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

CAUSES OF SCD

• CARDIAC ARRHYTHMIA
  – Ventricular tachycardia/fibrillation
  – Asystole without an escape rhythm

• PULSELESS ELECTRICAL ACTIVITY
  – Massive myocardial infarction
  – Massive pulmonary embolus
  – Pericardial tamponade
  – Aortic tear/rupture
Sinus Arrest with Junctional Escape

ASYSTOLE

PATHOPHYSIOLOGY OF VT/VF
Myocyte/myocardial tissue
- Conduction block
- Slow conduction
- Abnormal repolarization
  - Early afterdepolarizations
  - Reentry
  - Ventricular tachycardia
  - Ventricular fibrillation

Reentry-based VT

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
Ionic Currents during the Action Potential

Early Afterdepolarizations Initiating VT

Long QT EAD Torsades de Pointes

DISEASES & CONDITIONS PREDISPOSING TO SCD

STRUCTURAL HEART DISEASE:

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

SCD
CLINICIAN’S VIEW
### DISEASES/CONDITIONS PREDISPOSING TO SCD WITH STRUCTURAL HEART DISEASE WITH OR WITHOUT CHF, BUT WITHOUT LOW LVEF

- Hypertrophic Cardiomyopathy
- Arrhythmogenic Right Ventricular Cardiomyopathy
- Cardiac Sarcoidosis
- Anomalous Coronary Arteries
- Mitral Valve Prolapse
- Adult Congenital Heart Disease
- Severe Restrictive Disease

### DISEASES & CONDITIONS PREDISPOSING TO SCD: NO STRUCTURAL HEART DISEASE

**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) Acute myocardial ischemia
- B) Severe electrolyte imbalance
- C) Drug-related long QT syndrome
- D) Proarrhythmic effects of drugs
- E) Interactions with genetic polymorphisms

### VULNERABLE PLAQUE

**ACUTE CORONARY THROMBOSIS**
VT — VF during acute myocardial necrosis (STEMI)

CHRONIC ISCHEMIC HEART DISEASE

LV Ejection Fraction: 30%

VT — VF IN A PATIENT WITH CHRONIC MI

SCD RISK STRATIFICATION
ISCHEMIC HEART DISEASE: SURVIVAL AFTER MI

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

LV FUNCTION AS PREDICTOR OF SCD IN ISCHEMIC HEART DISEASE

GISSI-2 SURVIVAL
Sudden Cardiac Death in the Young

<table>
<thead>
<tr>
<th>Cardiac Abnormalities</th>
<th>Sudden Deaths, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Hypertrophy</td>
<td>33 (18)</td>
</tr>
<tr>
<td>Arteriography</td>
<td>21 (12)</td>
</tr>
<tr>
<td>Nonspecific cardiology</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Diffuse arterial stiffness</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Carotid artery pathology</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Increased cardiac output</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Increased cardiac output, other reasons</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Presence of high-grade outflow tract obstruction</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Presence of conduction abnormality</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Previous cardiac death</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>
| 1.0 3.0 5.0 7.0 9.0 11.0 13.0 any cause identified in 64/126; 44/126 no cause identified

Morphologic Features of the Myocardial Substrate for SCD in HCM

RISK FACTORS FOR SUDDEN CARDIAC DEATH IN HCM
ACC/ESC Clinical Expert Consensus Document on HCM (European Heart Journal 2003;24:1965)

**MAJOR**
- Cardiac arrest (VT/VF)
- Spontaneous sustained VT
- Unexplained syncope
- Family history of premature SCD
- Maximum LV thickness >30 mm
- Abnormal BP response to exercise
- Non-sustained VT

**POSSIBLE IN INDIVIDUALS**
- Atrial fibrillation
- Myocardial ischemia
- LV outflow obstruction
- High-risk mutation
- Intense physical effort

RISK FACTORS FOR SUDDEN CARDIAC DEATH IN HCM

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

Risk of SCD in HCM
Elliott PM et al. J Am Coll Cardiol 2000; 36:2212

<table>
<thead>
<tr>
<th>Number of risk factors</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5%</td>
</tr>
<tr>
<td>1</td>
<td>10%</td>
</tr>
<tr>
<td>2</td>
<td>15%</td>
</tr>
<tr>
<td>3</td>
<td>40%</td>
</tr>
</tbody>
</table>
Non-sustained VT in HCM

HCM: Specific Mutations & Survival

Kaplan-Meier curves for survival in patients in HCM families carrying TNNT2 arginine 92 tryptophan mutation
Moolman JC et al J Am Coll Cardiol 1997;29:549

LAMIN A/C (LMNA) MUTATIONS AND DCM

ARRHYTHMOGENIC RV DYSPLASIA

Schematic Picture of Desmoplastic Structure
The Risk of SCD in ARVC/D

ARRHYTHMOGENIC RV DYSPLASIA:
RISK FACTORS FOR SCD

- Premature SCD in family
- Syncope
- Severe RV dysfunction
- LV involvement
- Hemodynamically unstable VT
- Congestive heart failure
- Epsilon waves

The Risk of SCD in ARVD/C
Lemola K et al. Heart 2005;91:1167

SCD after Surgical Correction of CHD
Silka MJ et al. JACC 1998;32:245

Table 1. Specific Congenital Heart Defects and Incidence of Sudden and Non-sudden Cardiac Death

<table>
<thead>
<tr>
<th>Defect</th>
<th>SCD</th>
<th>NSCD</th>
<th>Total Follow-Up</th>
<th>SCD</th>
<th>NSCD</th>
<th>Total Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASD</td>
<td>622</td>
<td>377</td>
<td>999</td>
<td>7,996</td>
<td>0</td>
<td>9,996</td>
</tr>
<tr>
<td>VSD</td>
<td>24,4%</td>
<td>2,272</td>
<td>2,272</td>
<td>2,272</td>
<td>0</td>
<td>2,272</td>
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<tr>
<td>BAV</td>
<td>11%</td>
<td>58</td>
<td>58</td>
<td>58</td>
<td>0</td>
<td>58</td>
</tr>
<tr>
<td>AS</td>
<td>21</td>
<td>137</td>
<td>158</td>
<td>158</td>
<td>0</td>
<td>158</td>
</tr>
<tr>
<td>PR</td>
<td>12</td>
<td>29</td>
<td>41</td>
<td>41</td>
<td>0</td>
<td>41</td>
</tr>
<tr>
<td>LVOT</td>
<td>10</td>
<td>40</td>
<td>50</td>
<td>50</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>TGA</td>
<td>30</td>
<td>142</td>
<td>172</td>
<td>172</td>
<td>0</td>
<td>172</td>
</tr>
<tr>
<td>Total</td>
<td>1,590</td>
<td>680</td>
<td>2,270</td>
<td>2,270</td>
<td>0</td>
<td>2,270</td>
</tr>
</tbody>
</table>

Notes: ASD = atrial septal defect; VSD = ventricular septal defect; BAV = bicuspid aortic valve; AS = aortic stenosis; PR = pulmonic stenosis; LVOT = left ventricular outflow tract; TGA = transposition of the great arteries; "Incidence/1,000 person-years" includes both sudden and non-sudden cardiac deaths.

SCD after Surgical Correction of TOF
Gatzoulis MA et al. Lancet 2000;356:975

VT and SCD Late after Repair of TOF
Gatzoulis MA et al. Lancet 2000;356:975
SCD LATE AFTER SURGICAL CORRECTION OF CONGENITAL HEART DISEASE

For defects such as AS and d-TGA, the risk of SCD is much higher than the age-matched general population. This risk increases primarily > 20 years after the operation. Patients with syncope or non-sustained VT, especially in the presence of poor systolic function, dilation and hypertrophy of the systemic ventricle, should be protected with ICD therapy.

Late SCD after TOF repair is rare. Patients with sustained VT, and patients with syncope in the setting of trans-annular patch and QRS>180 ms, probably need protection with ICD. The role of PCS for risk stratification is not well established.

SCD IN PATIENTS WITH MVP

- The risk is very small in minimally symptomatic or asymptomatic, echocardiographically diagnosed patients. This risk, is probably present only in patients with redundant mitral valve leaflets. 237 such patients followed for a mean period of 6.2 years, 2 SCD in patients with redundant leaflets.
- There may be abnormalities of ventricular repolarization in a subgroup of patient with MVP. Their clinical utility is uncertain.
- In patients with syncope and documented spontaneous or PCS-induced sustained ventricular arrhythmia, and no other probable explanation for syncope, ICD should be considered.

DISEASES/CONDITIONS PREDISPOSING TO SCD WITHOUT STRUCTURAL HEART DISEASE

- **CHANNELOPATHIES/PRIMARY ELECTRICAL DISTURBANCES**
  - A) Long QT syndromes
  - B) Brugada syndrome
  - C) Familial catecholaminergic polymorphic VT
  - D) Short QT syndrome
  - E) Other repolarization abnormalities
  - F) Wolff-Parkinson-White syndrome
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>LQTI</td>
<td>KCNQ1 (KVLT1)</td>
<td>β1K+ channel α subunit</td>
</tr>
<tr>
<td>LQTI</td>
<td>KCNQ2 (HERB)</td>
<td>β1K+ channel α subunit</td>
</tr>
<tr>
<td>LQTI</td>
<td>SCN5A</td>
<td>β1Na+ channel α subunit</td>
</tr>
<tr>
<td>LQTI</td>
<td>ANK2</td>
<td>Ankyrin-B</td>
</tr>
<tr>
<td>LQTI</td>
<td>KCNQ1 (small)</td>
<td>β1K+ channel β subunit</td>
</tr>
<tr>
<td>LQTI</td>
<td>KCNQ2 (MRP1)</td>
<td>β1K+ channel β subunit</td>
</tr>
<tr>
<td>LQTI</td>
<td>KCNQ2</td>
<td>β1K+ channel α subunit</td>
</tr>
<tr>
<td>LQTI</td>
<td>CACNA1</td>
<td>Cav1.2 Calcium channel α subunit</td>
</tr>
</tbody>
</table>

LQTS 9

Mutant Cavolin-3 Induces Persistent Late Sodium Current and Is Associated With Long-QT Syndrome

LQTS 10

SCN4B-Encoded Sodium Channel β4 Subunit in Congenital Long-QT Syndrome

LQTS 11

Mutation of an α-Akinase-anchoring protein causes long-QT syndrome

LQTS 12
LQTS and Torsades de Pointes

Risk Stratification in the Long QT Syndrome

Sauer AJ et al. JACC 2007;49:329

CARDIAC ARREST/SCD IN LQTS:
Gender differences

CARDIAC ARREST/SCD IN LQTS:
Gender/QT duration relationship

CARDIAC ARREST/SCD IN LQTS:
Gender /Symptom relationship
Risk Stratification in Long QT Syndrome: Genotype & Gender

BRUGADA SYNDROME

Natural History of Brugada Syndrome

Risk Stratification in Brugada Syndrome

Familial catecholaminergic polymorphic VT

Familial catecholaminergic polymorphic VT
Familial catecholaminergic polymorphic VT: Bidirectional VT in a Child

Malignant PVT and SCD in 2 Unrelated Families
Swan H et al. JACC 1999;34:2035

SHORT QT SYNDROME

AF with rapid ventricular response in WPW Syndrome
ACQUIRED LONG QT
Drug-related Repolarization Abnormality

CAUSES OF ACQUIRED LONG QT

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

SCD RISK STRATIFICATION
AVAILABLE TESTING METHODS/PREDICTIVE MARKERS

NON-INVASIVE
- Ventricular Systolic Function (Echo, MUGA, MRI)
- Ambulatory Cardiac Rhythm Monitoring for VEA/NSTV
- T-Wave Alternans
- Exercise Testing
- HR Variability
- Baroreflex Sensitivity
- SAECG
- Genetic Markers

INVASIVE
- Programmed Cardiac Stimulation (PCS)
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

Sensitivity of PCS in ischaemic heart disease is acceptable, but its PPA is poor.

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 applicable in “channelopathies”, except for Brugada Syndrome.

SCD RISK STRATIFICATION IN CHF
T-Wave Alternans

Spectral Method Detects Microvolt T Wave Alternans

Survival in Congestive Heart Failure

Survival in Non-Ischemic Cardiomyopathy

542 patients
EF <=40%
NSR, no prior arrhythmias

SURVIVAL IN NON-ISCHEMIC CARDIOMYOPATHY
ALPHA Investigators JACC 2007;50:1896

SCD TREATMENT & PREVENTION

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

AVID/CIDS/CASH Metanalysis

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: PRIMARY PREVENTION

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

SCD TREATMENT & PREVENTION

I) IMPLANTABLE CARDIOVERTER DEFIBRILLATOR (ICD) THERAPY

II) DRUG THERAPY (Beta blocker therapy)

III) CATHETER ABLATION (WPW syndrome)

IV) SURGERY (Anomalous coronary arteries, severe CAD, e.g. LMCA stenosis)
Implantable Cardioverter Defibrillator

**DETECTION & TERMINATION OF VT BY ICD**

Ventricular Tachycardia  Sinus Rhythm

![Graph showing probability of survival over years for Defibrillator vs Conventional therapy](image)

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

**SCD-HeFT STUDY**

**PRIMARY PREVENTION OF SCD**

**MADIT-II SURVIVAL RESULTS**


![Graph showing comparison of Defibrillator vs Conventional therapy](image)

**ICD THERAPY IN ISCHAEMIC CARDIOMYOPATHY OR CHF**

**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
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

Cumulative Rates for First Appropriate ICD Intervention in Patients with 1, 2, 3 or More Risk Factors Who Had Received Devices for Primary Prevention  
Maron BJ et al. JAMA 2007;298:405

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)

ICD THERAPY IN ARVC/D

RECOMMENDATIONS FOR ICD THERAPY IN ARVD/C

- Patients with syncope, heart failure, or LV involvement
- As secondary prevention therapy in patients with documented sustained VT and hypotension

EFFECTIVENESS OF BETA BLOCKER THERAPY IN LQTS

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

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

Risk Profile & Treatment Algorithm: Brugada Protocol

DEBUT Trial
Nademanee et al. Circulation 2003;107:2221

BRUGADA SYNDROME: EFFECTIVENESS OF ICD THERAPY IN 258 PATIENTS WITH BRUGADA PATTERN ON ECG

ICD THERAPY IN "CHANNELOPATHIES": INDICATIONS

LOTS PRESENTING WITH CARDIAC ARREST
LOTS WITH
RECURRENT SYNCOPE ON BETA BLOCKER Rx
POSITIVE FAMILY Hx FOR SUDDEN DEATH
CHILD WITH MARKEDLY PROLONGED QT AT BASELINE
IDIOPATHIC VF
PATIENTS WITH SPONTANEOUS BRUGADA PATTERN
WHO ARE SYMPTOMATIC OR HAVE A POSITIVE FAMILY HISTORY
PATIENTS WITH INDUCED (SODIUM CHANNEL BLOCKERS) BRUGADA PATTERN WHO ARE SYMPTOMATIC
THE ROLE OF PCS IS CONTROVERSIAL

Drug therapy in CPVT
### Treatment of CPVT

- Beta blocker therapy strongly indicated in all CPVT patients. About 30% of the patients with CPVT treated with beta blockers still develop cardiac arrhythmias over long-term follow-up.

- ICD therapy in survivors of cardiac arrest.

- ICD therapy in patients with documented CPVT or syncope during maximally tolerated doses of beta blocker therapy.

### Management of Patient with ARCA or ALCA

- All ALCA patients require surgical repair.

- ARCA patients with well-defined symptoms or studies indicating myocardial ischemia require surgical repair.

- Asymptomatic ARCA patients risk-benefit dilemma.

- ICD consideration only if a satisfactory repair is not possible.

### 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

![Image of WPW Syndrome](image)

### 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.

### 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.