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

1/23/09

1NASPE, May 2000
2American Heart Association 2000
3National Cancer Institute 2001
4National Transportation Safety Board, 2000
5Center for Disease Control 2001

EPIDEMIOLOGIST’S VIEW

SUDDEN DEATHS - INCIDENCE AND TOTAL EVENTS

OVERALL INCIDENCE IN ADULT POPULATION
HIGH CORONARY RISK SUB-GROUP
ANY PRIOR CORONARY EVENT
E.F. < 30%; HEART FAILURE
OUT-OF-HOSPITAL CARDIAC ARREST SURVIVORS
CONVALESCENT PHASE VT/VF AFTER M. L

PERCENT / YEAR

EVENTS / YEAR

0 1 2 5 10 20 30

0 100 200 300

( x 1000 )
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
Reentry
Abnormal repolarization
Early afterdepolarizations

Ventricular tachycardia
Ventricular fibrillation

Reentry-based VT

Pastore et al. Circ Res. 2000;87:1157-1163
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

(1) action potential prolongation

(2) marked action potential prolongation during terminal repolarization (early afterdepolarization)

(3) triggered activity
Early Afterdepolarizations Initiating VT

Long QT $\rightarrow$ EAD $\rightarrow$ Torsades de Pointes
SCD
CLINICIAN’S VIEW

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
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
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 3. Nontraumatic Sudden Deaths with an Identifiable
Cardiac Abnormality during Recruit Training, 1977–2001 (n = 64)

<table>
<thead>
<tr>
<th>Cardiac Abnormality</th>
<th>Sudden Deaths, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiomyopathy</td>
<td>23 (36)</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>13 (20)</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>8 (13)</td>
</tr>
<tr>
<td>Idiopathic dilated cardiomyopathy</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Right ventricular dysplasia</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Coronary artery pathology</td>
<td>39 (51)</td>
</tr>
<tr>
<td>Anomalous coronary artery</td>
<td>21 (31)</td>
</tr>
<tr>
<td>Atherosclerotic coronary artery disease</td>
<td>10 (16)</td>
</tr>
<tr>
<td>Coronary artery hypoplasia</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Coronary aneurysm</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Intramyocardial coronary bridge</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Coronary dissection</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Miscellaneous cardiac findings</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Bicuspid aortic valve stenosis</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Embolic myocardial infarction</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

* Some numbers have been rounded.

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

Black bars=SCD, hatched bars=CHF or Tx, white bars=total mortality
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
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
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 Nonsudden Cardiac Death

<table>
<thead>
<tr>
<th>Defect</th>
<th>No. (%) of Ps</th>
<th>Total Follow-Up (pts)</th>
<th>Sudden Cardiac Death</th>
<th>Nonsudden Cardiac Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>No.</td>
<td>1/000 Pt-yr</td>
</tr>
<tr>
<td>ASD</td>
<td>622 (86%)</td>
<td>7,984</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>VSD</td>
<td>527 (87%)</td>
<td>6,354</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>AVSD</td>
<td>254 (87%)</td>
<td>2,217</td>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>PDA</td>
<td>625 (82%)</td>
<td>8,753</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PS</td>
<td>241 (91%)</td>
<td>3,568</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>AS</td>
<td>160 (94%)</td>
<td>1,806</td>
<td>10</td>
<td>5.4</td>
</tr>
<tr>
<td>CoA</td>
<td>539 (92%)</td>
<td>6,366</td>
<td>9</td>
<td>1.5</td>
</tr>
<tr>
<td>TOF</td>
<td>445 (91%)</td>
<td>7,082</td>
<td>11</td>
<td>1.5</td>
</tr>
<tr>
<td>d-TGA</td>
<td>172 (95%)</td>
<td>1,413</td>
<td>7</td>
<td>4.9</td>
</tr>
<tr>
<td>Total</td>
<td>3,589</td>
<td>45,887</td>
<td>41</td>
<td>0.9</td>
</tr>
</tbody>
</table>

AS = aortic stenosis; ASD = atrial septal defect; AVSD = atrioseptal defect; PDA = patent ductus arteriosus; PS = pulmonary stenosis; pt-yr = patient-years; Ps = patients; d-TGA = dextro-transposition of the great arteries; TOF = tetralogy of Fallot; VSD = ventricular septal defect.
SCD after Surgical Correction of CHD
Silka MJ et al. JACC 1998;32:245

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.

ANOMALOUS LEFT CORONARY ARTERY
Surgically treatable cause of SCD
### SCD in Coronary Artery Anomalies
*Taylor AJ et al. Am Heart J 1997;133:428*

<table>
<thead>
<tr>
<th>Patient age (yr)</th>
<th>Anomaly</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>24</td>
<td>LCA</td>
<td>Suicide</td>
</tr>
<tr>
<td>24</td>
<td>RCA</td>
<td>Walking</td>
</tr>
<tr>
<td>17</td>
<td>LCA</td>
<td>Running</td>
</tr>
<tr>
<td>17</td>
<td>RCA</td>
<td>Nonanomalous</td>
</tr>
<tr>
<td>18</td>
<td>LCA</td>
<td>Basketball</td>
</tr>
<tr>
<td>19</td>
<td>LCA</td>
<td>Unspecified accident</td>
</tr>
<tr>
<td>19</td>
<td>RCA</td>
<td>Football</td>
</tr>
<tr>
<td>20</td>
<td>LCA</td>
<td>Basketball</td>
</tr>
<tr>
<td>20</td>
<td>RCA</td>
<td>Running</td>
</tr>
<tr>
<td>21</td>
<td>LCA</td>
<td>Unspecified accident</td>
</tr>
<tr>
<td>80</td>
<td>LCA</td>
<td>Unspecified accident</td>
</tr>
<tr>
<td>87</td>
<td>RCA</td>
<td>Nonanomalous</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient age (yr)</th>
<th>Anomaly</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>RCA</td>
<td>Homocide</td>
</tr>
<tr>
<td>28</td>
<td>LCA</td>
<td>Construction accident</td>
</tr>
<tr>
<td>28</td>
<td>RCA</td>
<td>Motor vehicle accident</td>
</tr>
<tr>
<td>28</td>
<td>RCA</td>
<td>Crushed by falling object</td>
</tr>
<tr>
<td>30</td>
<td>LCA</td>
<td>Alcohol poisoning</td>
</tr>
<tr>
<td>52</td>
<td>LCA</td>
<td>Unlisted cause of death</td>
</tr>
<tr>
<td>52</td>
<td>RCA</td>
<td>Cardiac arrest</td>
</tr>
<tr>
<td>53</td>
<td>RCA</td>
<td>Cardiac arrhythmia</td>
</tr>
<tr>
<td>54</td>
<td>RCA</td>
<td>Cardiac arrest</td>
</tr>
<tr>
<td>55</td>
<td>RCA</td>
<td>Cardiac arrest</td>
</tr>
<tr>
<td>61</td>
<td>RCA</td>
<td>Cardiac arrest</td>
</tr>
<tr>
<td>62</td>
<td>RCA</td>
<td>Cardiac arrest</td>
</tr>
</tbody>
</table>

LCA, Left coronary artery; RCA, right coronary artery.

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### Fibromuscular Dysplasia of Small Coronary Arteries in MVP
*Burke AP et al. Am Heart J 1997; 134:282*

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 patients 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>LQT1</td>
<td>KCNQ1 (KVLQT1)</td>
<td>$I_{Ks}K^+$ channel α subunit</td>
</tr>
<tr>
<td>LQT2</td>
<td>KCNH2 (HERG)</td>
<td>$I_{Kc}K^+$ channel α subunit</td>
</tr>
<tr>
<td>LQT3</td>
<td>SCN5A</td>
<td>$I_{Na}Na^+$ channel α subunit</td>
</tr>
<tr>
<td>LQT4</td>
<td>ANK B</td>
<td>Ankyrin-B</td>
</tr>
<tr>
<td>LQT5</td>
<td>KCNE1 (minK)</td>
<td>$I_{Ks}K^+$ channel β subunit</td>
</tr>
<tr>
<td>LQT6</td>
<td>KCNE2 (MiRP1)</td>
<td>$I_{Kr}K^+$ channel β subunit</td>
</tr>
<tr>
<td>LQT7</td>
<td>KCNJ2</td>
<td>$I_{Kr}K^+$ channel α subunit</td>
</tr>
<tr>
<td>LQT8</td>
<td>CACNA1</td>
<td>Cav1.2 Calcium channel α subunit</td>
</tr>
</tbody>
</table>
LQTS 9

Mutant Caveolin-3 Induces Persistent Late Sodium Current and Is Associated With Long-QT Syndrome
Matteo Vatta, PhD; Michael J. Ackerman, MD, PhD; Bin Ye, PhD; Jonathan C. Makielski, MD; Esme E. Uyhaner, MD; Erica W. Taylor, BS; David J. Tester, BS; Ravi C. Balijepalli, PhD; Jason D. Foell, BS; Zhouchi Li, PhD; Timothy J. Kamp, MD, PhD; Jeffrey A. Towbin, MD

LQTS 10

SCN4A-Encoded Sodium Channel β4 Subunit in Congenital Long-QT Syndrome
Argelio Medeiros-Domingo, MD; Toshihiko Kaki, MD, PhD; David J. Tester, BS; Pedro Ibarra-Torres, MD, Aji Itty, MD; Bin Ye, PhD; Carmen Valdivia, MD; Kanas Uceta, MD, PhD; Samad Canales-Quinones, PhD; Maria Teresa Tisdie-Luna, MD, PhD; Jonathan C. Makielski, MD; Michael J. Ackerman, MD, PhD
LQTS 11

Mutation of an A-kinase-anchoring protein causes long-QT syndrome

LQTS 12

[ECG image]

[Diagram image]
LQTS and Torsades de Pointes

GENOTYPE-PHENOTYPE SUMMARY OF THREE MOST COMMON LQT SYNDROMES
CARDIAC ARREST/SCD IN LQTS:  
Gender differences

Figure 1. Kaplan–Meier estimates of the probability of ACA or SCD by gender (values in parentheses are event rates).

Risk Stratification in the Long QT Syndrome  
Sauer AJ et al. JACC2007;49:329
CARDBIAC ARREST/SCD IN LQTS:
Gender/QT duration relationship

CARDBIAC 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

Risk Groups
- Higher Risk
  - HR: 6.4
  - Syncope AND Spontaneous pattern (10%)
- Intermediate Risk
  - Spontaneous ECG pattern (41%)
  - HR: 2.1
- Lower Risk
  - Negative baseline ECG with or without syncope (49%)
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; Natsuko Tsubo, PhD; Mirella Memmi, PhD; Gabriele Vignani, MD; Raffaella Bosse, MD; Vincenzo Sorrentino, MD; Gius Antonio Dzemeli, 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 atrioventricular 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 arrhythmogenic disease.

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 form 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 as a biallelic with 2 mutant alleles that occurred at 16 and 14 years, respectively, in the absence of the proband. Conclusion—We demonstrated that, in agreement with our hypothesis, hRyR2 is a gene responsible for catecholaminergic polymorphic ventricular tachycardia (Circulation. 2001;103:186-209.)

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

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.
PRE-EXCITED QRS COMPLEXES IN A PATIENT WITH WPW SYNDROME

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

HERG block
Increased action potential duration, EADs, and heterogeneity of repolarization
QT prolongation
Torsades de pointes degenerating to VF

channel in resting (closed) state
activation gate opens; drug enters vestibule

channel inactivation stabilizes drug binding

class I drug

+Em

closing of activation gate (deactivation) traps drug

-Em
CAUSES OF ACQUIRED LONG QT

Drugs

- Drugs that frequently cause torsade de pointes
  - Disopyramide
  - Doxepinide
  - Ibutilide
  - Procaainamide
  - Quinidine
  - Sotalol

- Drugs clearly associated with torsade de pointes but with low incidence:
  - Amiodarone
  - Arsenic trioxide
  - Erythromycin
  - Droperidol
  - Haloperidol
  - Thioridazine
  - 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
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 (Echocardiogram, MUGA Scan, MRI)
- Ambulatory Cardiac Rhythm Monitoring for VEA/NSVT
- 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

Visible

Microvolt Level

Spectral Method Detects Microvolt T Wave Alternans

ECG

128 Beats

TIME SERIES

SPECTRUM

Resp

Alternans

FFT
542 patients
EF $\leq 40$
NSR, no prior arrhythmias

<table>
<thead>
<tr>
<th>Group</th>
<th>Total</th>
<th>Survivors</th>
<th>Deaths</th>
</tr>
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<tbody>
<tr>
<td>TWA -</td>
<td>186</td>
<td>95</td>
<td>41</td>
</tr>
<tr>
<td>TWA +</td>
<td>161</td>
<td>83</td>
<td>49</td>
</tr>
<tr>
<td>IND</td>
<td>195</td>
<td>66</td>
<td>38</td>
</tr>
</tbody>
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**SURVIVAL IN NON-ISCHEMIC CARDIOMYOPATHY**

**ALPHA Investigators JACC 2007;50:1896**

Figure 1
Freedom From Cardiac Death + Life-Threatening Arrhythmias
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
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

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

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**PRIMARY PREVENTION OF SCD**  
**MADIT-II SURVIVAL RESULTS**

![Graph showing survival rates for defibrillator and conventional treatment](image)

<table>
<thead>
<tr>
<th>Year</th>
<th>No. At Risk</th>
<th>Probability of Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Defibrillator</td>
<td>742</td>
</tr>
<tr>
<td></td>
<td>Conventional</td>
<td>490</td>
</tr>
</tbody>
</table>

SCD-HeFT STUDY

Mortality by Intention-to-treat

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HR</th>
<th>97.5% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone vs. Placebo</td>
<td>1.06</td>
<td>0.86, 1.30</td>
<td>0.529</td>
</tr>
<tr>
<td>ICD Therapy vs. Placebo</td>
<td>0.77</td>
<td>0.62, 0.96</td>
<td>0.007</td>
</tr>
</tbody>
</table>

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

Fig. 1. Diagram summarizing the results of 321 patients with ARVC/D implanted with an ICD, with a mean follow-up of 37 ± 26 months. 167-178,717
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 QTc

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 “CHANCELOPATHIES”: 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 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

Table 1 Prognosis in relation to drug treatment

<table>
<thead>
<tr>
<th></th>
<th>β Blocker</th>
<th>Ca blocker</th>
<th>Na blocker</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive</td>
<td>17</td>
<td>3</td>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>Dead</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>3</td>
<td>4</td>
<td>28</td>
</tr>
</tbody>
</table>

Ca blocker, calcium channel blocker; Na blocker, sodium channel blocker

TABLE 3. Events at Follow-Up in CPVT Patients According to Genotype

<table>
<thead>
<tr>
<th></th>
<th>Non-heterozygous</th>
<th>CPVT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up, mo</td>
<td>49 ± 39</td>
<td>52 ± 36</td>
<td>NS</td>
</tr>
<tr>
<td>eVT/VF on β blockers</td>
<td>7/10</td>
<td>11/20</td>
<td>NS</td>
</tr>
<tr>
<td>ICD</td>
<td>6</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>ICD follow-up, mo</td>
<td>21 ± 10</td>
<td>19 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>ICD shock</td>
<td>1/6</td>
<td>2/6</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD, n, or n%. eVT indicates sustained ventricular tachycardia; and VF, ventricular fibrillation.
*ICD was implanted in 5 patients with eVT and in 0 patients with pVT/VF.
†Appropriate shocks as assessed by ICD-stored electrogram analysis.
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
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