T-Wave Alternans and Risk Stratification for Sudden Cardiac Death

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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

- General population
- Patients with high coronary-risk profile
- Patients with previous coronary event
- Patients with ejection fraction <35%, congestive heart failure
- Patients with previous out-of-hospital cardiac arrest
- Patients with previous myocardial infarction, low ejection fraction, and ventricular tachycardia

Incidence of Sudden Death (% of group) vs. No. of Sudden Deaths per Year

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD</td>
<td>20% MIs, 15% SCD</td>
</tr>
<tr>
<td>Heart failure</td>
<td>20% SCD</td>
</tr>
<tr>
<td>Apnea (2-4% of adults)</td>
<td>Major comorbid factor</td>
</tr>
<tr>
<td>Brugada and LQT3</td>
<td>SCD more prevalent at night</td>
</tr>
</tbody>
</table>

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

Quiet Standing

Frightened

Schwartz & Malliani *Am Heart J* 1975
TWA in Patient with Acute Anterior Wall Myocardial Infarction

Ventricular Fibrillation
Progression from TWA to Polymorphic VT

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

- TWA Overlooked Until Computer Detected.

Later, During Recovery: Episode of VTACH

Computer Processed Data: Superimposed A&B Beats

Raw data: Confirms TWA
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

T-Wave Heterogeneity (uV)

- No TWA or Multupling
- Low TWA (<1mV)
- High TWA (>1mV)
- Multupling
- Complex Forms
- Discordant TWA Episode

N=12
* p<0.05

* * *
Orderly Progression to Multiple T-wave Oscillations

Nearing & Verrier *Circ Res* 2002
Crescendo in T-wave Oscillations Preceding VF

T-wave Area

Min after Occlusion

Nearing & Verrier *Circ Res* 2002
Clear and Present Danger
Surge in TWA Provides 20- to 30-Min Warning Period Prior to Ventricular Tachyarrhythmias

TWA (Tonset to Tpeak)
Complex forms (Energy)
N = 24 patients

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 $\geq 128$ 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 = 80 μV

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
Medians / Templates: A Closer Look

TWA Value / Micro Volts

Noise Value / Micro Volts
Arrhythmia Risk Stratification with TWA

**High-risk groups**
- EP population:
- ICD patients: Hohnloser 1998
- Heart failure: Klingeneheben 2000, Bloomfield 2006

**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 75\(^{\text{th}}\) 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

Odds Ratio of Cardiac Arrest or Death from Arrhythmia

Verrier et al JCE 2003
Exercise- and Mental Stress-Induced TWA in ICD Patients and Normals

Kop et al Circulation 2004

<table>
<thead>
<tr>
<th></th>
<th>Normal, HR = 81±3</th>
<th>ICD = 81±4</th>
<th>Exercise Stage 1</th>
<th>Exercise Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental Arithmetic</td>
<td>5.6±3</td>
<td>10.1±4</td>
<td>10.2±3</td>
<td>12.4±3</td>
</tr>
<tr>
<td>Exercise Stage 1</td>
<td>9.6±3</td>
<td>10.1±3</td>
<td>10.2±3</td>
<td>12.4±3</td>
</tr>
<tr>
<td>Exercise Peak</td>
<td>12.4±3</td>
<td>12.1±5</td>
<td>12.4±3</td>
<td>NS</td>
</tr>
</tbody>
</table>
Elevated TWA in Patients with Stable CAD during Routine Treadmill Testing

N=32
* p<0.001

TWA (µV)

Normal  CAD

Baseline  Exercise

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

Verrier ISHNE 2005
Selected References