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

[Bar chart showing annual deaths in the U.S.A.]

NASPE, May 2000
American Heart Association 2000
National Cancer Institute 2001
National Transportation Safety Board, 2000
National Fire Protection Association, 2001
National Fire Protection Association, 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


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
**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
C) Arrhythmogenic right ventricular dysplasia/CMs
D) Anomalous coronary arteries
E) Adult congenital heart diseases
F) 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**

Plaque Rupture With Thrombosis

LAD: TOTAL OCCLUSION

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
LQTS and Torsades de Pointes

Prospective Longitudinal F/U in LQTS
Moss et al. Circulation 1991;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 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
Risk Stratification in Brugada Syndrome

PRE-EXCITED QRS COMPLEXES IN A PATIENT WITH WPW SYNDROME

SHORT QT SYNDROME
Familial catecholaminergic polymorphic VT

Mutations in the Cardiac RYR2 Receptor Gene Underlie Catecholaminergic Polymorphic Ventricular Tachycardia

Sylvia C. Patel, MD, PhD, Clyde Snowling, MD, PhD, Shellia M. Toy, PhD, Maria A. Vlahakes, MD, MSc, Stephen E. Shooter, MD, and Peter S. Schwartz, MD, PhD

Background—Catecholaminergic polymorphic ventricular tachycardia is a rare but fatal disease characterized by recurrent, often life-threatening episodes of polymorphic ventricular tachycardia. Mutations in the cardiac ryanodine receptor 2 (RYR2) gene are thought to cause familial catecholaminergic polymorphic ventricular tachycardia. RYR2 encodes a calcium-release channel (CCCH-Ca<sup>2+</sup>-release channel) and a major cardiac ion channel. The disease is characterized by a high risk of sudden cardiac death. Mutations in the cardiac ryanodine receptor 2 (RYR2) gene are thought to cause familial catecholaminergic polymorphic ventricular tachycardia. RYR2 encodes a calcium-release channel and a major cardiac ion channel. The disease is characterized by a high risk of sudden cardiac death.

Familial catecholaminergic polymorphic VT

Normal cardiac myocyte in diastole during stress

Cardiac myocyte in diastole during stress with mutant ryanodine receptor (RYR2)

Mutant ryanodine receptor (RYR2)
Familial catecholaminergic polymorphic VT: Bidirectional VT in a Child

ACQUIRED LONG QT
Drug-related Repolarization Abnormality
CAUSES OF ACQUIRED LONG QT

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 VIBANSVT
- 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

LV FUNCTION AS PREDICTOR OF SCD
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

Visible

Microvolt Level

Spectral Method Detects Microvolt T Wave Alternans

MGH / MIT Results

Arrhythmia Free Survival

### Survival in Congestive Heart Failure

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Total number of subjects at risk:

- TWA - 186
- TWA + 161
- IND 195


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### 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


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

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

PVC Hypothesis:

PVC ↔ VT ↔ VF
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

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

Patients Without Event (%)

Days After Randomization

Placebo (n = 743)
Encainide or Flecainide (n = 755)

P = 0.001

AVID/CIDS/CASH Metanalysis

Secondary prevention of post-MI patients treated with placebo vs. encainide/flecainide

Treat 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
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

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

Defibrillator

Conventional

No. At Risk
Defibrillator 742 592 (0.91) 274 (0.94) 110
Conventional 490 329 (0.90) 170 (0.78) 65

P = 0.007

Probability of Survival

0.0 0.4 0.6 1.0

Year

0 1 2 3 4

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 ≥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

LONG QT SYNDROME PRESENTING WITH CARDIAC ARREST
LONG QT SYNDROME 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