Non Invasive Risk Stratification for Post Infarction Patient

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Sudden Cardiac Death (SCD) Risk Stratification

- A decline in cardiac arrest caused by VT/VF and a concomitant increase in pulseless electric activity/asystole

![Incidence chart showing a decline in cardiac arrest caused by VT/VF and an increase in pulseless electric activity/asystole from 1995-1997 to 2005-2008.](image)
The pathophysiology of VT/VF in the Presence of LV Dysfunction or MI

(1) anatomic substrate (generally fixed) abnormalities

(2) autonomic abnormalities

(3) arrhythmia vulnerability
Anatomic Substrate Abnormalities
Anatomic Substrate Abnormalities

**Myocardial scar**

- Cardiac imaging
  - Global left ventricular function/ejection fraction
  - Myocardial scar assessment (MRI, SPECT, PET)

- ECG depolarization abnormalities
  - ECG QRS duration
  - ECG QRS fractionation
  - Signal-averaged ECG
LV ejection fraction (LVEF)

- A crude marker for overall scar burden is global LV systolic function

- The link between reduction in LVEF and risk of SCD-VT/VF in patients with MI and or LV dysfunction is well established

  Circulation. 1984;69:250–258

- LVEF became the major inclusion criteria for trials evaluating ICDs for the primary prevention of SCD


- LVEF is a potent predictor of overall mortality and non-SCD, which limits its specificity as a predictor for SCDVT/VF

- LVEF alone has been insufficient to predict patients who would benefit from ICD therapy post MI

Anatomic Substrate Abnormalities

**Strain Curves in Patients After MI**

- Strain imaging provided better prediction of arrhythmic events (VT/VF) and SCD than LVEF, particularly in patients with LVEF >35%

[Graphs showing strain curves with and without SCD]
Anatomic Substrate Abnormalities

Positron Emission Tomography (PET)

Neuronal cardiac imaging with 11C-HED PET

Anatomic Substrate Abnormalities

Positron Emission Tomography (PET)
Anatomic Substrate Abnormalities

Single Photon Emission Computed Tomography (SPECT) Imaging

![Graph showing events over follow-up days with different scar classifications. The graph shows a significant difference (P<0.05) between scars greater than 1 vascular territory and scars less than or equal to 1 vascular territory. The y-axis represents the percentage of events, and the x-axis represents follow-up days. At 1080 days, the percentage of events is 54% for scars greater than 1 vascular territory and 16% for scars less than or equal to 1 vascular territory.]
Cardiac MRI

Heterogeneous Scar

VT

Control

J Am Coll Cardiol 2011;57:184–94
Novel MRI Techniques for Tissue Characterization

Diffusion spectrum MRI tractography
VT Circuits in Scar With Surviving Islands of Electric Activity

Heterogeneous Scar
Algorithm for Determining the Gray Zone

More extensive tissue heterogeneity correlates with increased ventricular irritability by programmed electrical stimulation

Circulation. 2007;115:2006-2014
Infarct Tissue Heterogeneity Assessed With MRI Predicts Spontaneous Ventricular Arrhythmia in Patients With MI and ICD

Circ Cardiovasc Imaging. 2009;2:183-190
Relation of Voltage and Signal Intensity Mapping

- heterogeneous scar correlate well with results of electrophysiology voltage mapping of VT circuits.
ECG Depolarization Abnormalities

- ECG QRS duration
- ECG QRS fragmentation
- Signal-averaged ECG
Fragmentation of the QRS Complex
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

Braunwald’s Heart Disease 8th edition
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
Delayed Intrinsicoid Deflection of the QRS Complex is Associated With SCD
Evaluating Cardiac Autonomic Function
Evaluating Cardiac Autonomic Function

- Heart rate variability
- Heart rate turbulence
- Baroreceptor sensitivity
- Imaging: SPECT (MIBG), PET (11C-meta-hydroxyephedrine)
Heart Rate Turbulence (HRT)

- **Turbulence onset (TO):** A percentage of relative change of the mean of 2 RR intervals before and 2 RR intervals after a VPB.

- **Turbulence slope (TS):** The slope of the steepest regression line computed over the sequence of every 5 consecutive RR intervals following a VPB within the 15 RR intervals after the VPB.
Heart Rate Turbulence

PVC
--- > a transient drop in blood pressure

--- > triggers activation of baroreceptors

--- > immediate vagal inhibition, and increase in heart rate

--- > augmented myocardial contractility following a VPB

--- > increase in blood pressure

--- > opposite reaction with subsequent decrease in sinus node activity

--- > biphasic HRT curve of acceleration and deceleration
Heart Rate Turbulence

**Normal**
- VPC compensatory pause
- Early acceleration
- Late declaration

**Abnormal**

J Am Coll Cardiol. 2008;52:1353-1365
HRT and Baroreceptor Sensitivity

- HRT significantly correlated with phenylephrine-derived slope of blood pressure and RR interval \( (r = 0.66, \ p < 0.0001) \)

---> HRT is mediated by baroreflex response


- HRT predict overall mortality, independent of LVEF, after MI

Lancet. 1999;353:1390–1396

- HRT was also independently predictive of fatal or nonfatal cardiac arrest after MI

J Am Coll Cardiol. 2007;50:2275–2284
Prognostic Significance of Turbulence Slope in Heart Failure Patients With EF >35%
Regional Myocardial Sympathetic Denervation Predicts the Risk of Sudden Cardiac Arrest in Ischemic Cardiomyopathy

PET imaging

<table>
<thead>
<tr>
<th>Flow ($^{13}$NH$_3$)</th>
<th>Viability ($^{18}$FDG)</th>
<th>Sympathetic Innervation ($^{11}$C-HED)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANT</td>
<td>LAT</td>
<td>INF</td>
</tr>
<tr>
<td>SEP</td>
<td>LAT</td>
<td>INF</td>
</tr>
<tr>
<td>INF</td>
<td>AN</td>
<td>INF</td>
</tr>
</tbody>
</table>

J Am Coll Cardiol. 2014;63:141–149
SPECT Assessment of Global Cardiac Sympathetic Innervation

A. Composite Primary Endpoint

B. Heart Failure Progression

C. Arrhythmic Event

D. Cardiac Death

E. All-cause Mortality

J Am Coll Cardiol. 2010;55:2212–2221
SPECT Assessment of Global Cardiac Sympathetic Innervation

A Composite Primary Endpoint

B Cardiac Death

C Composite Primary Endpoint

D Cardiac Death

E Composite Primary Endpoint

F Cardiac Death

G Composite Primary Endpoint

H Cardiac Death

J Am Coll Cardiol. 2010;55:2212–2221
Measures of ECG Repolarization
Measures of ECG Repolarization

- T-wave alternans
- QT dispersion/variability
- QRS-T angle
- QT interval
T Wave Alternans (TWA)

- 1st Electrocardiographic alternans in 1908 by Hering

- A harbinger of malignant ventricular arrhythmia

NEJM 1992;326:271-272
Mechanisms Underlying TWA

ECG

Repolarization (T-wave) Alternans

Spatial Dispersion

Temporal Dispersion

Intracardiac

Beats A B A
Region 2
Depolarize Block Depolarize

Beats A B A
Region 1
APD Long APD Short APD Long

APD restitution slope < 1

APD restitution slope > 1

Progress in Cardiovascular Diseases, Vol. 51, No. 2, 2008: pp 118-127
Discordant Alternans Leading to VF

Verrier RL. et al. JACC 2011
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
Spectral TWA Method

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

ECG

128 Beats

TIME SERIES

SPECTRUM

FFT

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
Provocative Testing/Screening for Nonsustained arrhythmias

- Electrophysiology study

- Ventricular ectopy and nonsustained VT on ambulatory ECG monitoring
Severe LV Dysfunction and No Inducible VT After MI
Delayed QRS Transition in the Precordial Leads of an ECG as a Predictor of SCD
Early Repolarization Increases VT/VF and SCD in an AMI
Early Repolarization Increases VT/VF and SCD in an AMI

![Graph showing the proportion of event-free patients over days of follow-up for Early repolarization (+) and Early repolarization (-) groups. The p-value is 0.001 (Log-rank test).]

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>ER (+)</th>
<th>ER (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>99 88 76 64 48 32 21 11 5 1 0</td>
<td>1032 928 725 526 415 281 151 66 19 0 0</td>
</tr>
</tbody>
</table>
Wide QRS-T Angle on the 12-lead ECG as a Predictor of Sudden Death Beyond the LV Ejection Fraction

- A wide QRS-T angle greater than $90^\circ$ is associated with an increased risk of SCA independent of the left ventricular ejection fraction.
### Adjusted Hazard Ratios for the Capacity of the Individual Parameters to Predict SCD in the Acute and Early Post-MI Periods

<table>
<thead>
<tr>
<th>Impairment</th>
<th>Hazard Ratio* (95% Confidence Interval)</th>
<th>p Value</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 to 4 Weeks After Index MI</td>
<td>10 to 14 Weeks After Index MI</td>
<td></td>
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<tr>
<td>Autonomic tone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate variability (SDNN &lt;105 vs. ≥105 ms)</td>
<td>1.24 (0.50–3.27)</td>
<td>2.15 (0.95–4.87)</td>
<td>0.65</td>
</tr>
<tr>
<td>Baroreflex sensitivity (&lt;6.1 vs. ≥6.1 ms/mm Hg)</td>
<td>2.01 (0.76–5.27)</td>
<td>2.71 (1.10–6.67)</td>
<td>0.16</td>
</tr>
<tr>
<td>Heart rate turbulence (abnormal onset or slope vs. both normal)</td>
<td>1.42 (0.54–3.75)</td>
<td>2.91 (1.13–7.48)</td>
<td>0.47</td>
</tr>
<tr>
<td>Electrical substrate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise repolarization alternans (non-negative vs. negative)</td>
<td>2.42 (0.96–7.71)</td>
<td>2.75 (1.08–7.02)</td>
<td>0.060</td>
</tr>
<tr>
<td>Holter repolarization alternans (≥5 vs. &lt;5 μV)</td>
<td>2.09 (0.95–4.60)</td>
<td>2.94 (1.10–7.87)</td>
<td>0.067</td>
</tr>
<tr>
<td>QRS width (≥114 vs. &lt;114 ms)</td>
<td>1.35 (0.54–3.36)</td>
<td>1.75 (0.76–3.99)</td>
<td>0.53</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>2.68 (1.21–5.92)</td>
<td>2.72 (1.23–5.99)</td>
<td>0.014</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (≤0.30 vs. &gt;0.30)</td>
<td>3.06 (1.39–6.74)</td>
<td>3.30 (1.43–7.63)</td>
<td>0.005</td>
</tr>
</tbody>
</table>
Rate of SCD With Resuscitation According to Time After MI

- LVEF ≤30% (n=3852)
- LVEF, 31–40% (n=4998)
- LVEF >40% (n=2406)

Major Primary Prevention Studies Using Early (≤40 Days After MI) ICD Implantation

<table>
<thead>
<tr>
<th>Study</th>
<th>Timing After MI</th>
<th>Inclusion Criteria</th>
<th>Outcome</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUSTT (1999),(^{15})\textsuperscript{,} randomized</td>
<td>≤1 mo in 16% of cohort</td>
<td>LVEF ≤40% and positive EPS</td>
<td>Overall survival benefit with EPS-guided ICDs</td>
<td>Small number in early post-MI period (n=56); only 29% on β-blockers</td>
</tr>
<tr>
<td>DINAMIT (2004),(^{12}) randomized</td>
<td>6–40 d</td>
<td>LVEF ≤35% and autonomic dysfunction</td>
<td>No survival benefit</td>
<td>Reduction in arrhythmic death offset by increase in nonarrhythmic cardiac deaths</td>
</tr>
<tr>
<td>BEST+ICD (2005),(^{27}) randomized</td>
<td>&lt;1 mo</td>
<td>LVEF ≤35% and positive EPS</td>
<td>No survival benefit</td>
<td>Only 12% of sample size; EPS protocol inclusive of nonprognostic VF or polymorphic VT</td>
</tr>
<tr>
<td>IRIS (2009),(^{17}) randomized</td>
<td>5–31 d</td>
<td>LVEF ≤40% and autonomic dysfunction or NSVT</td>
<td>No survival benefit</td>
<td>Reduction in arrhythmic death offset by increase in nonarrhythmic cardiac deaths</td>
</tr>
<tr>
<td>Westmead EPS/ICD studies (2009, 2010),(^{28,29}) observational</td>
<td>3–40 d</td>
<td>LVEF ≤40% and positive EPS</td>
<td>Observational benefit</td>
<td>ICDs implanted only if EPS positive; nonrandomized; single center</td>
</tr>
</tbody>
</table>

Circulation. 2014;129:2426-2435
한국인 심근경색 환자 및 심부전환자에서 비침습적 방법을 이용한 급성심장사 발생의 위험도 평가 연구

Korean noninvasive Risk Evaluation study for sudden cardiac DEath From INfarction or heart failurE. (K-REDEFINE study)

d기관, 전향적 관찰연구
Multicenter, prospective observational study

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Core Lab
삼성서울병원
Conclusions

• It is unlikely that any single measure will have sufficient discrimination to be used in isolation SCD in patients with MI

• The impact of contemporary revascularization may decrease the proportion of patients with ischemic heart disease, therefore validation of risk stratification tools in the nonischemic population or the development of a separate risk stratification scheme may be required

• Further evaluations of multivariate parallel or serial risk stratification are needed in the future