SUDDEN CARDIAC DEATH
Electrophysiological Substrates
An update

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Depressed LVEF as the Primary Indication for AICD "What is wrong?"

- **Depressed LVEF as a marker of SCD is neither sensitive nor specific (In MADIT-II and SCD-HfT only a minority of patients had appropriate ICD.**
- **Combining low LVEF with other current SCD risk stratifiers has not helped to decrease the "redundancy" in the use of primary ICD prophylaxis.**
- **It ignores Patient with better LVEF who may be SCD candidates**

Electrophysiological Substrates for SCD in Patients with Organic HD (Post-MI Remodeled heart, Ischemic and nonischemic CMP)

- **Abnormal conduction due to altered connexin, extracellular matrix, and scar tissue.**
- **AP prolongation and Dispersion of Repolarization.**
- **Altered neurohumoral signaling.**
- **Alterations in intracellular calcium kinetics.**

- ***The above mechanisms interact with a distinct genetic background***

Current Risk Stratifiers of SCD

Electrophysiologic Surrogates

- **Measures of conduction disorder: SAECG, % of scar tissue in CMR**
- **Measures of Dispersion of Repolarization:**
  QT dispersion, TWA
- **Measures of Autonomic System:**
  a) Direct: sympathetic nerve activity, 1231-MIBG scan
  b) ECG-based: HRV, Baroreceptor Sensitivity, HR Turbulence, QT dynamicity
- **Measures of altered calcium kinetics?**

Functional Contractile Surrogates

- **LVEF****
- **LV mass**
- **NYH class**

Biochemical Markers

- **C-reactive protein**
- **Homocysteine level**
- **Serum matrix metalloproteinase**
- **BNP, serum proteome analysis (Hpα1), Micro RNAs (*mi*R1), etc**

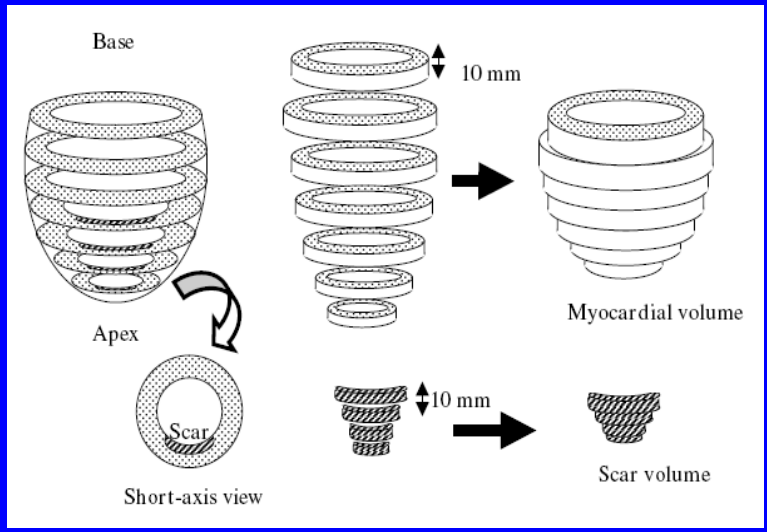
***Genetic Markers ???**

SCD and Conduction Disorders

* Experimental and Clinical Data on scar tissue and Extracellular matrix including Connexin 43, MMP and TIMP.

*Clinical surrogate Markers:
-SAECG
-Quantification of Scar Tissue by CMR

Quatitative Characterization of Myocardial Infarction by Cardiovascular Magnetic Resonance Predicts Future CV Events in Patients with Ischemic Cardiomyopathy. ***Yokota et al, J Cardiovas Magnetic Resonance2008;10:17-24***



Calculation of Scar Volume and Scar% of the Myocardium

Quatitative Characterization of Myocardial Infarction by Cardiovascular Magnetic Resonance Predicts Future CV Events in Patients with Ischemic Cardiomyopathy. ***Yokota et al, J Cardiovas Magnetic Resonance2008;10:17-24***

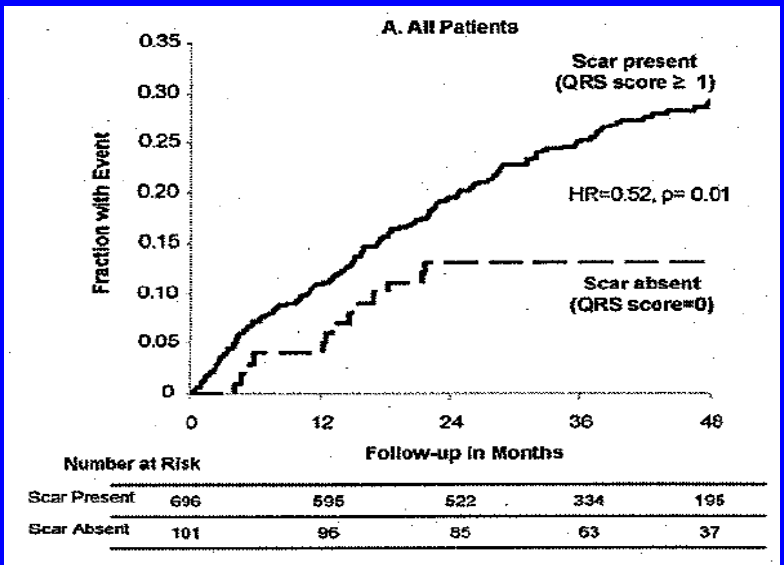
Table 2: Predictors of cardiovascular events

	Cardiovascular events (+)	Cardiovascular events (-)	*p* – value
Scar volume (cm^3)	16.8 ± 12.4	11.7 ± 12.6	0.023
Scar % of the myocardium (%)	10.2 ± 6.9	7.2 ± 6.7	0.037
LVEF (%)	25 ± 10	27 ± 13	0.26
LVEDV (ml)	234 ± 76	230 ± 88	0.41
LVESV (ml)	180 ± 73	175 ± 90	0.40
LVED mass/volume (g/ml)	0.73 ± 0.25	0.84 ± 0.32	0.06

Values are expressed as a mean ± SD. LVEF = left ventricular ejection fraction; LVEDV = left ventricular end diastolic volume; LVESV = left ventricular end systolic volume.

ECG Index of Myocardial Scar enhances Prediction of Defibrillator Shocks: An analysis of the SCD in Heart Failure Trial

Strauss et al, Heart Rhythm 2011;8:38-45



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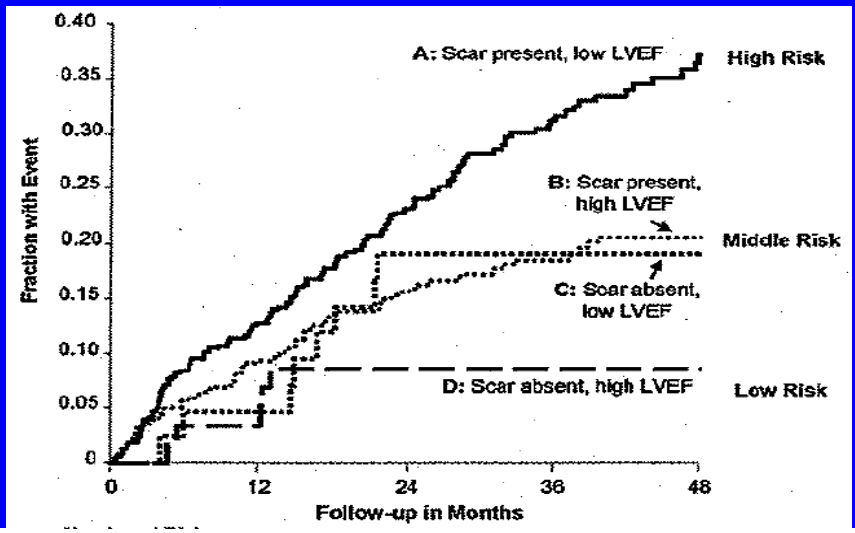

SCD and Dispersion of Repolarization
Clinical Surrogate Markers:
***QT Dispersion**
*** T-wave Alernans**

Microvolt T-Wave Alternans
Physiological Basis, Methods of Measurement, and Clinical Utility—Consensus Guideline

by International Society for Holter and Noninvasive Electrocardiology
Richard L. Verrier, PHD,* Thomas Klingenheben, MD,†‡ Marek Malik, PHD, MD,§ Nabil El-Sherif, MD,_ Derek V. Exner, MD, MPH,¶ Stefan H. Hohnloser, MD,‡ Takanori Ikeda, MD,# Juan Pablo Martı´nez, PHD,** Sanjiv M. Narayan, MD, PHD,†† Tuomo Nieminen, MD, PHD,*‡‡ David S. Rosenbaum, MD§§
Boston, Massachusetts; Bonn and Frankfurt, Germany; London, England; Brooklyn, New York;
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J Am coll cardiol 2012;58:1309

Microvolt T-Wave Alternans
Physiological Basis, Methods of Measurement, and Clinical Utility—Consensus Guideline

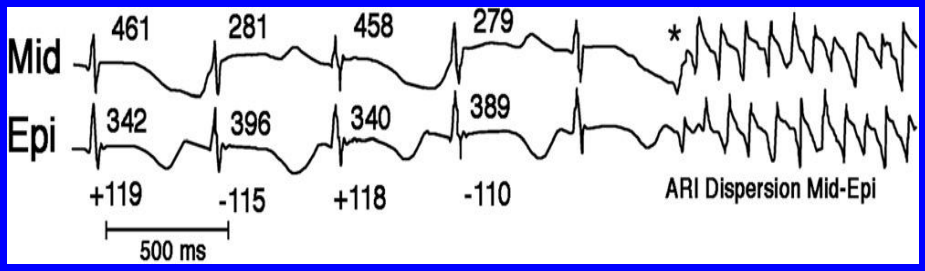


Figure 3

SCD and alterations in neuroendocrine signaling:

- **↑adrenergic and ↓ cholinergic activity can modulate susceptibility to SCD.**
- **Resting HR is an independent risk for SCD in middle aged men.**
- **There is data showing heritability of HRV**
- **Polymorphic variations in β-1 and β-2 adrenergic receptors can influence mortality in patients with dilated CMP**

***. Regional cardiac hyperinnervation (nerve sprouting) and ventricular tachyarrhythmis**

Clinical Surrogate Measures of Autonomic System

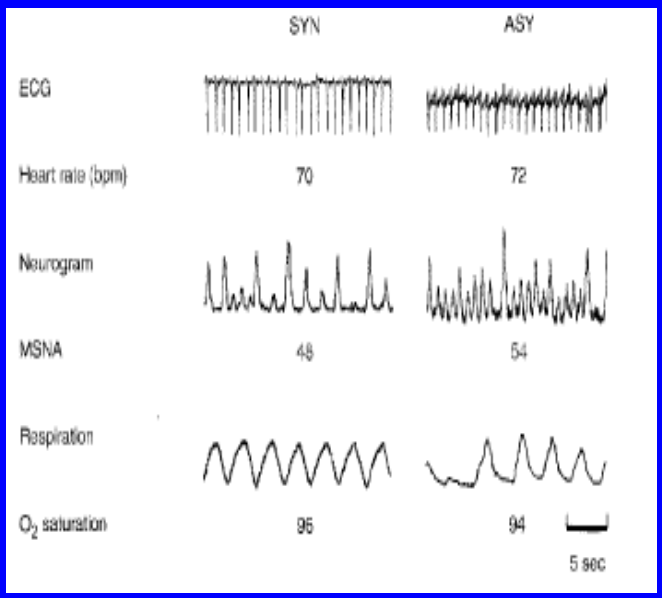
a) Direct: sympathetic nerve activity, 1231-MIBG scan

b) ECG-based: HRV, Baroreceptor Sensitivity, HR Turbulence, QT Dynamicity

CRT improves the Autonomic Nervous System

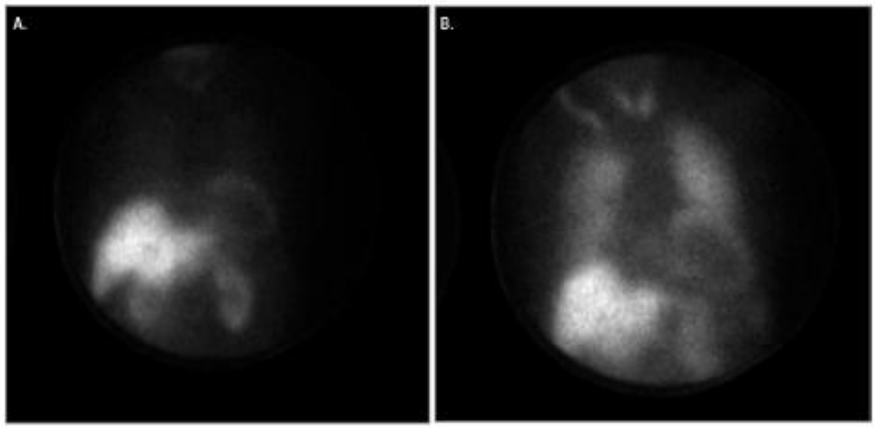
Sympathetic Nerve Activity After Thoracoscopic CRT In CHF

Najem et al, J Cardiac Failure



Cardiac Sympathetic Activity Pre and Post Resynchronization Therapy evaluated by 1231-MIBG Myocardial Scintigraphy

Nishioka et al, J Nucl Cardiol 2007;14:852-9



Heart/mediastinum count before (A=1.66) and after CRT (B=2.01)

Myocardial Iodine-123 *Meta*-Iodobenzylguanidine Imaging and Cardiac Events in Heart Failure

Results of the Prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) Study

Jackson et al, L Am Coll cardiol 2010;55:2212

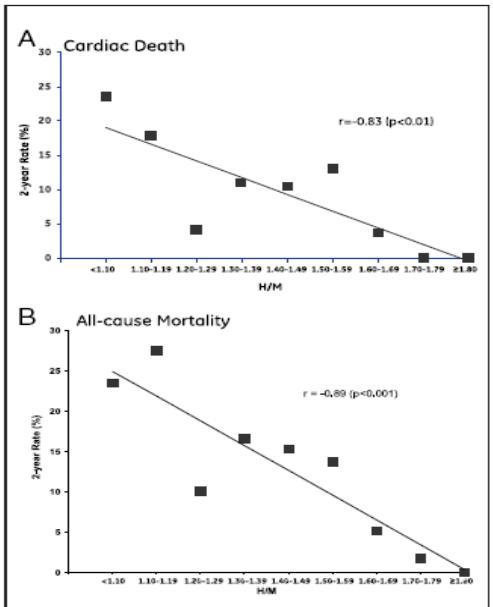


Figure 3 2-Year Cardiac Death and All-Cause Mortality Rates Versus H/M

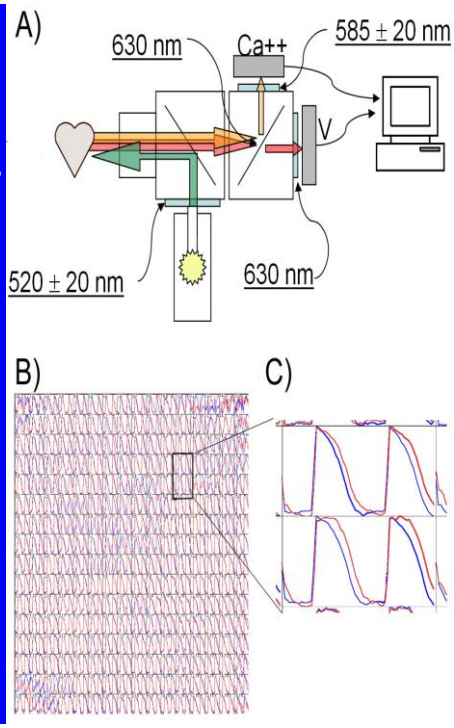
Two-year cardiac death (A) and all-cause mortality (B) rates show progressive decline from >20% for heart/mediastinum ratio (H/M) <1.10 to 0% for H/M ≥1.80.

SCD and altered Calcium Kinetics

- **Calcium/Voltage Alternans**
- **Calcium Oscillatory Responses**
- **Calcium/Voltage Uncoupling**

Optical mapping Of Voltage and intracellular Ca signals

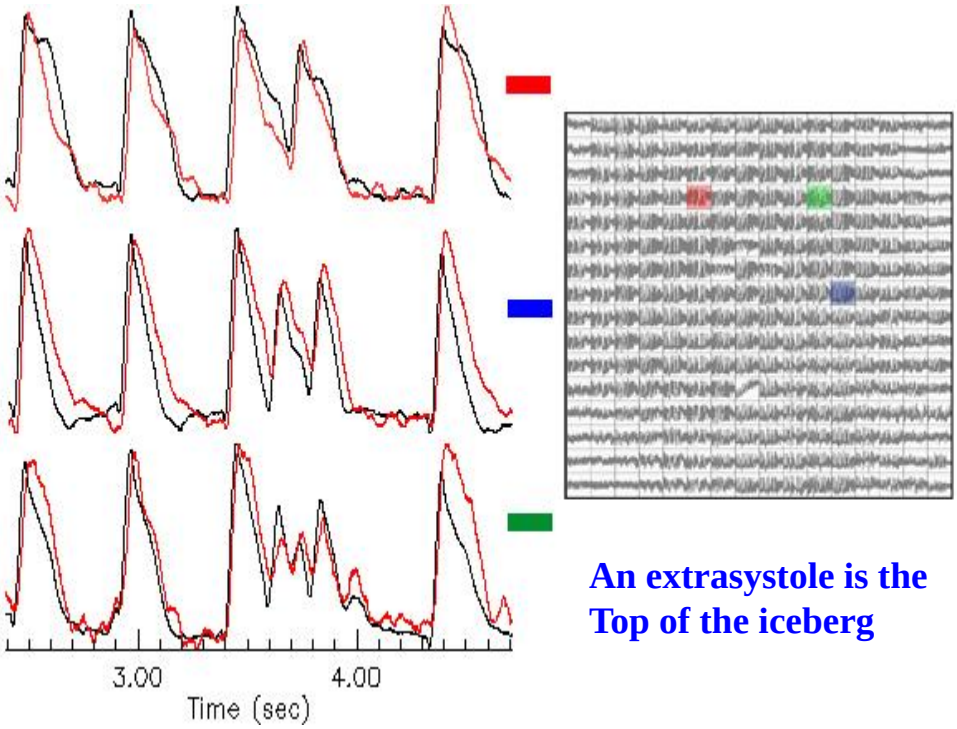
The Model: Guinea pig perfused heart subjected to ischemia/re-perfusion



The kinetics of spontaneous calcium oscillations and arrhythmogenesis in the in vivo heart during ischemia/reperfusion

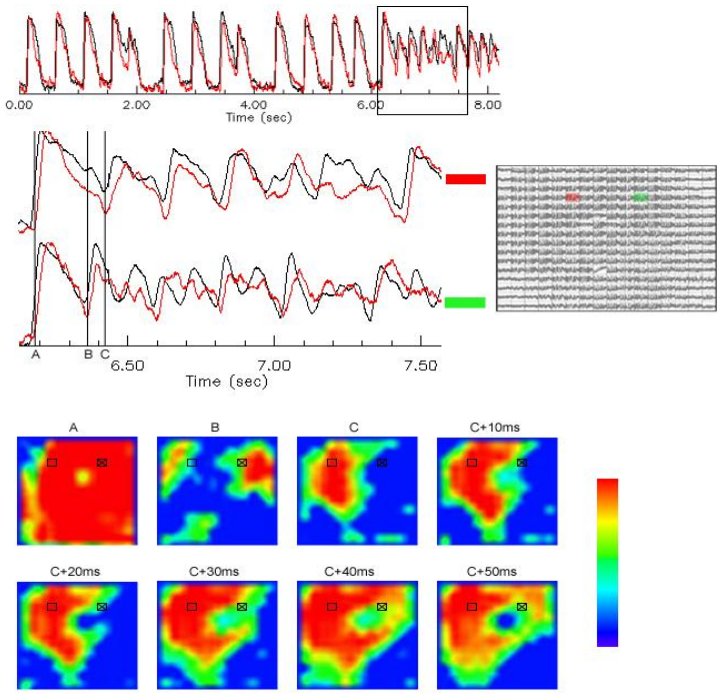
Lakireddy et al, Heart rhythm2006;3:58-66

- **Alterations of the kinetics of Ca cycling, e.g., during ischemia/reperfusion, can result in spontaneous release of calcium from the SR during diastole. The spontaneous calcium release can result in after-potentials that can reach threshold and generate one or more full action potentials, resulting in arrhythmias.**

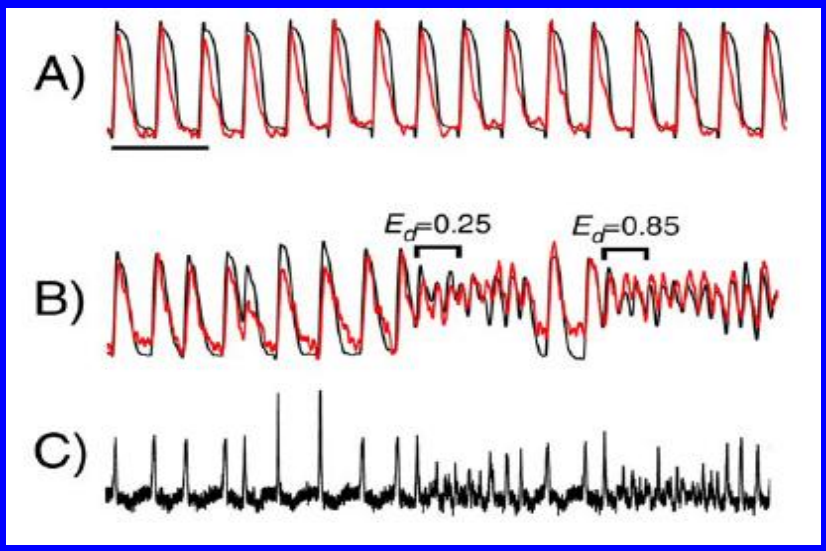


An extrasystole is the Top of the iceberg

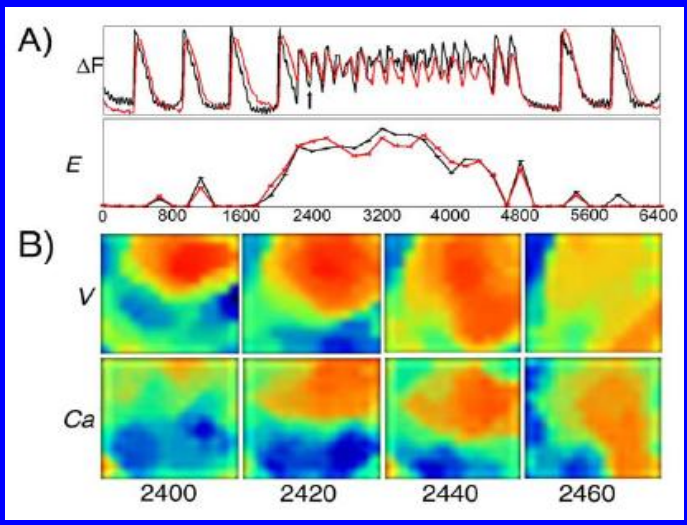
An extra-systole Results in wave Break and onset Of VF



Early voltage/calcium uncoupling predestinates the duration Of ventricular tachyarrhythmias during ischemia/reperfusion Himel, et al. Heart Rhythm 2009;6:1395-65

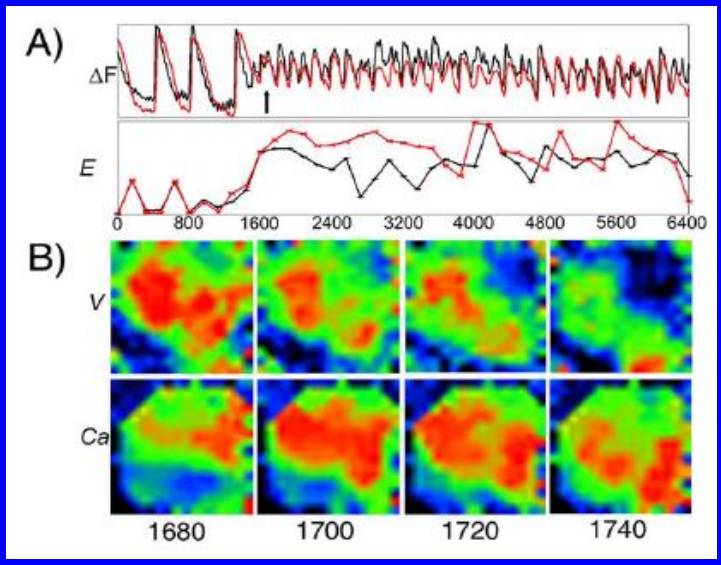


Self-terminating VT



Early voltage/calcium uncoupling predestinates the duration of ventricular tachyarrhythmias during ischemia/reperfusion
Himel, et al. Heart Rhythm 2009;6:1395-65

Non self-terminating VT



Early voltage/calcium uncoupling predestinates the duration of ventricular tachyarrhythmias during ischemia/reperfusion
Himel, et al. Heart Rhythm 2009;6:1395-65

SCD and altered Calcium Kinetics

- Calcium/Voltage Alternans
- Calcium Oscillatory Responses
- Calcium/Voltage Uncoupling

- With the exception of TWA there is no surrogate clinical markers of calcium oscillations and Cai/Vm uncoupling

Sudden Cardiac Death and Genetic Factors

*Family clustering of SCD victims

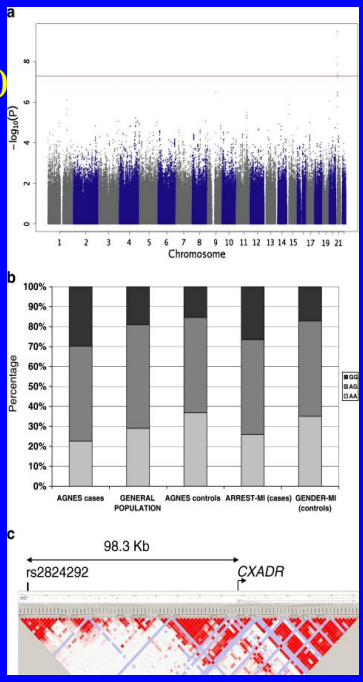
* **Genetic Polymorphism:**
Silent polymorphism or mutations of genes are prevalent in the general public and may contribute to enhanced susceptibility to SCD under specific circumstances such as acute ischemia, hypokalemia, pro-arrhythmic response to drugs, etc.

* **Modifier Genes:** genes that are not involved in the genesis of the disease but modify the severity of the phenotype.

Genome-wide association study (GWAS) identifies a susceptibility locus at 21q21 for VF in acute myocardial infarction

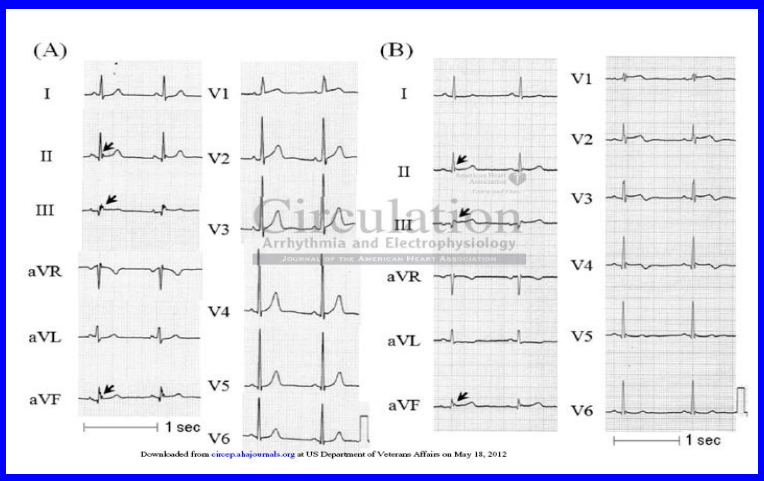
Bezzina et al, Nat Genet v2010;42:688

The closest gene to this SNP is CXADR, which encodes a viral receptor previously implicated in myocarditis, dilated CMP, and cardiac conduction disorder, but never implicated in Arrhythmia susceptibility.



EarlyRepolarization is an independent predictor of occurrence Of VF in the very early phase of acute myocardial infarction

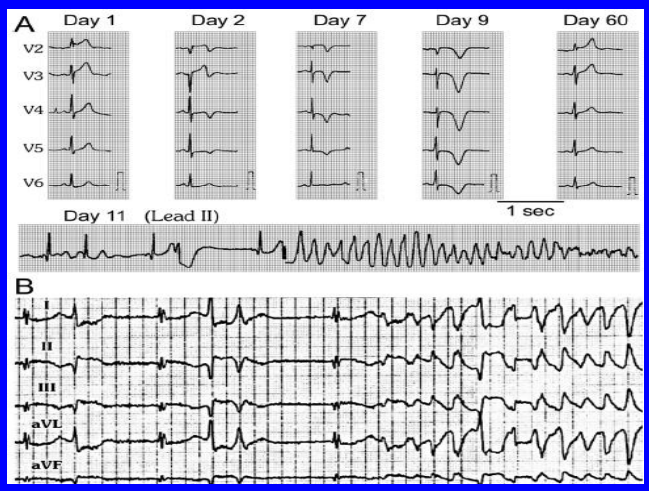
Naruse et al, Circulation, April 24, 2012



Summary: 10% of 220 consecutive patients with AMI developed VF within 48 hours. ER, time from onset to admission<180 min, and Killip class>1 were independent predictors of VF

Torsade de Pointes following acute myocardial infarction: Evidence of a deadly link with a common genetic variant

Crotti et al, Heart Rhythm 2012;9:1104-12



A common KCNH2-K897T polymorphism is associated with increased risk of TdP in the subacute phase of myocardial infarction

A common missense variant in the neuregulin 1 gene is associated with both schizophrenia and sudden cardiac death

Adriana Huertas-Vazquez, PhD,[*] Carmen Teodorescu, MD, PhD,[*] Kyndaron Reinier, PhD,[*] Audrey Uy-Evanado, MD,[*] Harpriya Chugh, BS,[*] Katherine Jerger, BS,[*] Jo Ayala, BS,[*] Karen Gunson, MD,[†] Jonathan Jui, MD,[‡] Christopher Newton-Cheh, MD, MPH,[§] Christine M. Albert, MD, MPH,[‖] Sumeet S. Chugh, MD, FHRS[*]

From the [*]The Heart Institute, Cedars-Sinai Medical Center, Los Angeles, California, [†]Pathology and [‡]Emergency Medicine, Oregon Health & Science University, Portland, Oregon, [§]Cardiovascular Research Center & Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts, and [‖]Center for Arrhythmia Prevention, Division of Preventive Medicine, Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.

Huertas-Vasquez et al, Heart Rhythm, 2013; 10:994-8

FUTURE MANAGEMENT OF SCD

* Modification of risk factors in the general public.
* Prophylactic ICD in moderate vs high risk groups
* Develop algorithm(s) for risk stratification of SCD of a "relatively small" number of EP/contractile/metabolic/genetic markers each with "low-to-moderate" positive predictive value.
* Improvement of contractile function decreases both sudden and non-sudden cardiac death (New drugs-Devices "CRT/LVAD").
* New agents that reverse remodeling signaling pathways (calcineurin, JACK-STAT, ras?)
* Gene Therapy?

There is a race among basic and clinical scientists to find the holy grail "an algorithm with 100% positive predictive accuracy for SCD


THANK YOU
NABIL EL-SHERIF