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
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

(1) action potential prolongation
(2) marked action potential prolongation during terminal repolarization (early afterdepolarization)
(3) triggered activity
Early Afterdepolarizations Initiating VT

Long QT $\rightarrow$ Torsades de Pointes $\rightarrow$ 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
   Alcoholics, 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

LAD: TOTAL OCCLUSION

VT → VF during acute myocardial necrosis (STEMI)
CHRONIC ISCHEMIC HEART DISEASE

LV Ejection Fraction: 30%

VENTRICULAR TACHYCARDIA IN A PATIENT WITH CHRONIC MI
ECG in Long QT Syndrome

GENES IDENTIFIED TO DATE IN LQT SYNDROME

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene (historical name)</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>KCNQ1 (KVLQT1)</td>
<td>(I_{K1})K⁺ channel (\alpha) subunit</td>
</tr>
<tr>
<td>LQT2</td>
<td>KCNH2 (HERG)</td>
<td>(I_{K1})K⁺ channel (\alpha) subunit</td>
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<tr>
<td>LQT3</td>
<td>SCN5A</td>
<td>(I_{Na})Na⁺ channel (\alpha) subunit</td>
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<tr>
<td>LQT4</td>
<td>ANK3</td>
<td>Ankyrin-B</td>
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<tr>
<td>LQT5</td>
<td>KCNE1 (minK)</td>
<td>(I_{K2})K⁺ channel (\beta) subunit</td>
</tr>
<tr>
<td>LQT6</td>
<td>KCNE2 (MIRP1)</td>
<td>(I_{K2})K⁺ channel (\beta) subunit</td>
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<td>LQT7</td>
<td>KCNJ2</td>
<td>(I_{K21})K⁺ channel (\alpha) subunit</td>
</tr>
<tr>
<td>LQT8</td>
<td>CACNA1</td>
<td>Cav1.2 Calcium channel (\alpha) subunit</td>
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LQTS and Torsades de Pointes

PROSPECTIVE LONGITUDINAL F/U IN LQTS
Moss et al. Circulation 1991; 84: 1136

Cumulative probability of experiencing a follow-up cardiac event.
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)
- QTc 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

- **Higher Risk**
  - Spontaneous ECG pattern
  - Syncope
  - HR: 6.4
  - 10% of the population

- **Intermediate Risk**
  - Spontaneous ECG pattern
  - HR: 2.1
  - 41% of the population

- **Lower Risk**
  - Negative baseline ECG with or without syncope
  - 49% of the population

PRE-EXCITED QRS COMPLEXES IN A PATIENT WITH WPW SYNDROME

[ECG Image]
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. Pinon, MD, PhD; Carlo Napolitano, MD, PhD; Natascia Toso, PhD; Mirella Menucci, PhD; Gabriele Vignati, MD; Raffaella Bito, 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 digoxin toxicity. We speculated that a genetically determined susceptibility to 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 determined 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 syncope episodes. The fourth mutation was identified in the proband, in 4 clinically affected family members, and in none of 3 unaffected family members in a kindred with 3 sudden deaths that occurred at 16 and 14 years, respectively, in the sisters of the proband.

Conclusions—We demonstrate that, in agreement with our hypothesis, hRyR2 is a gene responsible for catecholaminergic polymorphic ventricular tachycardia. (Circulation. 2001;103:1994-200.)

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

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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
  - Amiodarone
  - Arsenic trioxide
  - Erythromycin
  - Droperidol
  - Haloperidol
  - Thoridazine
  - Methadone

Heart block
- Hypokalemia, hypomagnesemia
- Acute myocardial infarction
- Subarachnoid hemorrhage and other CNS injury
- Liquid protein diets and other forms of starvation
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

Microvolt Level

Spectral Method Detects Microvolt T Wave Alternans
MGH / MIT Results
Arrhythmia Free Survival

Alternans Test

EP Study

Months

Survival in Congestive Heart Failure

Total number of subjects at risk:

- TWA - 186
- TWA + 161
- IND 195

Bloomfield DM, et al. ACC 2003,


542 patients
EF <=40%
NSR, no prior arrhythmias
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 QT<sub>C</sub>

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


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

atrial electrogram

ventricular electrogram

21 J
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

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\text{Moss AJ. N Engl J Med. 2002;346:877-83.}
\]
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

MLVWT
NSVT
FH/syncope
Abn BP
2 or more RF
Risk ratio
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

LQTS PRESENTING WITH CARDIAC ARREST

LQTS WITH
- RECURRENCE 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