SUDDEN CARDIAC DEATH

EPIDEMIOLOGY, PATHOPHYSIOLOGY, PREVENTION & THERAPY

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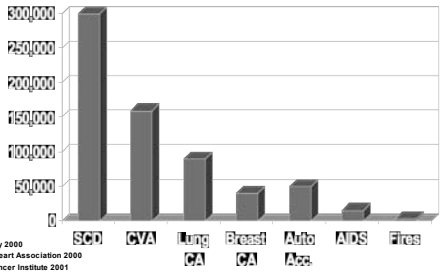
SUDDEN CARDIAC DEATH(SCD): Definition

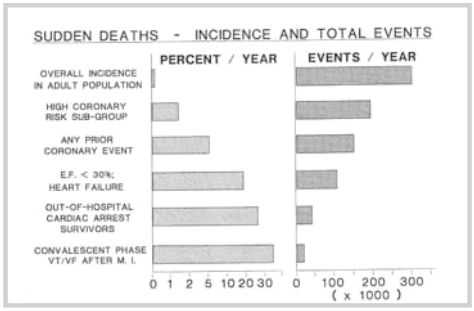
DEATH DUE TO A CARDIAC CAUSE IN A CLINICALLY STABLE PATIENT, WITH OR WITHOUT PRE-EXISTING HEART DISEASE, WITHIN A PERIOD OF UP TO ONE HOUR AFTER AN ABRUPT AND DRASTIC CHANGE IN CLINICAL STATUS

EPIDEMIOLOGIST'S VIEW
ANNUAL DEATHS IN U.S.A

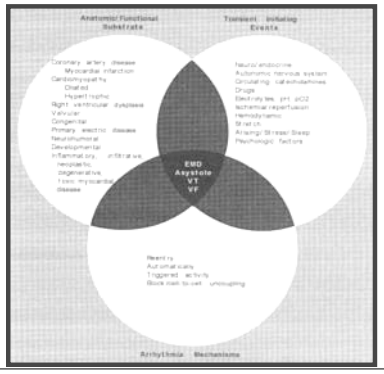


[1]NASPE, May 2000
[2]American Heart Association 2000
[3]National Cancer Institute 2001
[4]National Transportation Safety Board, 2000
[5]Center for Disease Control 2001
[6]NFPA, US Facts & Figures, 2000

EPIDEMIOLOGIST'S VIEW

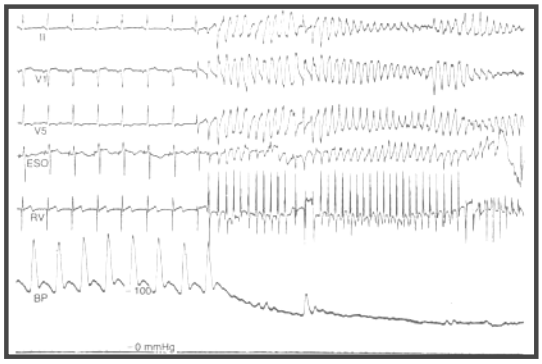


Mechanisms of SCD



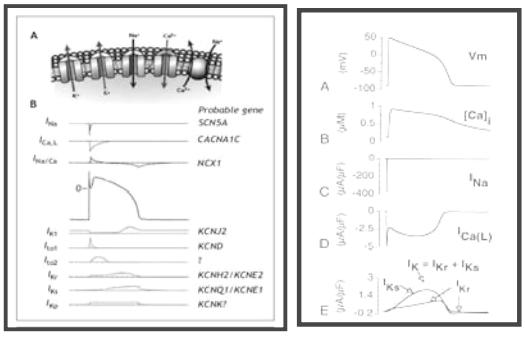
CAUSES OF SCD

- CARDIAC ARRHYTHMIA
  - Ventricular tachycardia/fibrillation
  - Asystole without an escape rhythm
- ELECTROMECHANICAL DISSOCIATION
  - Massive myocardial infarction
  - Pericardial tamponade

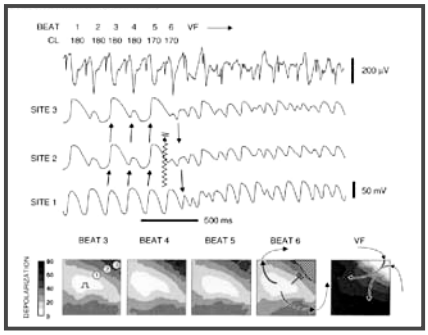


PATHOPHYSIOLOGY OF VT/VF

Ionic Currents during the Action Potential

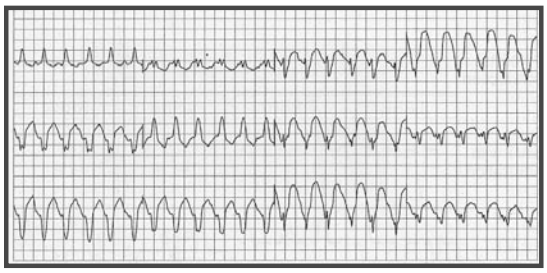


Reentrant Activation Initiating VT/VF

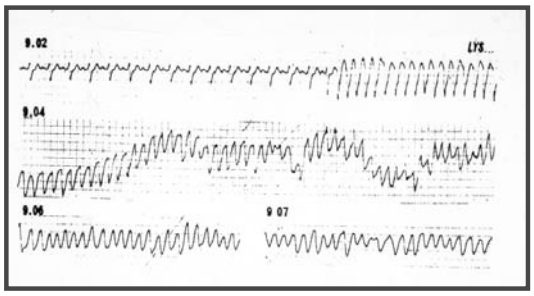


Pastore et al. Circulation. 1999;99:1385-1394.

REENTRY → VT



VT → VF IN A PATIENT WITH CHRONIC MI

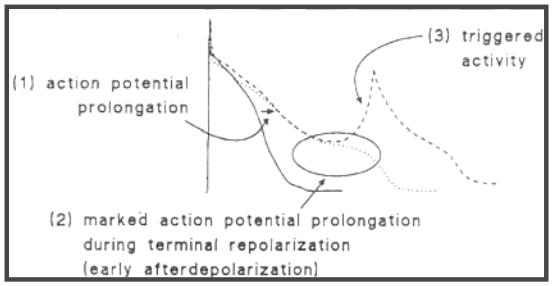


Factors Promoting Re-entrant Arrhythmias

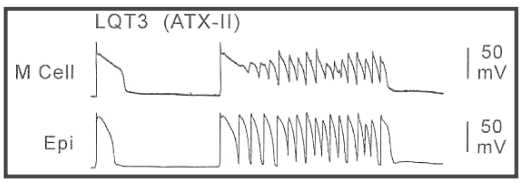
Decreased conduction velocity
- Partially depolarized tissue with inactivated sodium channels; myocardial ischemia
- Scarring, disruption of architecture; chronic MI, cardiomyopathies
- Remodeling/redistribution of connexins; ischemic heart disease, cardiomyopathies, CHF

Heterogenous refractoriness
- Myocardial ischemia/infarction
- Inflammation
- Electrolyte abnormalities/drugs

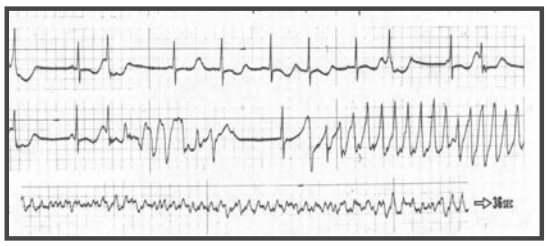
EARLY AFTERDEPOLARIZATIONS



Early Afterdepolarizations Initiating VT



Long QT → Torsades de Pointes → VF



SCD
CLINICIAN'S VIEW

DISEASES & CONDITIONS PREDISPOSING TO SCD

STRUCTURAL HEART DISEASE: ACQUIRED

A) Acute myocardial infarction
B) Chronic ischemic heart disease
C) Hypertensive heart disease
D) Dilated non-ischemic cardiomyopathy
   Alcoholic, post-inflammatory
E) Mixed dilated and hypertrophic: valve disease
F) Infiltrative cardiomyopathy
G) Cardiac sarcoidosis

DISEASES & CONDITIONS PREDISPOSING TO SCD

STRUCTURAL HEART DISEASE:

CONGENITAL

A) Hypertrophic cardiomyopathies
B) Congenital dilated cardiomyopathies
B) Arrhythmogenic right ventricular dysplasia/CMs
C) Anomalous coronary arteries
D) Adult congenital heart diseases
E) Mitral valve prolapse

DISEASES & CONDITIONS PREDISPOSING TO SCD

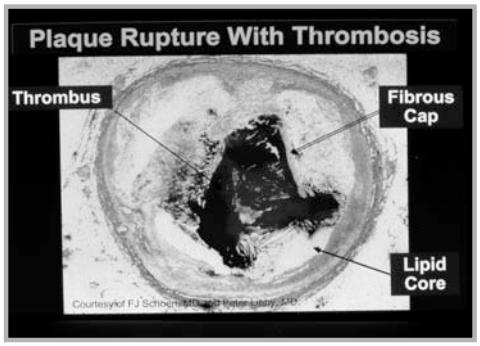
CHANNELOPATHIES/PRIMARY ELECTRICAL DISTURBANCES

A) Long QT syndromes
B) Brugada syndrome
C) Wolff-Parkinson-White syndrome
D) Familial catecholaminergic polymorphic VT
E) Short QT syndrome
F) Other repolarization abnormalities

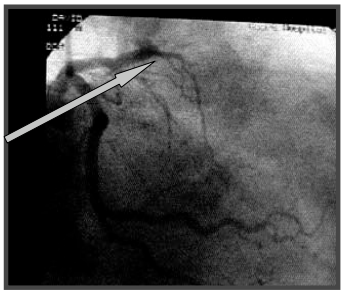
DISEASES & CONDITIONS PREDISPOSING TO SCD

REVERSIBLE CONDITIONS

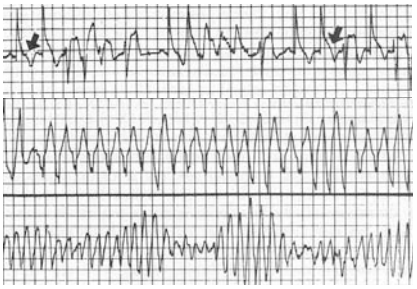
A) Myocardial ischemia
B) Severe electrolyte imbalance
C) Acquired long QT syndrome
D) Proarrhythmic effects of drugs
E) Interactions with genetic polymorphisms



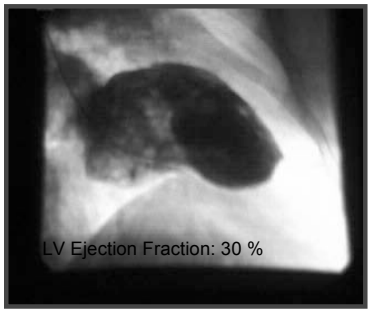
ACUTE CORONARY THROMBOSIS



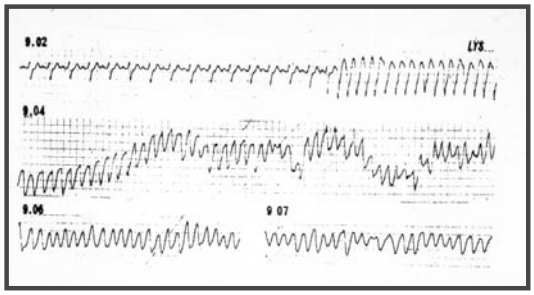
VT VF during acute myocardial necrosis (STEMI)



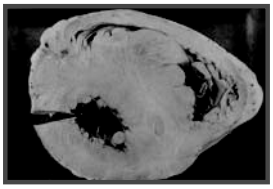
CHRONIC ISCHEMIC HEART DISEASE

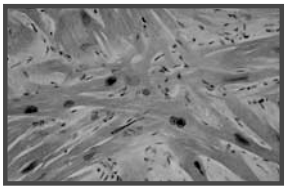


VENTRICULAR TACHYCARDIA IN A PATIENT WITH CHRONIC MI

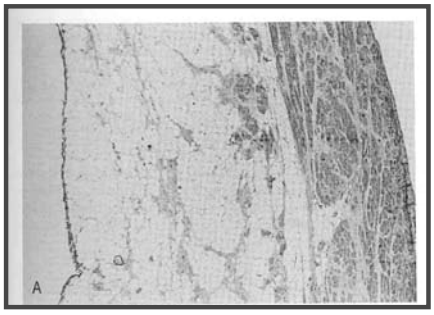


Hypertrophic Cardiomyopathy

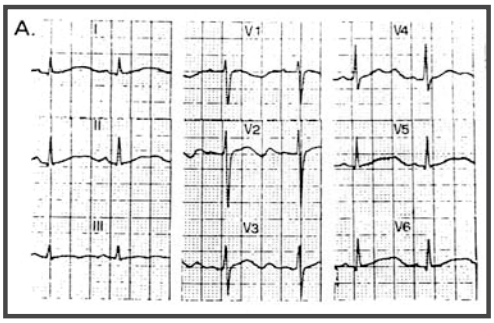




ARRHYTHMOGENIC RV DYSPLASIA



ECG in Long QT Syndrome

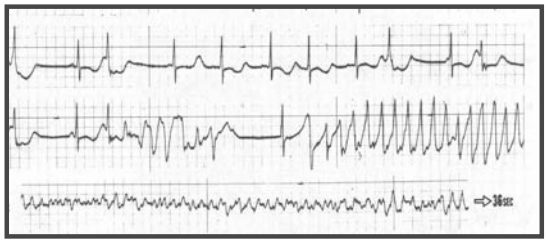


GENES IDENTIFIED TO DATE IN LQT SYNDROME

Nomenclature, gene names, and proteins associated with LQTS

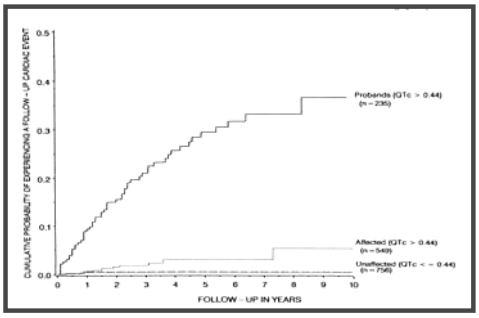
Disease	Gene (historical name)	Protein
LQT1	*KCNQ1* (KVLQT1)	$I_{Ks}K^+$ channel α subunit
LQT2	*KCNH2* (HERG)	I_KK^+ channel α subunit
LQT3	SCN5A	$I_{Na}Na^+$ channel α subunit
LQT4	ANKB	Ankyrin-B
LQT5	*KCNE1* (minK)	$I_{Ks}K^+$ channel β subunit
LQT6	*KCNE2* (MiRP1)	I_KK^+ channel β subunit
LQT7	KCNJ2	$I_{Kr2.1}K^+$ channel α subunit
LQT8	*CACNA1*	Cav1.2 Calcium channel α subunit

LQTS and Torsades de Pointes



PROSPECTIVE LONGITUDINAL F/U IN LQTS

Moss et al.Circulation1991;84:1136



LONG-TERM FOLLOW-UP IN LQTS

- 328 PROBANDS PRESENTING WITH SYNCOPE
- 1692 FAMILY MEMBERS

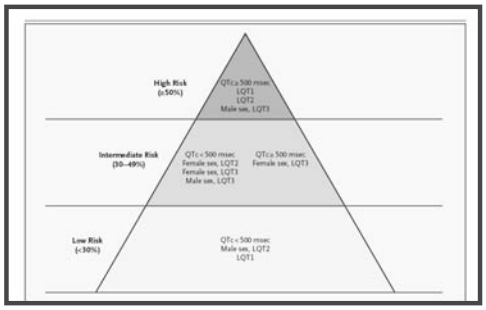
LQTS-RELATED DEATH 0.9% PER YEAR IN PROBANDS, HIGHER THAN BOTH AFFECTED AND UNAFFECTED FAMILY MEMBERS

3 RISK FACTORS IDENTIFIED FOR TOTAL GROUP WITH F/U (N=1496, 72 EVENTS)

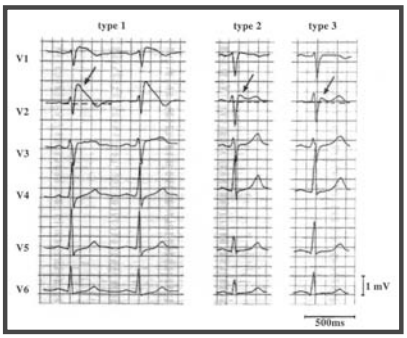
- QT_C DURATION
- CARDIAC EVENT AT PRESENTATION
- RESTING HEART RATE

Moss et al. Circulation 1991; 84: 1139-1144

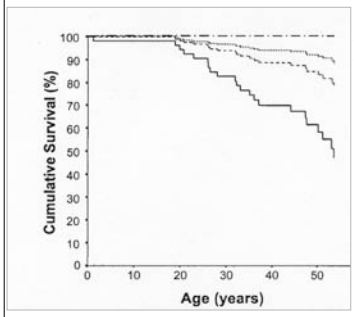
Risk Stratification in Long QT Syndrome: Genotype & Gender



BRUGADA SYNDROME



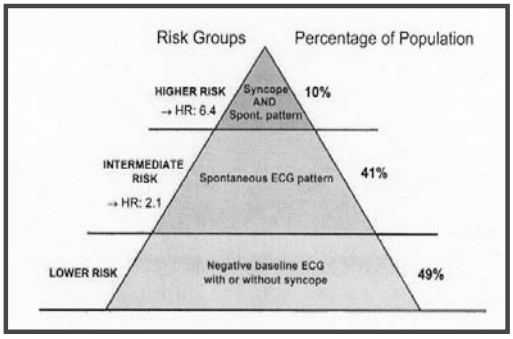
Natural History of Brugada Syndrome



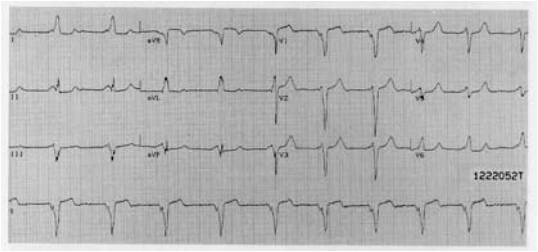
Syncope, - ECG baseline
Syncope, + ECG challenge
+ ECG baseline

Syncope, + ECG baseline

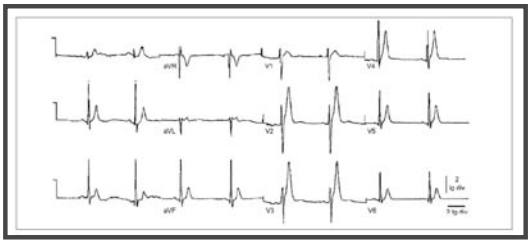
Risk Stratification in Brugada Syndrome



PRE-EXCITED QRS COMPLEXES IN A PATIENT WITH WPW SYNDROME



SHORT QT SYNDROME



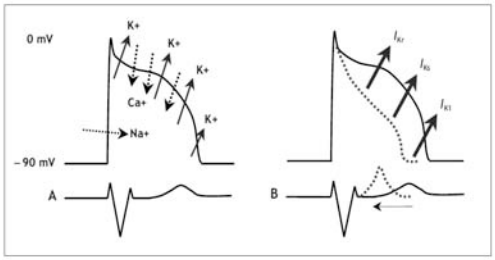


Fig. 2. A. Schematic representation of the normal action potential and the flux of ions. B. With gain-of-function mutations in any of 3 different potassium channels, the cardiac action potential shortens and the QT interval decreases.

Familial catecholaminergic polymorphic VT

Mutations in the Cardiac Ryanodine Receptor Gene (*hRyR2*) Underlie Catecholaminergic Polymorphic Ventricular Tachycardia

Silvia G. Priori, MD, PhD; Carlo Napolitano, MD, PhD; Natascia Tiso, PhD; Mirella Memmi, PhD; Gabriele Vignati, MD; Raffaella Bloise, MD; Vincenzo Sorrentino, MD; Gian Antonio Danieli, BSc

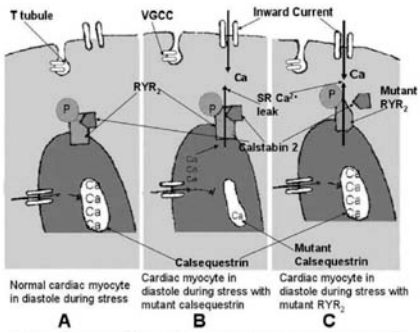
Background—Catecholaminergic polymorphic ventricular tachycardia is a genetic arrhythmogenic disorder characterized by stress-induced, bidirectional ventricular tachycardia that may degenerate into cardiac arrest and cause sudden death. The electrocardiographic pattern of this ventricular tachycardia closely resembles the arrhythmias associated with calcium overload and the delayed afterdepolarizations observed during digitalis toxicity. We speculated that a genetically determined abnormality of intracellular calcium handling might be the substrate of the disease; therefore, we considered the human cardiac ryanodine receptor gene (*hRyR2*) a likely candidate for this genetically transmitted arrhythmic disorder.

Methods and Results—Twelve patients presenting with typical catecholaminergic polymorphic ventricular tachycardia in the absence of structural heart abnormalities were identified. DNA was extracted from peripheral blood lymphocytes, and single-strand conformation polymorphism analysis was performed on polymerase chain reaction–amplified exons of the *hRyR2* gene. Four single nucleotide substitutions leading to missense mutations were identified in 4 probands affected by the disease. Genetic analysis of the asymptomatic parents revealed that 3 probands carried de novo mutations. In 1 case, the identical twin of the proband died suddenly after having suffered syncopal episodes. The fourth mutation was identified in the proband, in 4 clinically affected family members, and in none of 3 nonaffected family members in a kindred with 2 sudden deaths that occurred at 16 and 14 years, respectively, in the sisters of the proband.

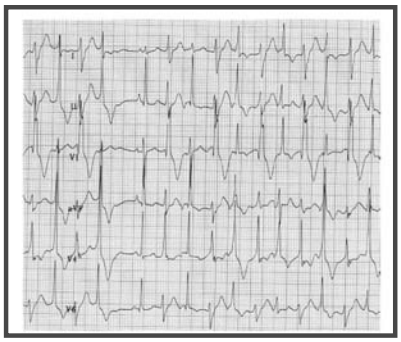
Conclusions—We demonstrated that, in agreement with our hypothesis, *hRyR2* is a gene responsible for catecholaminergic polymorphic ventricular tachycardia. (*Circulation*. 2001;103:196-200.)

Key Words: arrhythmia ■ genetics ■ tachycardia ■ ryanodine receptor calcium release channel

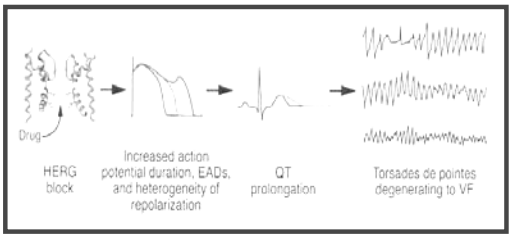
Familial catecholaminergic polymorphic VT

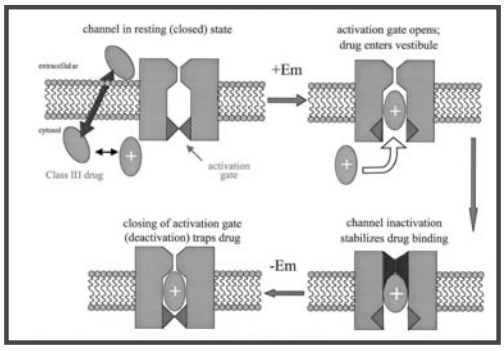


Familial catecholaminergic polymorphic VT:
Bidirectional VT in a Child

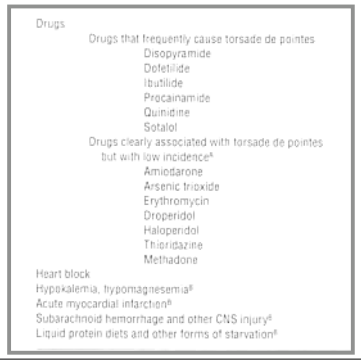


ACQUIRED LONG QT
Drug-related Repolarization Abnormality





CAUSES OF ACQUIRED LONG QT



- Drugs
  - Drugs that frequently cause torsade de pointes
    - Disopyramide
    - Dofetilide
    - Ibutilide
    - Procainamide
    - Quinidine
    - Sotalol
  - Drugs clearly associated with torsade de pointes but with low incidence[a]
    - Amiodarone
    - Arsenic trioxide
    - Erythromycin
    - Droperidol
    - Haloperidol
    - Thioridazine
    - Methadone
- Heart block
- Hypokalemia, hypomagnesemia[a]
- Acute myocardial infarction[a]
- Subarachnoid hemorrhage and other CNS injury[a]
- Liquid protein diets and other forms of starvation[a]

SCD
DETECTION OF RISK

RISK STRATIFICATION AND UNDERLYING HEART DISEASE

AVAILABLE TESTING METHODS/PREDICTIVE MARKERS

INVASIVE

- Programmed Cardiac Stimulation (PCS)

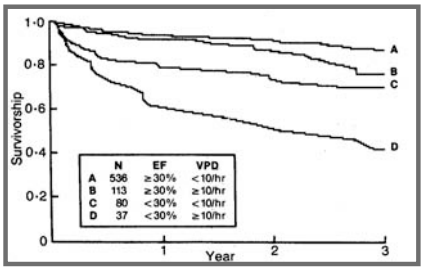
NON-INVASIVE

- Ventricular Systolic Function (Echocardiogram, MUGA Scan, MRI)
- Ambulatory Cardiac Rhythm Monitoring for VEA/NSVT
- T-Wave Alternans
- Exercise Testing
- HR Variability
- Baroreflex Sensitivity
- QT Dispersion
- SAECG
- Genetic Markers

LARGE NUMBERS OF PATIENTS AT RISK

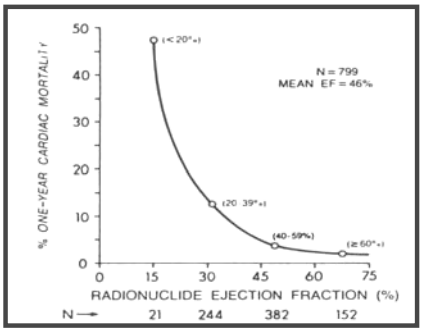
- Need simple, inexpensive, non-invasive diagnostic tests with high clinical accuracy
  - sensitivity: percentage of patients with the disease identified by the test. Need screening tests with high sensitivity not to miss any patients at high risk.
  - positive predictive accuracy (ppa): percentage of patients with a positive test that will go on to have an event. Need screening tests with high ppa to minimize unnecessary treatment with expensive therapies in patients not at high risk

LEFT VENTRICULAR DYSFUNCTION, VEA & SURVIVAL AFTER MI

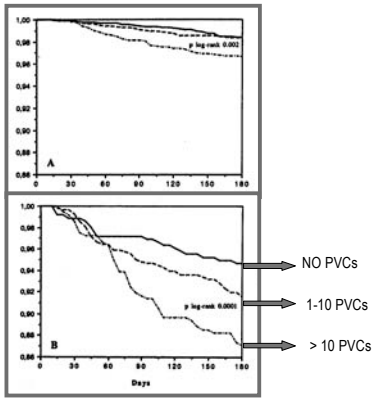


J. Thomas Bigger, Jr. Am J Cardiol 1986;57:8B

LV FUNCTION AS PREDICTOR OF SCD

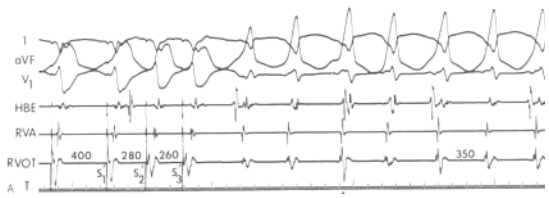


GISSI-2
SURVIVAL



PROGRAMMED CARDIAC STIMULATION (PCS):

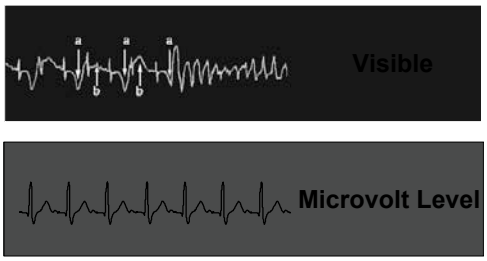
Introducing one or more timed, premature, paced ventricular beats, via electrode-catheters placed percutaneously inside the heart, in an effort to reproduce clinical VT in the Cardiac EP Laboratory



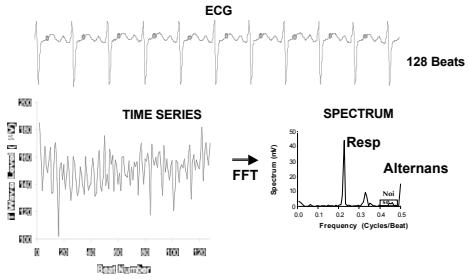
PCS: Limitations

- Sensitivity of PCS in ischaemic heart disease is acceptable, but its PPA is poor.
- In non-ischaemic CM, there is up to 40% incidence of clinical arrhythmic events in “non-inducible” group.
- There are no reproducible data to justify its clinical utility in HCM.
- Not even applicable in “channelopathies”.

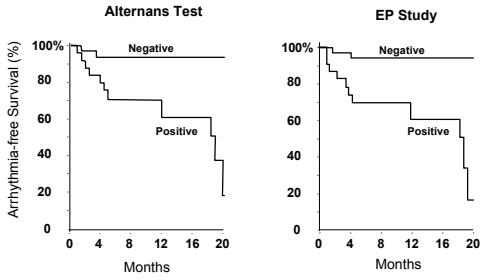
T-Wave Alternans



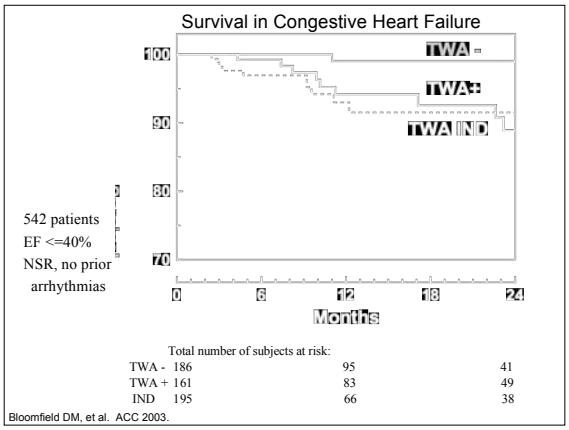
Spectral Method Detects Microvolt T Wave Alternans



MGH / MIT Results
Arrhythmia Free Survival



Rosenbaum, Jackson, Smith, Garan, Ruskin and Cohen N Engl J Med 1994;330:235-241



SCD
TREATMENT & PREVENTION

SCD
TREATMENT & PREVENTION

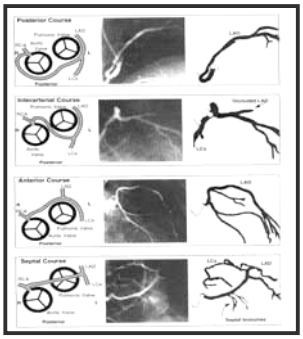
I) IMPLANTABLE CARDIOVERTER DEFIBRILLATOR (ICD) THERAPY

II) ANTIARRHYTHMIC DRUG THERAPY

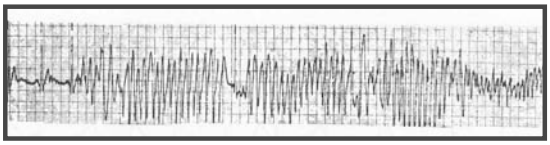
III) CATHETER ABLATION

IV) SURGERY

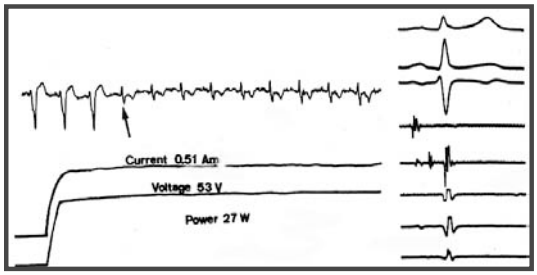
ANOMALOUS LEFT CORONARY ARTERY
Surgically treatable cause of SCD



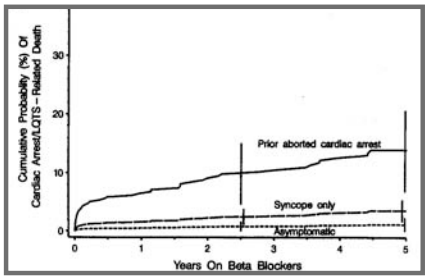
AF TRANSFORMING TO VF IN A PATIENT
WITH WPW SYNDROME
Rare form of SCD curable with catheter ablation



WPW Syndrome: Disappearance of Ventricular
Pre-excitation during RF Application

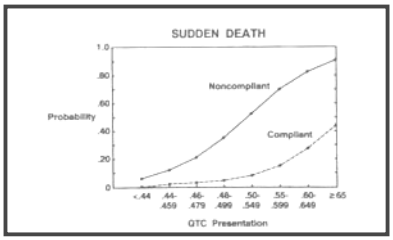


EFFECTIVENESS OF BETA BLOCKER THERAPY IN LQTS

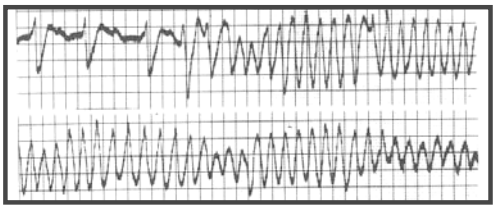


Arthur J. Moss et al. Circulation 2000;101:616

PROBABILITY OF SUDDEN DEATH IN CHILDREN WITH LQTS: RELATION TO QT_C



Garson et al. Circulation 1993;87:1866-1872

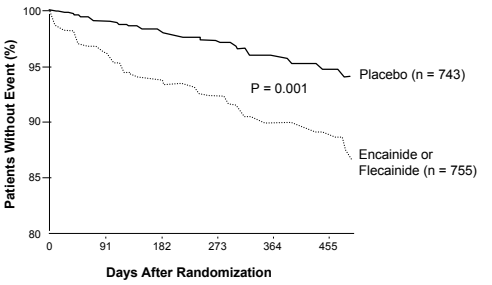


PVC Hypothesis:

PVC → VT → VF

CAST-I

Prognosis of Post-MI Patients Treated with Placebo vs. Encainide/Flecainide



Echt DS. N. Engl J Med. 1991;324:781-788.

SCD: SECONDARY PREVENTION

Treating survivors of out-of-hospital cardiac arrest with documented VT/VF

There are no controlled studies with placebo or no-treatment arm

Randomized trials: Implantable Cardioverter/Defibrillator (ICD) vs Antiarrhythmic Drugs (AADs)

- All randomized trials have shown that ICD therapy is superior to AAD (mostly amiodarone) therapy

AVID/CIDS/CASH Metanalysis

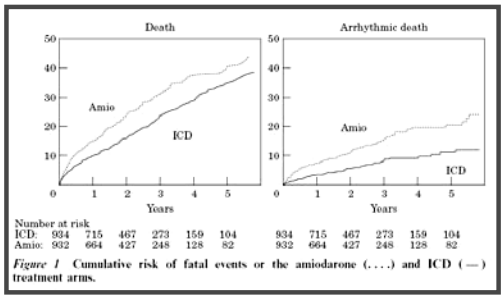


Figure 1 Cumulative risk of fatal events or the amiodarone (. . . .) and ICD (—) treatment arms.

Primary Prevention vs. Secondary Salvage

- Salvage rate for patients with sudden cardiac arrest is < 2%
- Therefore the major task is to identify patients at risk **prior to** the event
  - focus on primary prevention
  - identify and treat

SCD: Difficulties with Primary Prevention

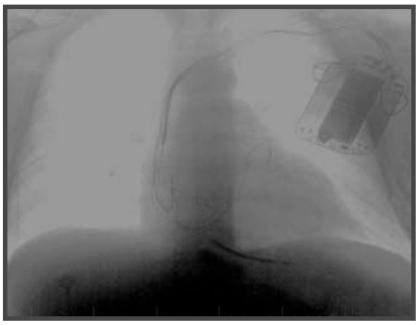
- Large numbers of patients at risk
  - Need for simple, inexpensive, non-invasive tests with high sensitivity
- Low incidence of sudden cardiac death among patients with known heart disease
  - Post myocardial infarction mortality rates ~5%
  - Low specificity of the tests for risk stratification

SCD: PRIMARY PREVENTION

ANTIARRHYTHMIC DRUG (AAD) TRIALS

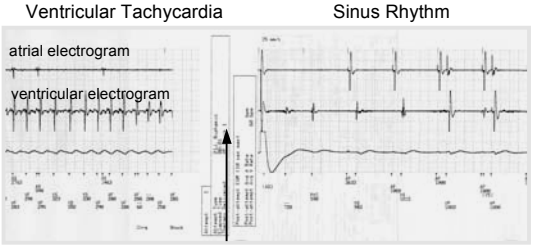
None of the several prospective, controlled, AAD trials, except for one, in high-risk patients (post-MI, CHF) showed any survival benefit with AAD

Implantable Cardioverter Defibrillator



DETECTION & TERMINATION OF VT BY ICD

Ventricular Tachycardia Sinus Rhythm



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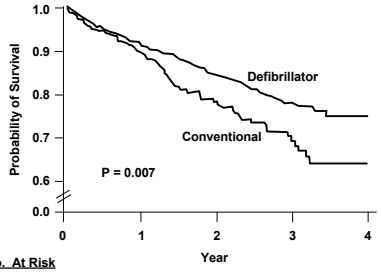
SCD: PRIMARY PREVENTION
ICD THERAPY

- 4 randomized, prospective trials showed survival benefit with ICD in:
  - Ischaemic heart disease and non-sustained VT (MUSTT)
  - Ischaemic heart disease and depressed LV function (MADIT I, MADIT II)
  - CHF and depressed LV function (ischaemic or non-ischaemic) (SCD-HeFT)
- ICD-related survival benefit not established in:
  - Patients undergoing surgical coronary revascularization
  - Implantation immediately after acute MI

PRIMARY PREVENTION OF SCD
MADIT-II SURVIVAL RESULTS



No. At Risk				
Defibrillator (0.78)	742	502 (0.91)	274 (0.94)	110
Conventional (0.69)	490	329 (0.90)	170 (0.78)	65

Moss AJ. *N Engl J Med.* 2002;346:877-883.

ICD THERAPY IN ISCHAEMIC AND NON-ISCHAEMIC CARDIOMYOPATHY: INDICATIONS

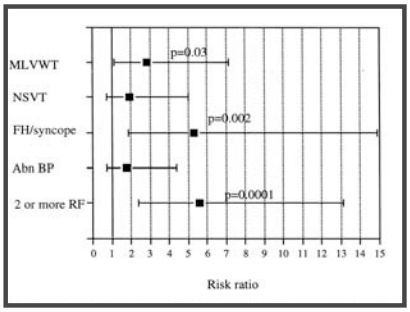
Chronic ischaemic heart disease with LVEF<40%, documented non-sustained VT, and electrically inducible VT/VF

Chronic/subacute ischaemic heart disease with LVEF<35%, and electrically inducible VT/VF

Chronic/subacute ischaemic heart disease with LVEF<30%

Ischaemic or non-ischaemic cardiomyopathy with LVEF<35%, and Class II or III congestive heart failure

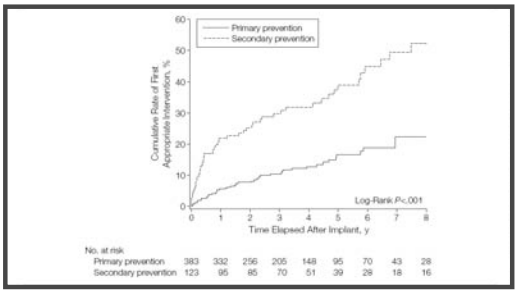
Multivariate Risk Ratios for 4 Risk Factors in HCM
The Bars Represent the Upper and Lower 95% Confidence Intervals
Elliott PM et al. J Am Coll Cardiol 2000; 36:2212



ICD THERAPY IN HCM: INDICATIONS

- Survivors of cardiac arrest (VT/VF)
- Spontaneous sustained VT
- Unexplained syncope
- Family history of premature SCD
- Maximum LV thickness $\geq$ 30 mm (controversial in absence of any other risk factor)
- Abnormal BP response to exercise
- Non-sustained VT
- Certain mutations in individuals (specific beta-myosin heavy chain and troponin T mutations)

Cumulative Rates for First Appropriate ICD Intervention in Patients Who Had Received Devices for Primary (n=383) and Secondary (n=123) Prevention
Maron BJ et al. JAMA 2007;298:405



ICD THERAPY IN "CHANNELOPATHIES": INDICATIONS

LQTS PRESENTING WITH CARDIAC ARREST

LQTS WITH

- RECURRENT SYNCOPE ON BETA BLOCKER Rx
- POSITIVE FAMILY Hx FOR SUDDEN DEATH
- CHILD WITH MARKEDLY PROLONGED QT AT BASELINE

IDIOPATHIC VF

- PATIENTS WITH BRUGADA SYNDROME, WHO ARE SYMPTOMATIC OR HAVE A POSITIVE FAMILY HISTORY AND A POSITIVE RESPONSE TO PCS

CONCLUSIONS

- Overall the vast majority of SCD results from VT/VF in patients with advanced organic heart disease with poor ventricular function
- The majority of SCD in young patients results from congenital cardiomyopathies or more rarely congenital electrical disturbances in the absence of structural heart disease
- There is no effectively preventive drug therapy for SCD
- ICD therapy remains the only known effective method for protection of patients at high risk