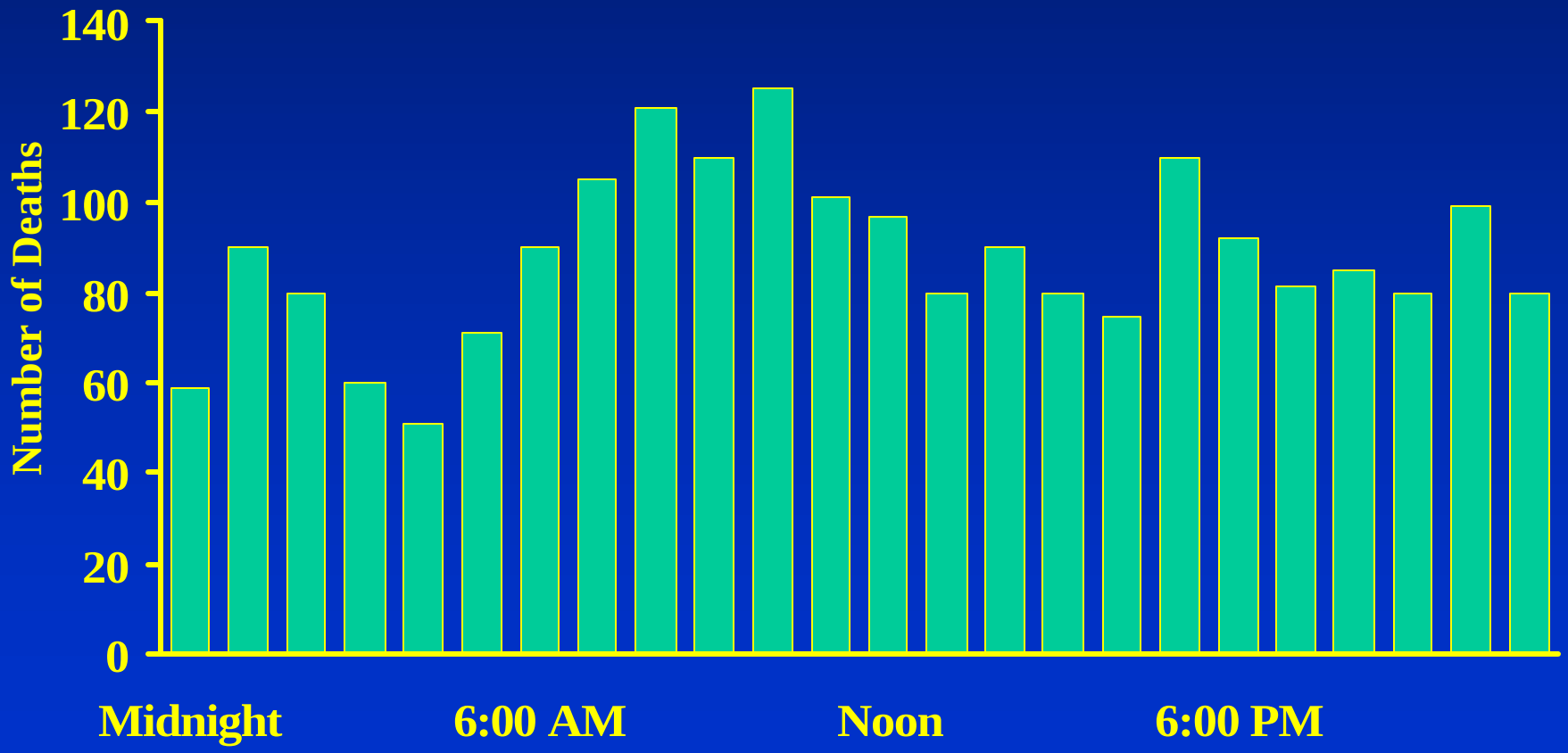
Huikuri & Myerburg *NEJM* 2001

Critical Role of Autonomic Triggers

- Circadian pattern of MI and sudden death
- Efficacy of beta-blockade in preventing sudden death
- Physical and mental stress are associated with MI and SCD risk
- Increased risk with depressed HRV and BRS

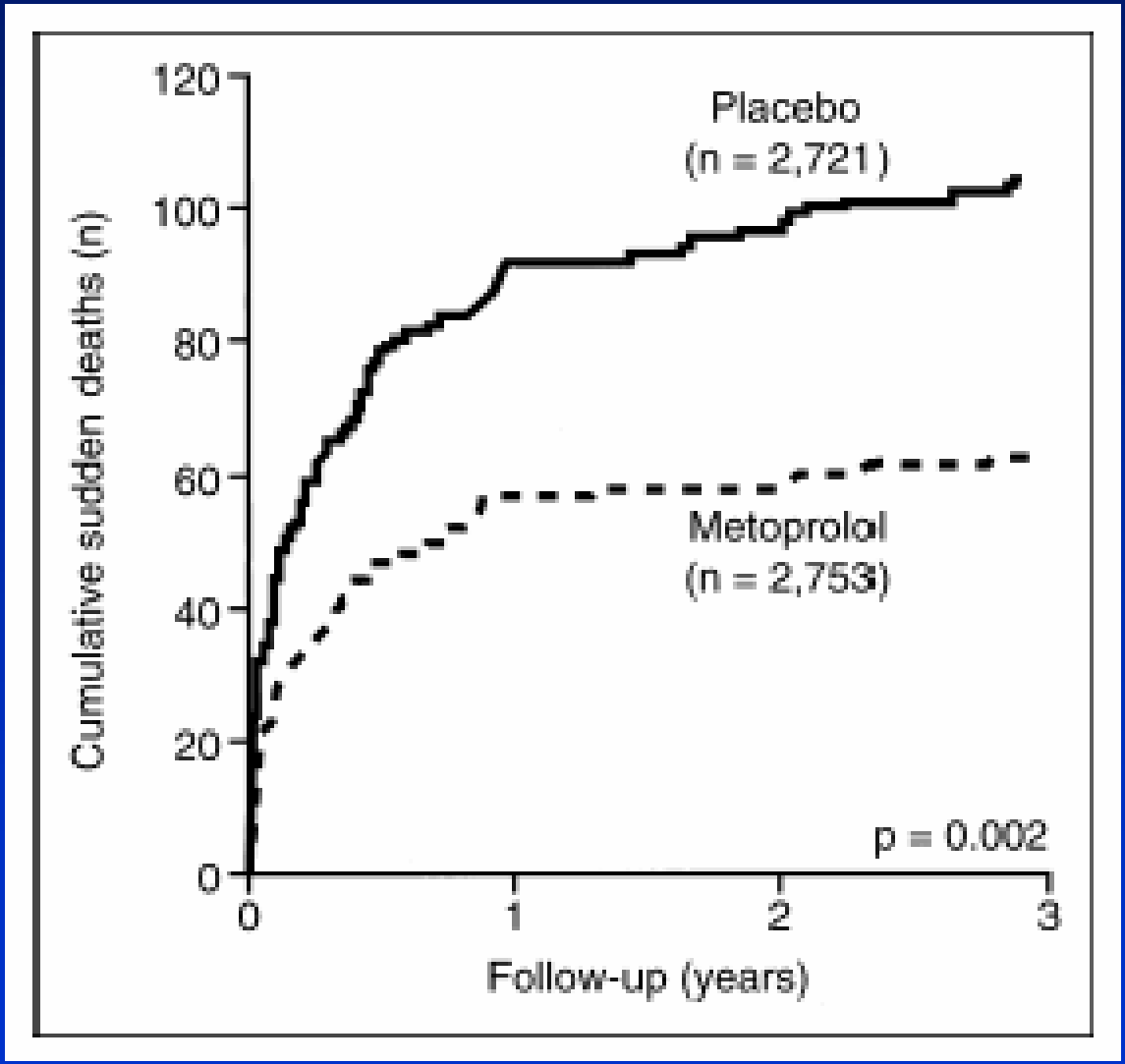
Circadian Variation of Sudden Cardiac Death

N=2,203 persons who died suddenly in Massachusetts during 1983



Muller et al *Circulation* 1987

Secondary Prevention of SCD with Metoprolol



Olsson et al *Eur Heart J* 1992

Patients at Risk for Nocturnal Cardiac Events

CAD	20% MIs, 15% SCD
Heart failure	20% SCD
Apnea (2-4% of adults)	Major comorbid factor
Brugada and LQT3	SCD more prevalent at night

Verrier & Josephson *Principles of Sleep Medicine* 2005

Requirements of Sudden Death Risk Stratifiers

- Sensitive to autonomic triggers (HRV, BRS)
- Capable of detecting electrical instability of myocardial substrate (TWA)
- Can be monitored during exercise and daily activities (ambulatory ECG)

Why TWA?

- Reflects a quantifiable, fundamental electrophysiologic property linked to VF.
- Compatible with exercise and ambulatory ECG monitoring
  - Thus, can expose latent electrical instability

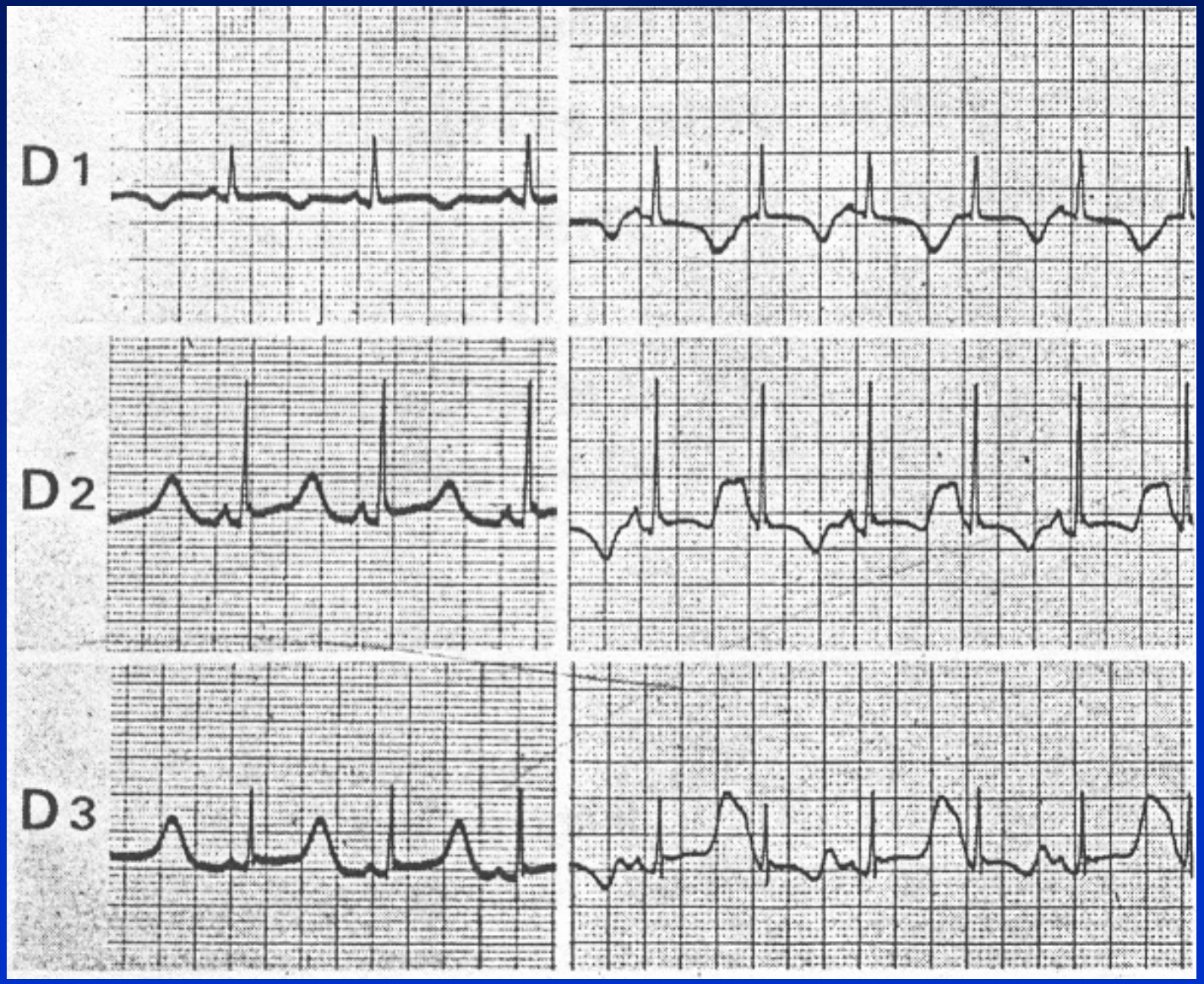
TWA Definition

Repeating ABAB pattern
in amplitude and shape of T wave

Pathologic States with TWA

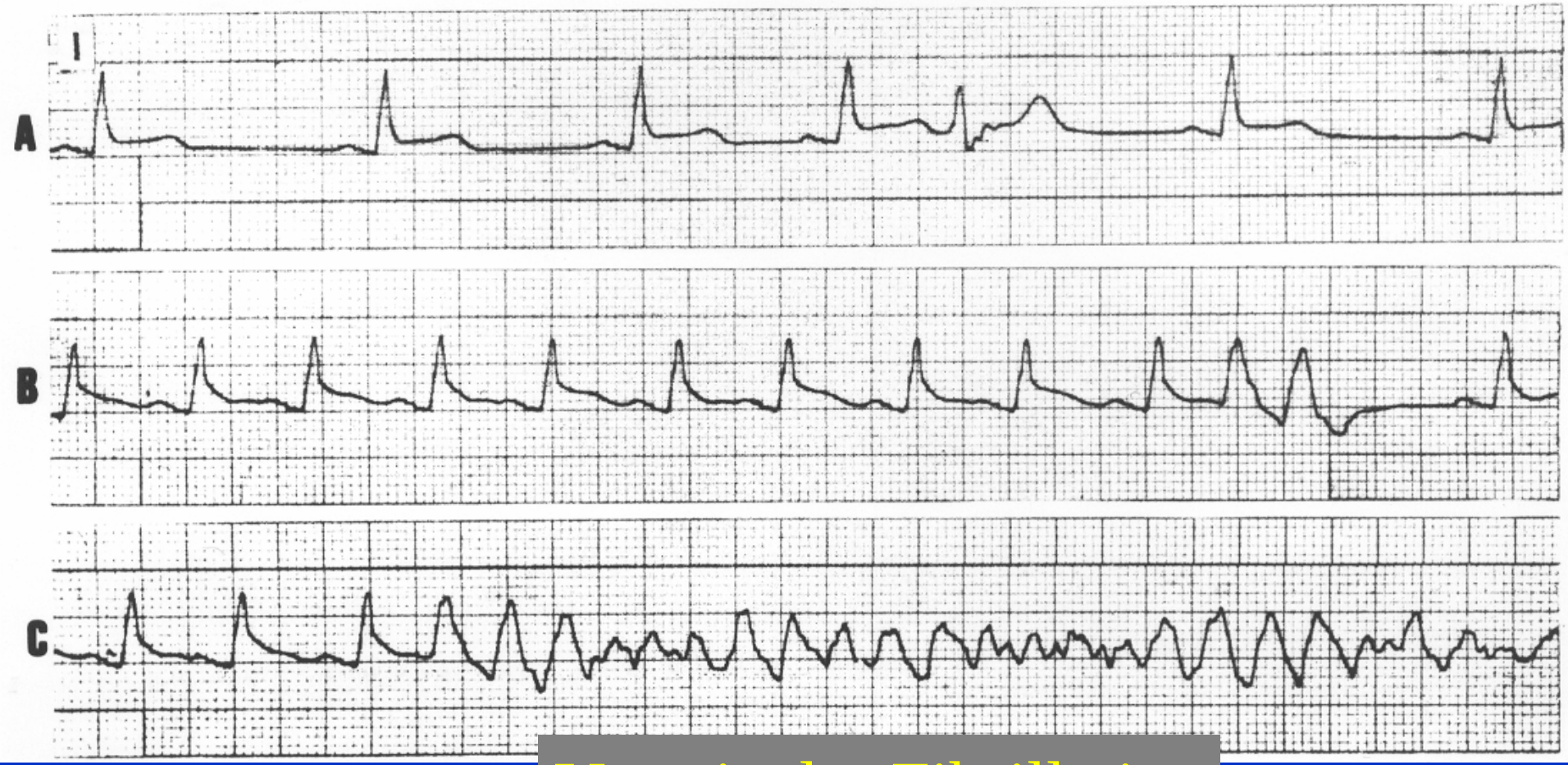
- Long QT Syndrome
- Myocardial Ischemia and Infarction
- Cardiomyopathies
- Heart Failure
- ICD Patients
- EP Patient Population
- Sudden Infant Death Syndrome
- Drug-Induced Torsade de Pointes

T-Wave Alternans in the Long QT Syndrome



Schwartz & Malliani *Am Heart J* 1975

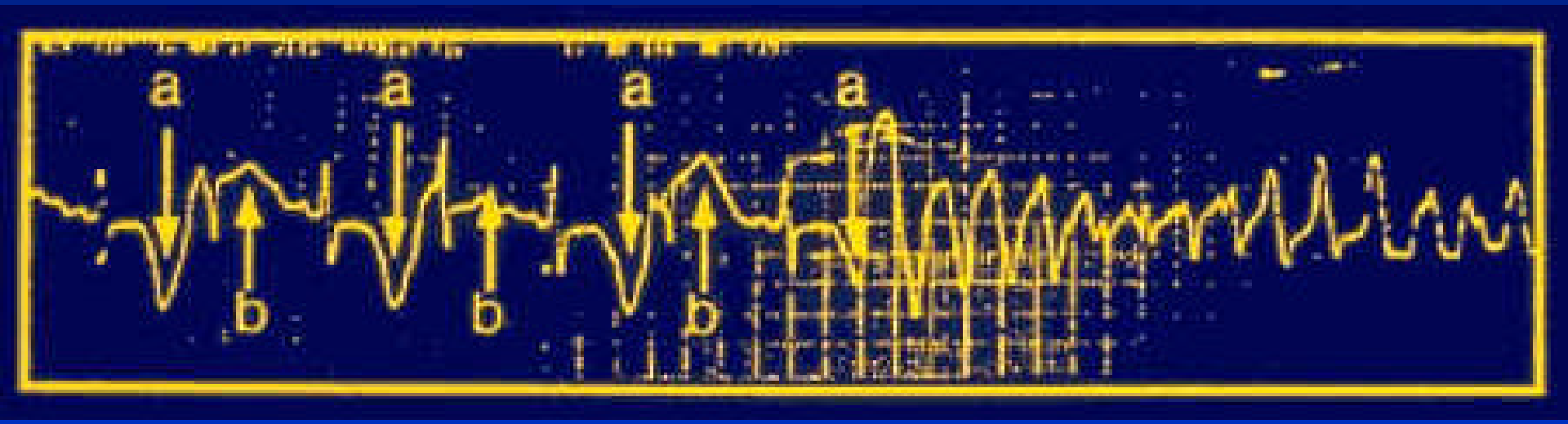
TWA in Patient with Acute Anterior Wall Myocardial Infarction



Ventricular Fibrillation

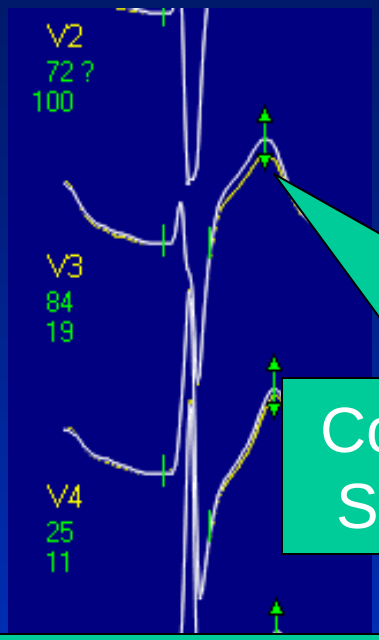
Pantridge *Neural Mechanisms* 1978

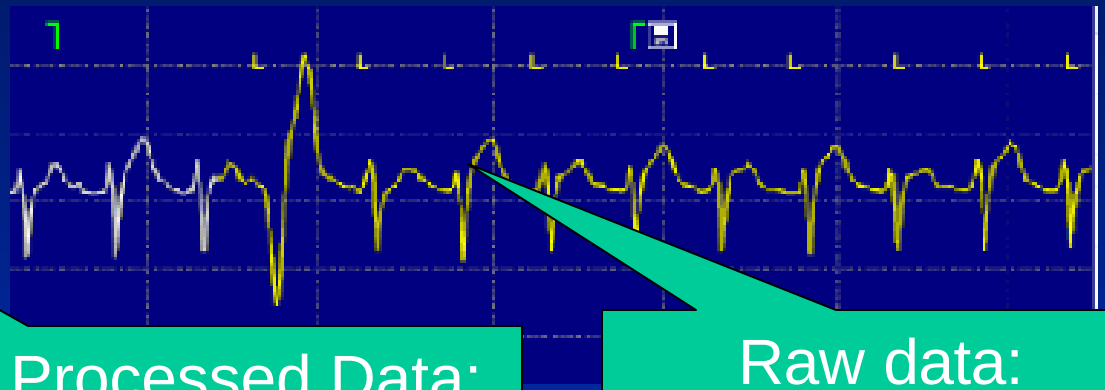
Progression from TWA to Polymorphic VT



Raeder et al *N Engl J Med* 1992

TWA Detection by GE's Case 8000 Treadmill with FDA-approved MMA Method

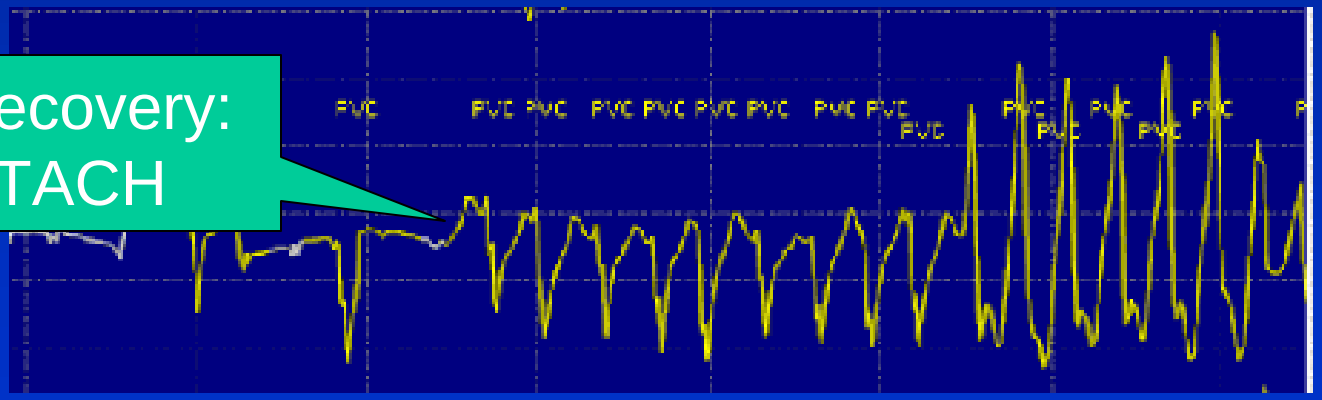




Computer Processed Data: Superimposed A&B Beats

Raw data: Confirms TWA

Later, During Recovery: Episode of VTACH



- TWA Overlooked Until Computer Detected.

GE Medical System's *Physicians Guide to TWA 2005*©

Experimental Evidence and Mechanisms Linking TWA to VF

TWA Predicts VF: Physiologic Interventions

- Increase TWA
  - Myocardial ischemia
  - Reperfusion
  - Sympathetic nerve stimulation
  - Behavioral arousal
  - Hypothermia
  - Rapid pacing (>200 beats/min in normal heart)
- Decrease TWA
  - Sympathectomy
  - Vagus nerve stimulation

Verrier & Nearing *JCE* 1994

TWA Predicts VF: Pharmacologic Interventions

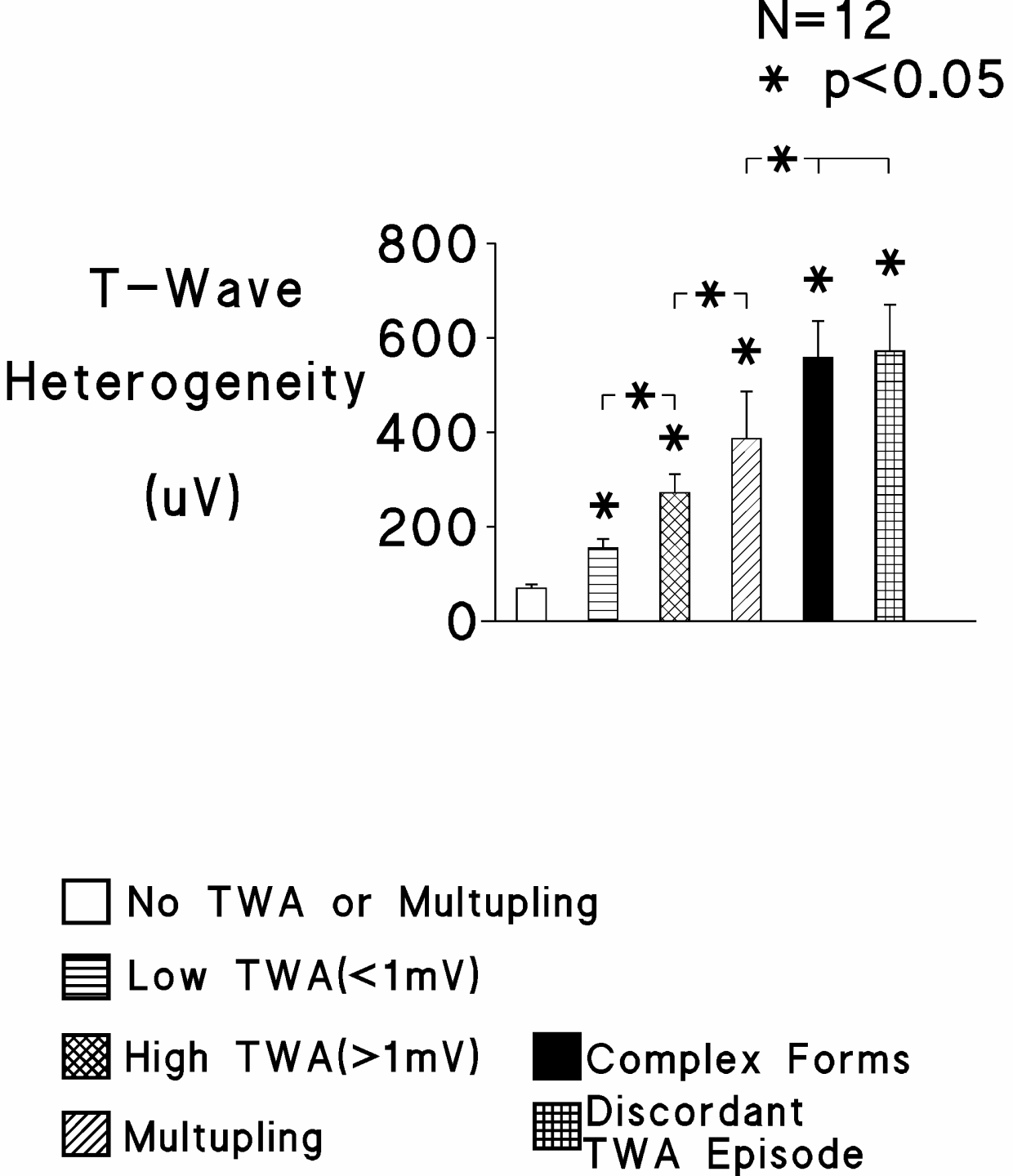
- Decrease TWA
  - Calcium channel blockade (verapamil, diltiazem, nexopamil)
  - Beta-adrenergic blockade (metoprolol)
  - NO Donor (nitroglycerin)
  - Amiodarone (clinical study)
- Increase TWA
  - Amiodarone prior to TdP onset

Electrophysiologic Basis for TWA's Predictive Power

- Assesses temporal spatial heterogeneity of repolarization

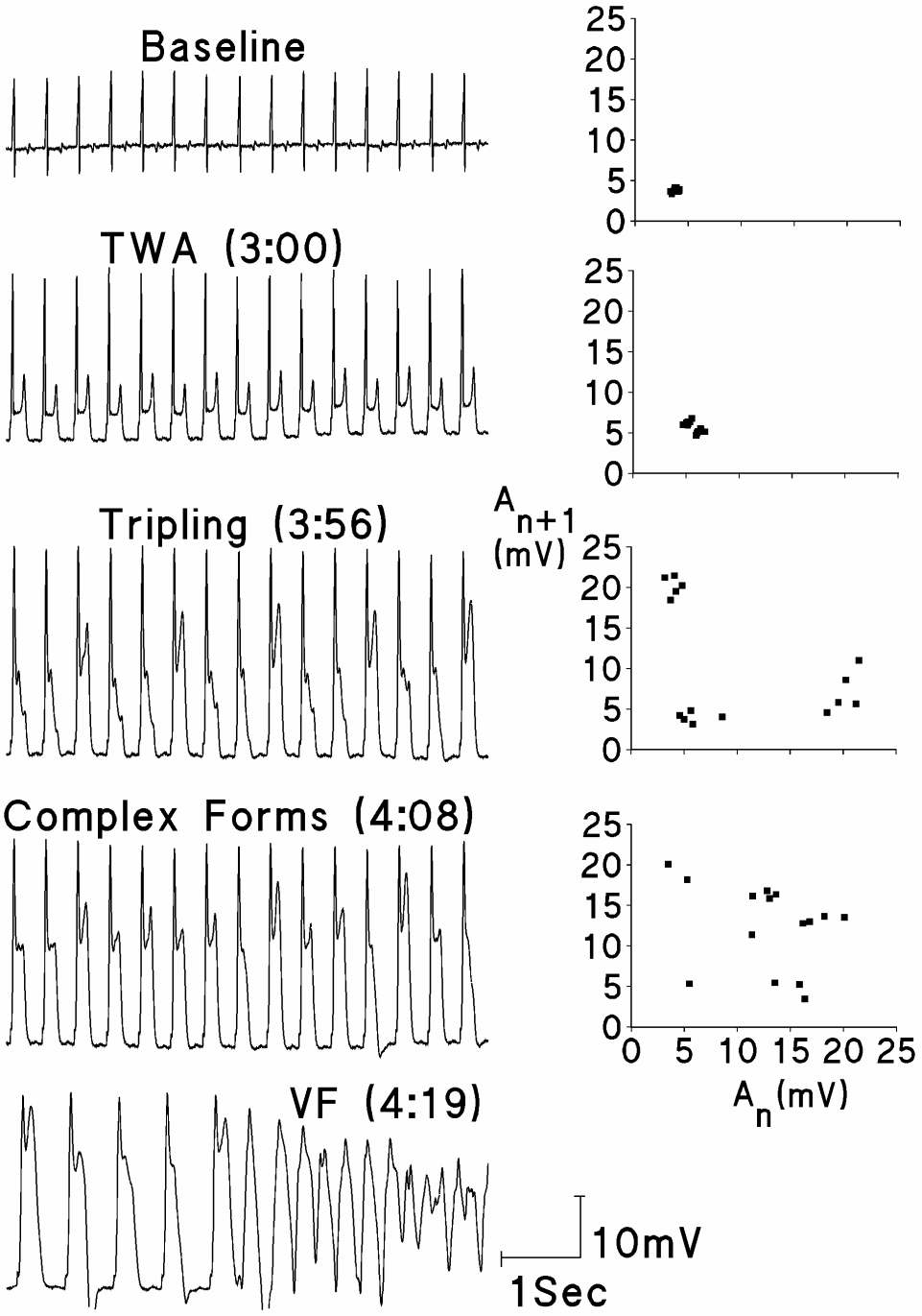
Verrier & Nearing *JCE* 1994

Spatial Heterogeneity Rises with Increased T-wave Complexity



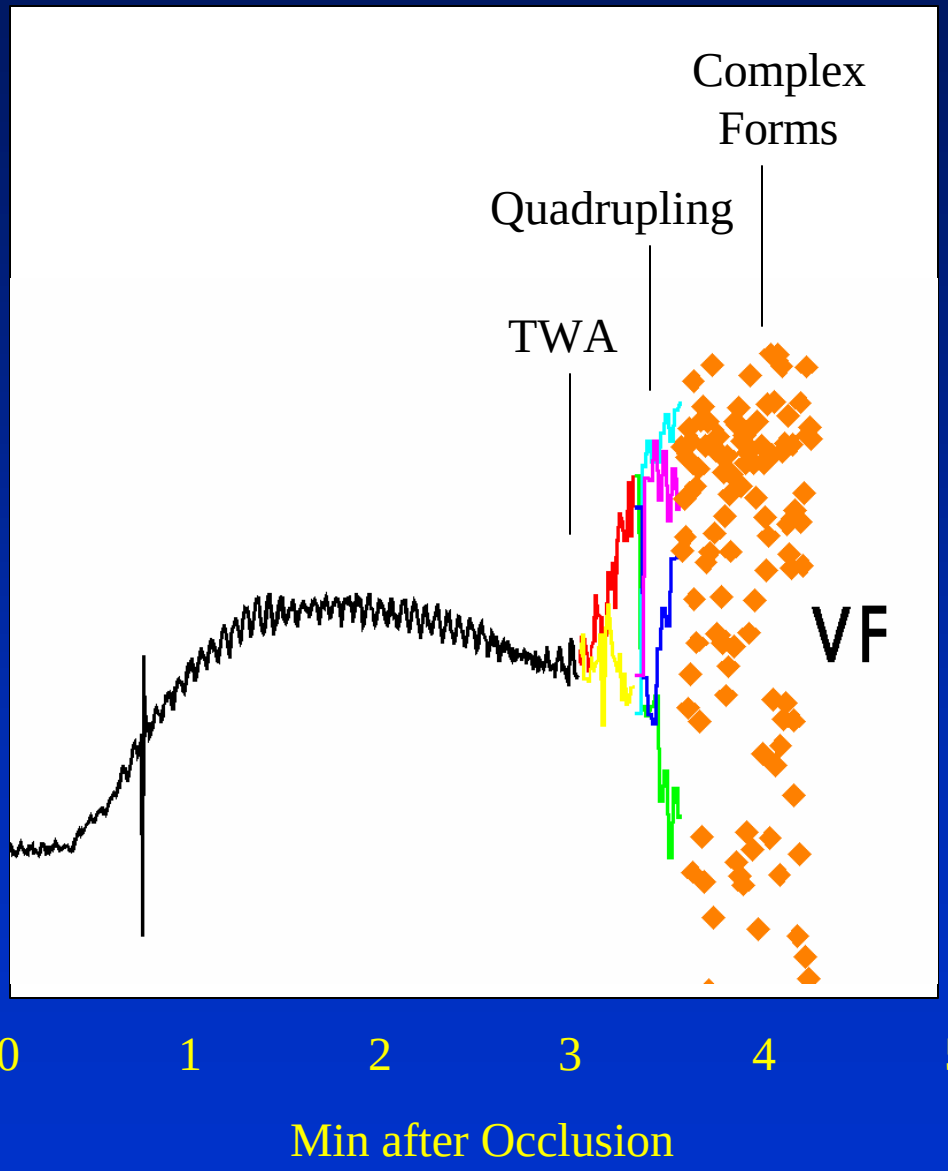
Nearing & Verrier
J Appl Physiol 2003

Orderly Progression to Multiple T-wave Oscillations



Nearing & Verrier *Circ Res* 2002

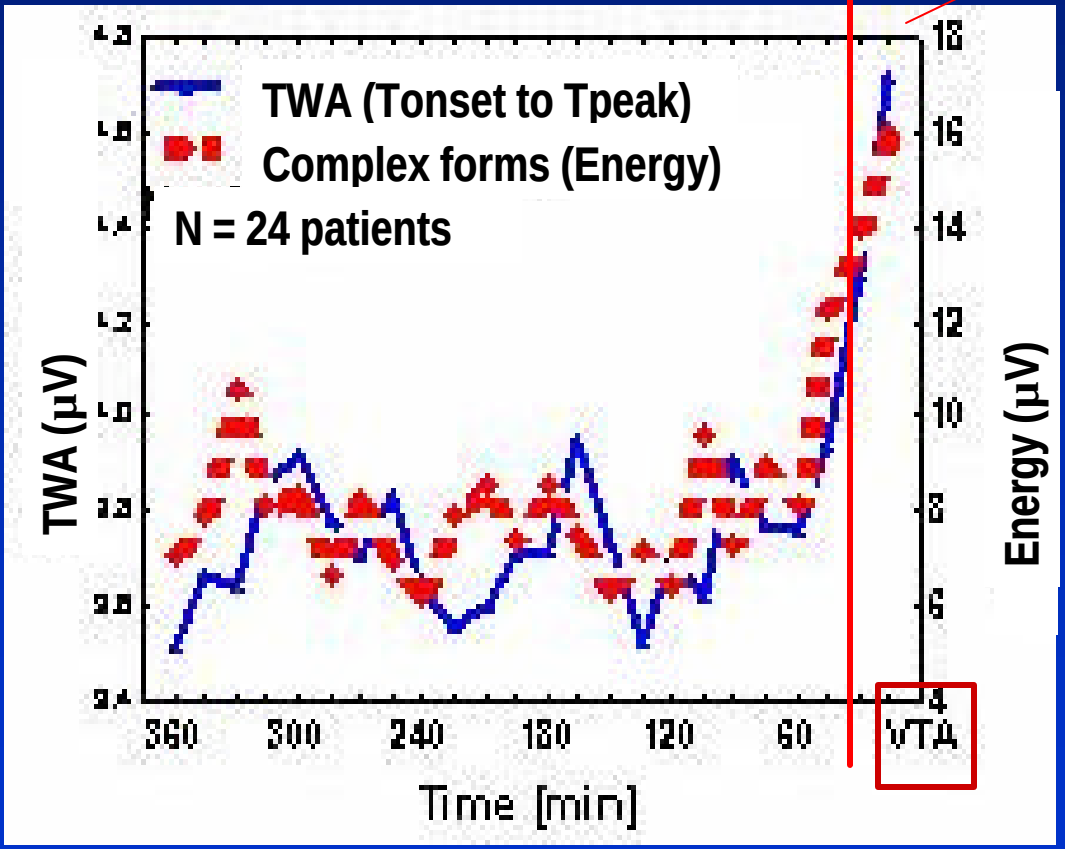
Crescendo in T-wave Oscillations Preceding VF



Nearing & Verrier *Circ Res* 2002

Clear and Present Danger

Surge in TWA Provides 20- to 30-Min Warning Period Prior to Ventricular Tachyarrhythmias



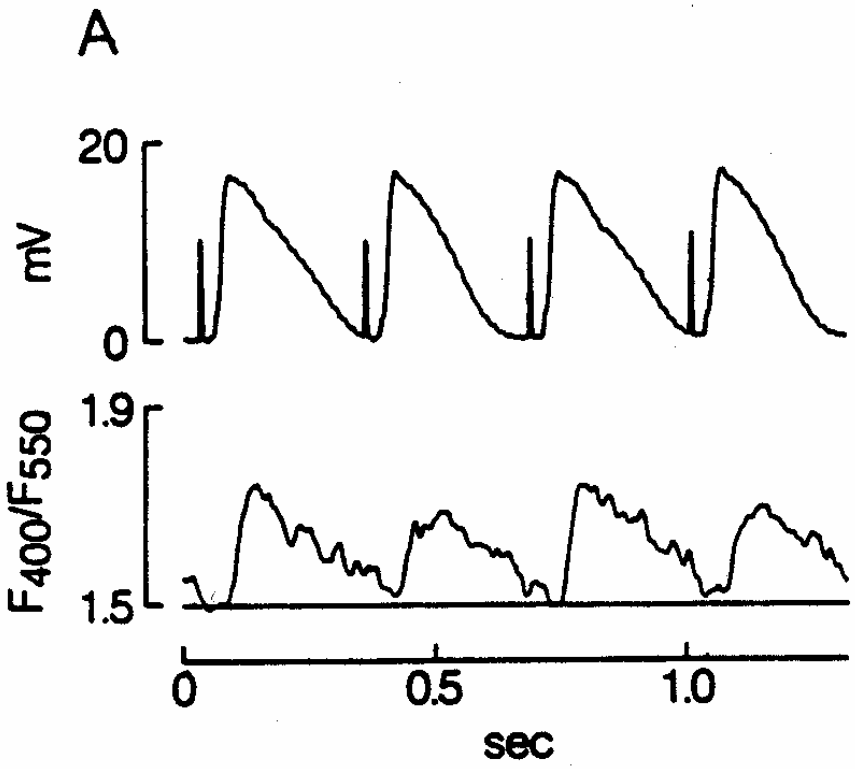
TWA analyzed by MMA method from Holter recordings

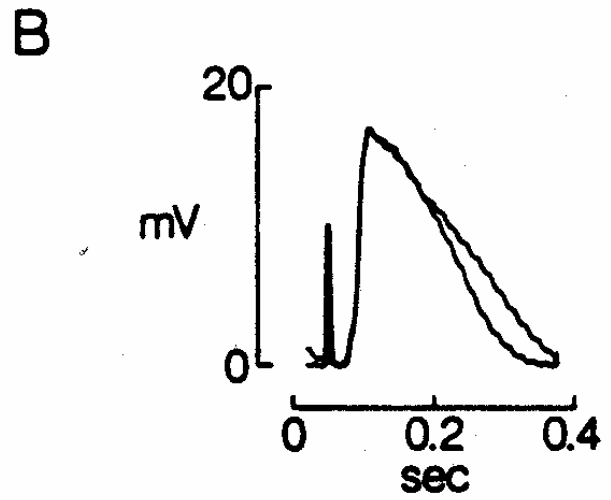
Shusterman & Goldberg *Circulation* [abstract] 2004

Ionic Mechanism of TWA

Abnormal Intracellular Calcium Handling

Alternation in Action Potential and Calcium Transients during Simulated Ischemia





Lee et al *Circulation* 1988

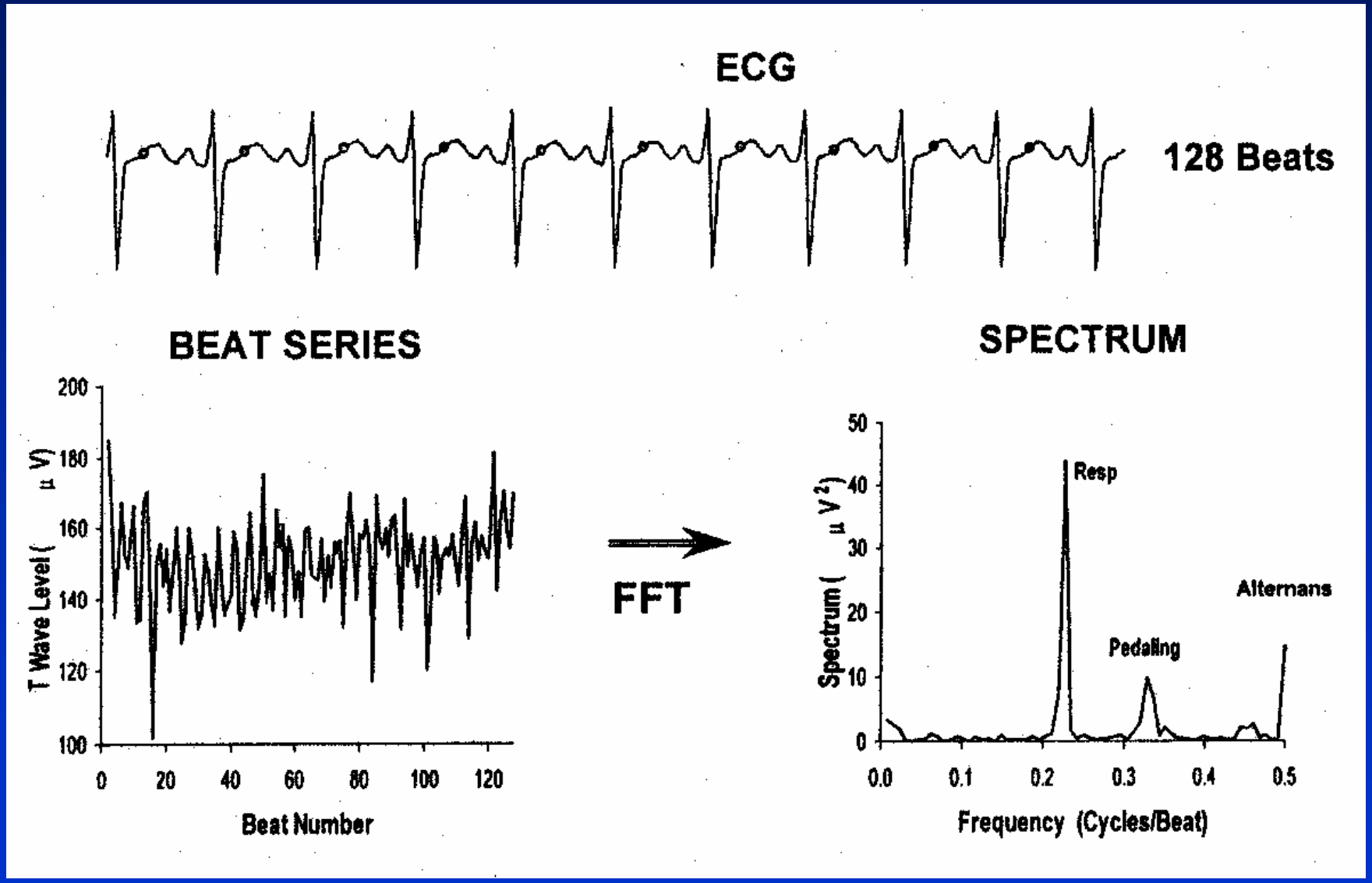
Clinical Assessment of TWA

- Spectral method– Fast Fourier Transform
  - Exercise
- Time-domain– Modified Moving Average
  - Exercise
  - Ambulatory ECG monitoring

Spectral Method

- Analyzes in frequency domain
  - TWA occurs at 0.5 cycle/beat
- Requires data stationarity for ≥128 beats
- Requires specialized electrodes to optimize signal to noise ratio
- 1-microvolt resolution
- Waveform not provided

Fast Fourier Transform Analysis of TWA

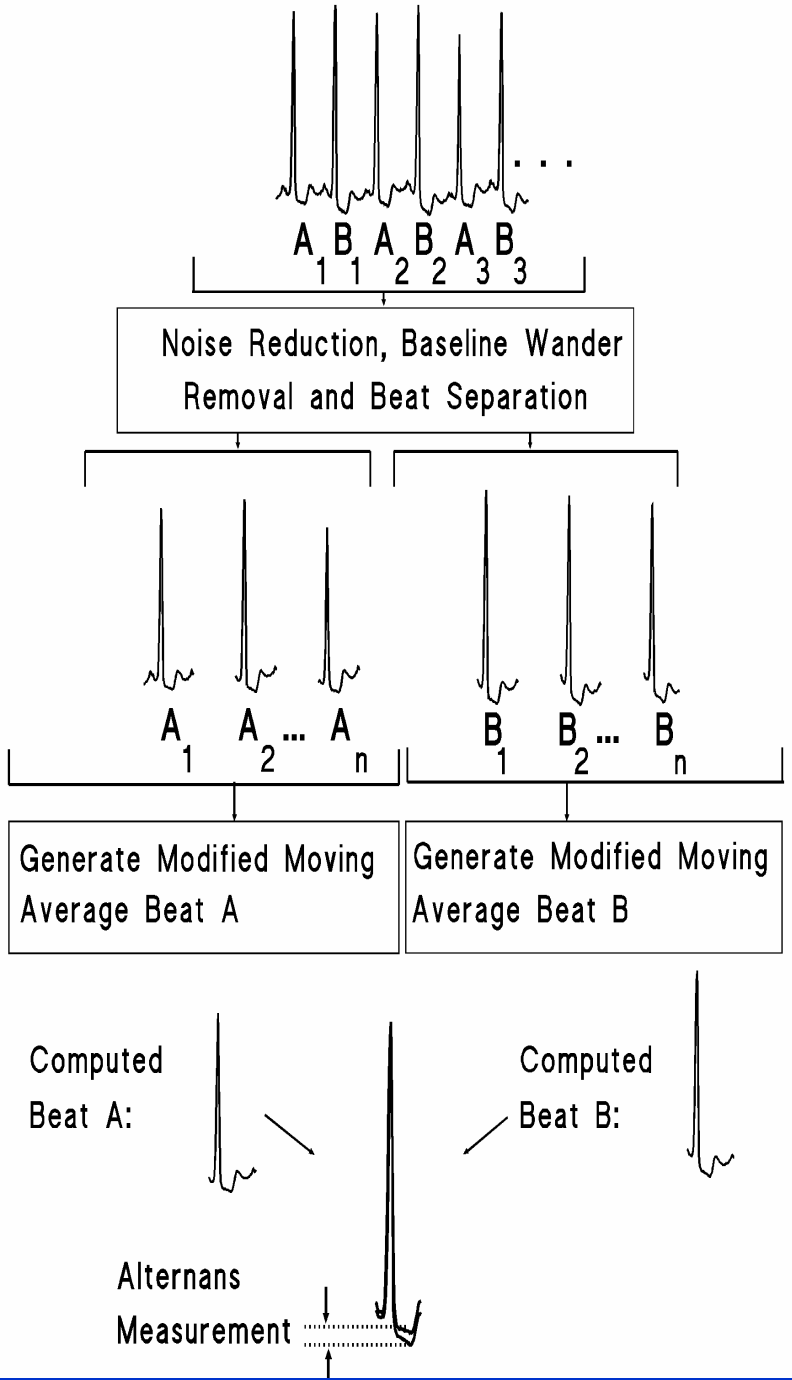


Verrier & Cohen *Foundations of Cardiac Arrhythmias* 2000

Modified Moving Average Method

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

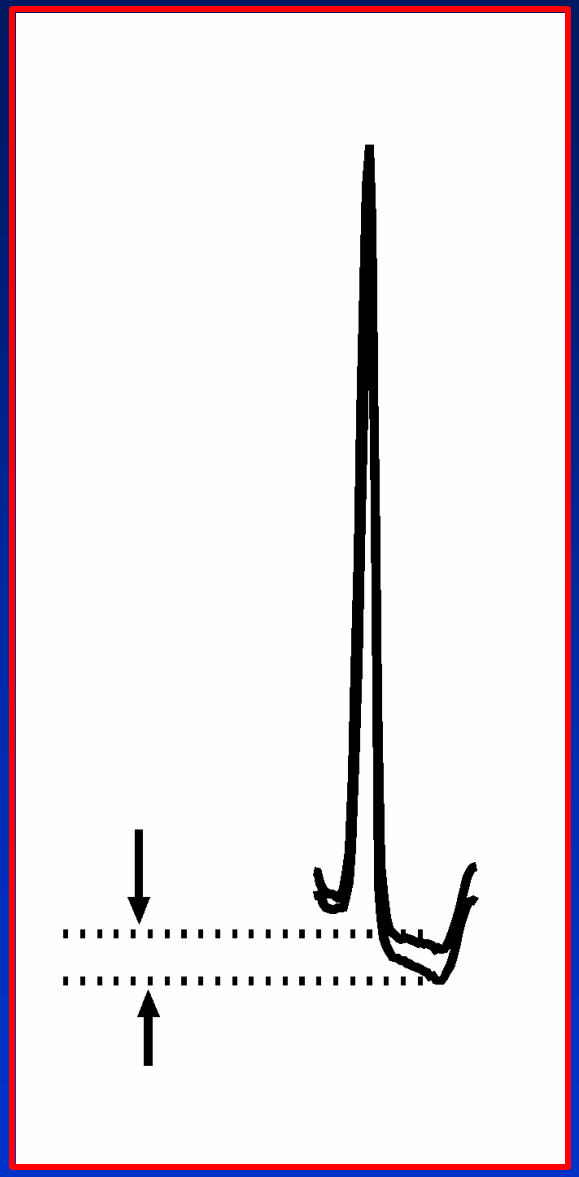
Modified Moving Average Analysis of T-Wave Alternans



Nearing & Verrier *J Appl Physiol* 2002

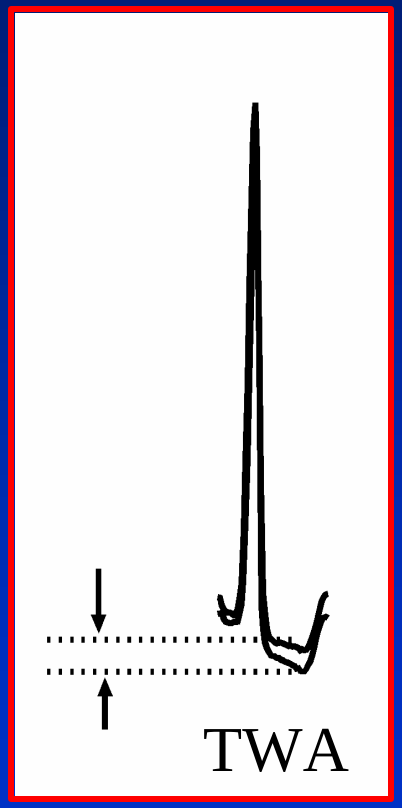
TWA Template Window

TWA = 80**µ**V



Adapted from Verrier et al *JCE* 2003

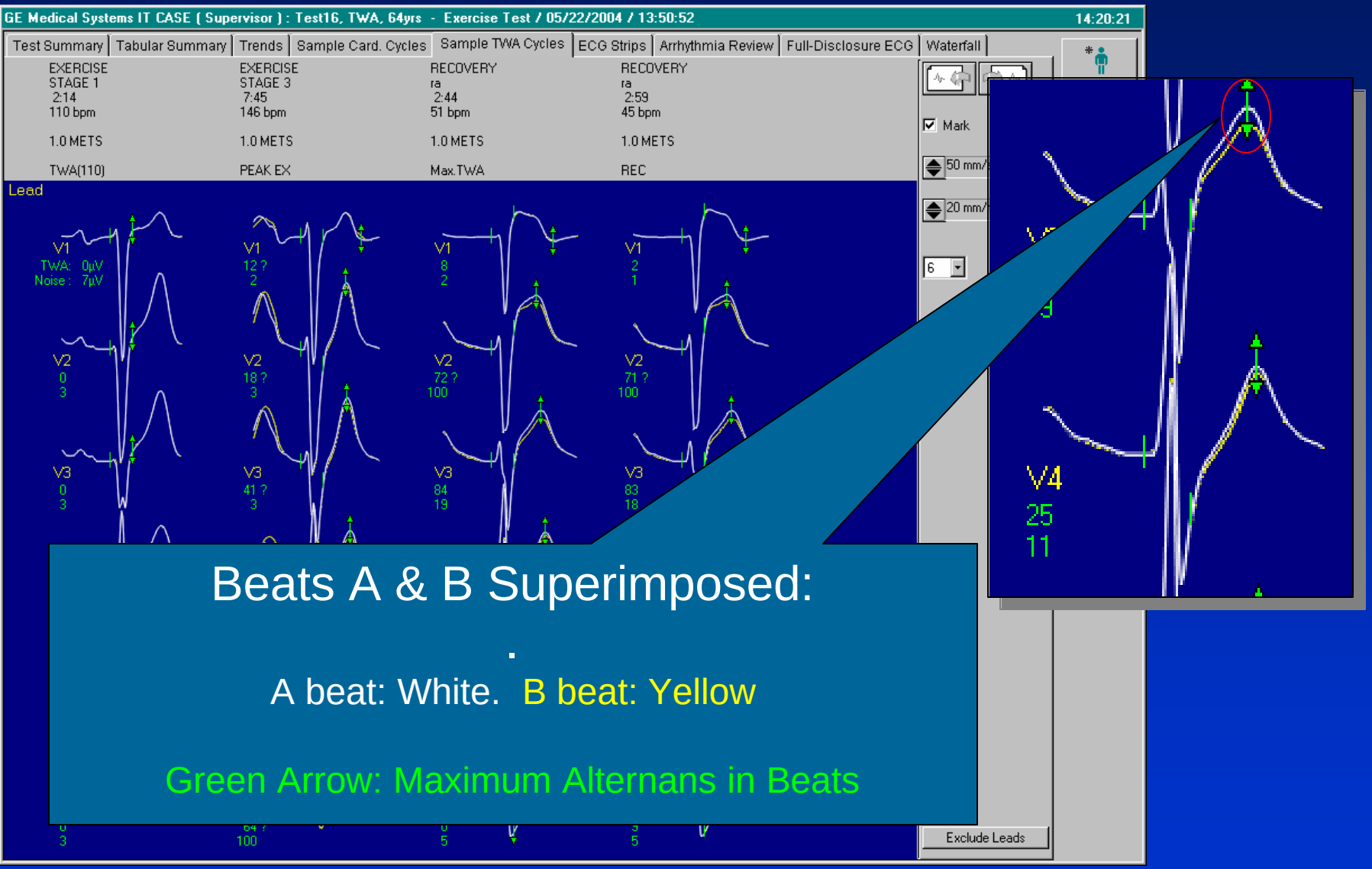
Analytical Features of TWA Median Template



- High-resolution superimposed ECGs for visual inspection
  - To rule out false TWA
  - To evaluate QRS changes
  - To confirm TWA visually down to ~20μV
  - To determine component of T-wave that alternates
    - Potential mechanistic insights

Verrier *Heart Rhythm Society* 2005

Medians / Templates: A Closer Look



Beats A & B Superimposed:

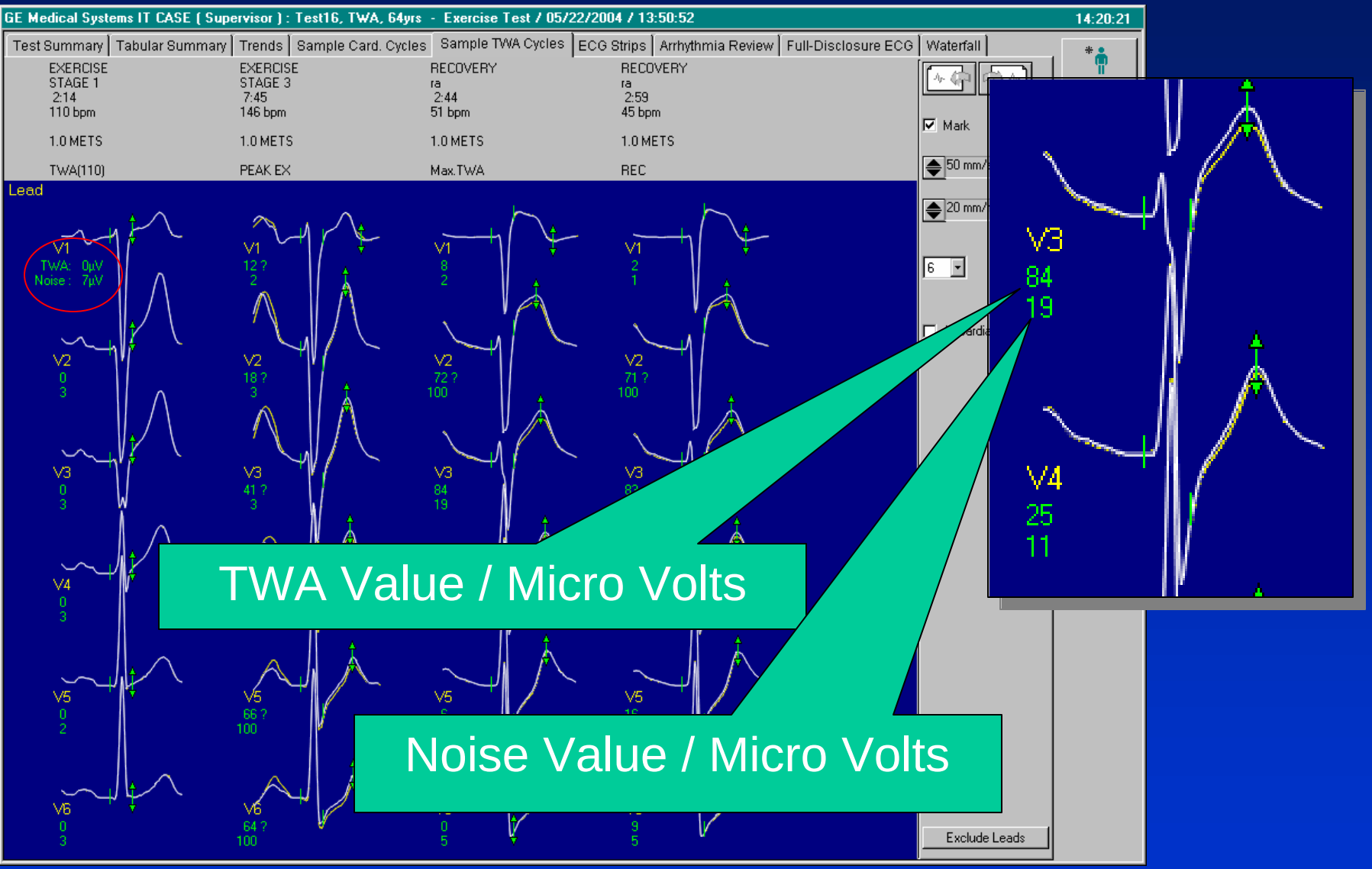
.

A beat: White. B beat: Yellow

Green Arrow: Maximum Alternans in Beats

GE Medical Systems' *TWA Physician's Guide* 2005

Medians / Templates: A Closer Look



Arrhythmia Risk Stratification with TWA

High-risk groups

- EP population:
  - Rosenbaum 1994, Estes 1997, Gold 2000, Klingenheben 2001, Rashba 2004
- ICD patients: Hohnloser 1998
- Heart failure: Klingenheben 2000, Bloomfield 2006
- Cardiomyopathy: Adachi 1999, Hohnloser 2003, Kitamura 2002, Kon-No 2001, Sakabe 2001

- *Moderate- to low-risk groups*
  - Post-MI:
    - Ikeda 2002
    - Verrier 2003
- *18 studies enrolled more than 100 patients*

Narayan *J Am Coll Cardiol* 2006

Ambulatory ECG Tracking of TWA in Post-MI Patients to Assess Risk of Cardiac Arrest or Arrhythmic Death:

Study Design

- Nested case-control with 2:1 matching (15 cases, 29 controls) on age (±5 yrs), sex, site of MI, LVEF (±3%), thrombolysis, beta-blockade
- AECG monitored early (15±10 days) post-MI
- Follow-up 21±8 months

Verrier et al *JCE* 2003

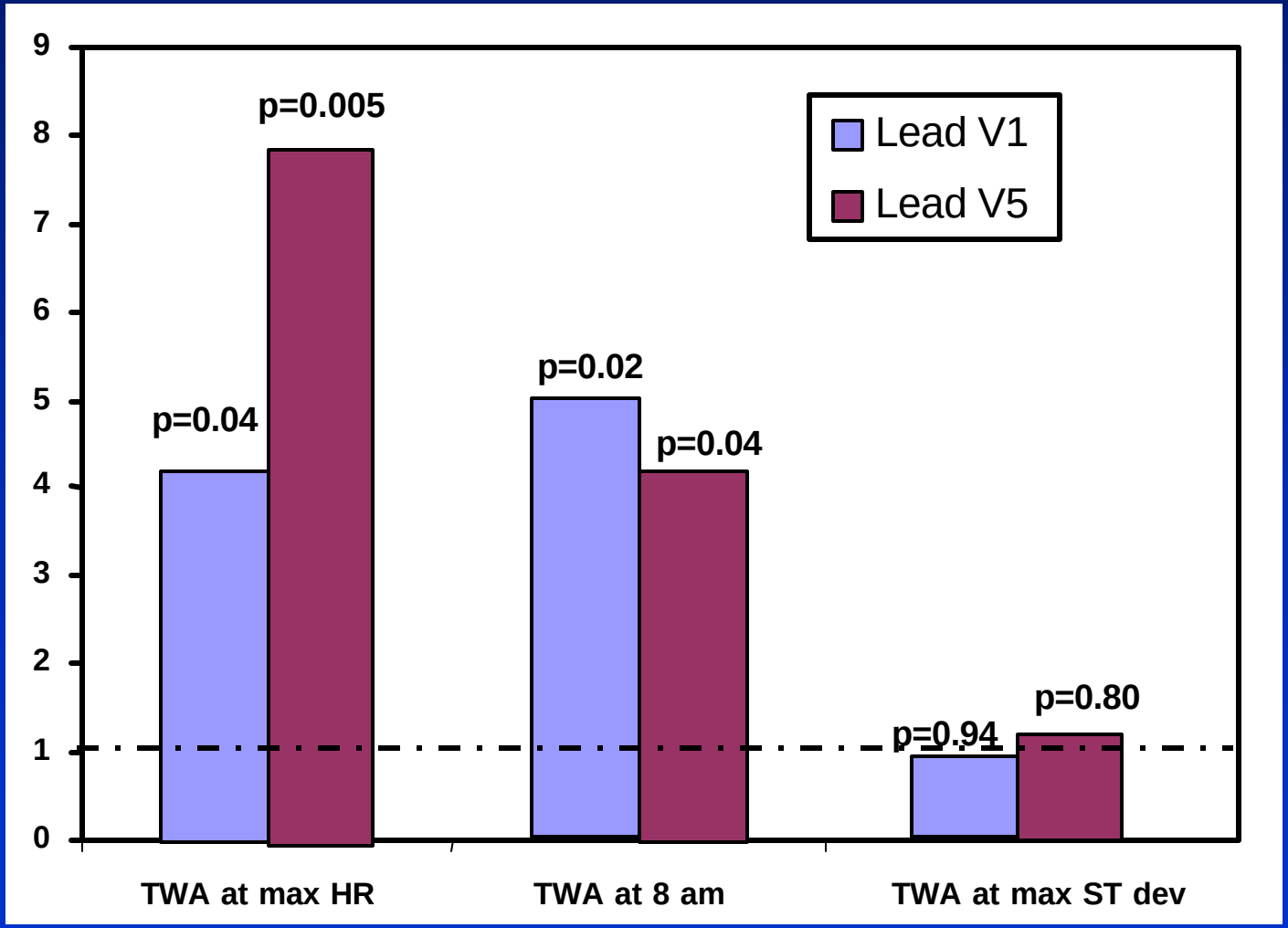
TWA Analysis and Risk Stratification

- TWA analysis by investigator blinded to outcomes
- *A priori* time points for TWA determinations:
  - 8:00 a.m.
  - Maximum heart rate
  - ST-segment deviation
- *A priori* cutpoint at 75th percentile of TWA in controls
- Odds ratios estimated as a measure of relative risk with logistic regression models controlling for all matching factors

Hypothesis

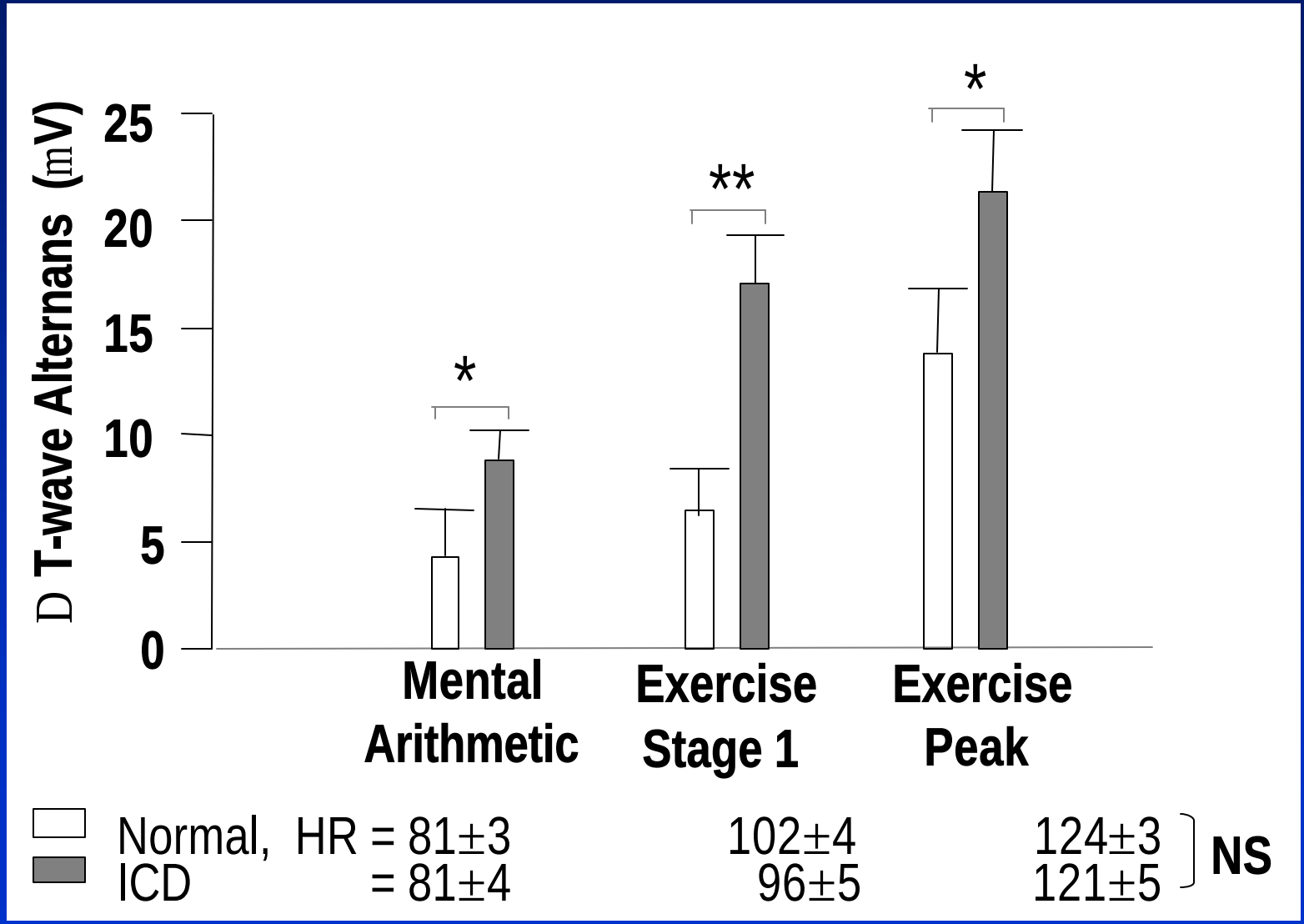
Post-MI patients at risk for arrhythmic death and cardiac arrest have electrical instability manifest as T-wave alternans.

AECG TWA and Arrhythmia Risk in Post-MI Patients



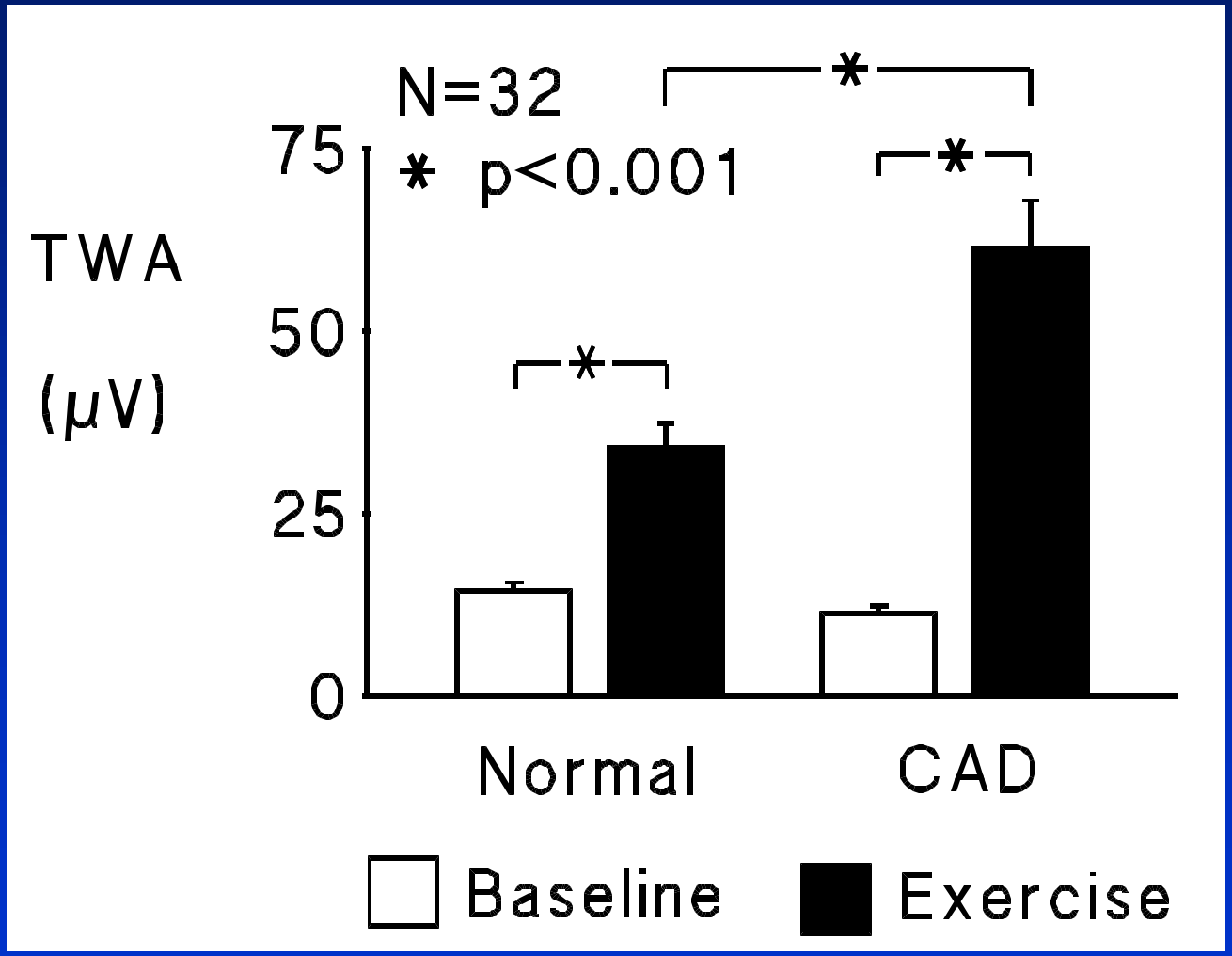
Verrier et al *JCE* 2003

Exercise- and Mental Stress-Induced TWA in ICD Patients and Normals



Kop et al *Circulation* 2004

Elevated TWA in Patients with Stable CAD during Routine Treadmill Testing



Nearing, Stone & Verrier J Am Coll Cardiol 2004

Summary and Conclusions

- TWA reflects fundamental property linked to risk for VF
- Can be quantified during routine clinical testing, including exercise and AECGs
- Useful in sudden death risk stratification
- May help to guide therapy

Future of TWA

- Multiparameter analysis
  - Autonomic function (HRV, BRS/HRT)
  - Cardiac electrical function (TWA)
- Multiple platforms

Future Platforms for TWA

- Exercise treadmill or ergometry
- Holter and in-hospital monitoring
- EP laboratory programmed stimulation
  - TWA magnitude and phase reversal
- ICDs:
  - TWA is harbinger of VF
  - Signal to initiate urgent therapy
- Alert central monitoring station

Selected References

- Nearing BD, Huang AH, Verrier RL. Dynamic tracking of cardiac vulnerability by complex demodulation of the T-wave. Science 1991;252:437-40.
- Nearing BD, Verrier RL. Modified moving average method for T-wave alternans analysis with high accuracy to predict ventricular fibrillation. J Appl Physiol 2002;92:541-549.
- Nearing BD, Verrier RL. Progressive increases in complexity of T-wave oscillations herald ischemia-induced VF. Circ Res 2002;91:727-732.
- Verrier RL, Nearing BD, LaRovere MT, Pinna GD, Mittleman MA, Bigger JT, Schwartz PJ for the ATRAMI Investigators. Ambulatory ECG-based tracking of T-wave alternans in post-myocardial infarction patients to assess risk of cardiac arrest or arrhythmic death. J Cardiovasc Electrophysiol 2003;14:705-711.
- Kop WJ, Krantz DS, Nearing BD, Gottdiener JS, Quigley JF, O'Callahan M, Delnegro AA, Friehling TD, Karasik P, Suchday S, Levine J, Verrier RL. Effects of acute mental and exercise stress on T-wave alternans in patients with implantable cardioverter defibrillators and controls. Circulation 2004;109:1864-1869.
- Verrier RL, Josephson ME. Cardiac arrhythmogenesis during sleep: mechanisms, diagnosis, and therapy. In: Kryger MH, Roth T, Dement WC, editors. Principles and Practice of Sleep Medicine, 4th edition. Philadelphia: WB Saunders, 2005:1171-1179.
- Verrier RL, Nearing BD, Kwaku KF. Noninvasive sudden death risk stratification by ambulatory ECG-based T-wave alternans analysis: evidence and methodological guidelines. Annals of Noninvasive Electrocardiology 2005;10:110-120.
- Bloomfield DM, Bigger JT, Steinman RC, Namerow PB, Parides MK, Curtis AB, Kaufman ES, Davidenko JM, Shinn TS, Fontaine JM. Microvolt T-wave alternans and the risk of death or sustained ventricular arrhythmias in patients with left ventricular dysfunction. J Am Coll Cardiol 2006;47:456-63.
- Narayan SM. T-wave alternans and the susceptibility to ventricular arrhythmias. J Am Coll Cardiol 2006;47:269-81.