SUDDEN CARDIAC DEATH

EPIDEMIOLOGY, PATHOPHYSIOLOGY, PREVENTION & THERAPY

Hasan Garan, M.D.
Columbia University Medical Center

SUDDEN CARDIAC DEATH (SCD)

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

0 50,000 100,000 150,000 200,000 250,000 300,000

SCD  CVA  Lung CA  Breast CA  Auto Acc.  AIDS  Fires

NASPE, May 2000
American Heart Association 2000
National Cancer Institute 2001
National Transportation Safety Board, 2000
Center 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.I.

PERCENT / YEAR

EVENTS / YEAR

0 1 2 5 10 20 30

0 100 200 300 (x 1000)
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

EARLY AFTERDEPOLARIZATIONS

(1) action potential prolongation

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

(3) triggered activity
Early Afterdepolarizations Initiating VT


Reentrant Activation Initiating VT/VF

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
- Cardiomyopathies
- Electrolyte abnormalities/drugs

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 disease: valvar
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) Other proarrhythmic effects of drugs
E) Interactions with genetic polymorphisms
ACUTE CORONARY THROMBOSIS

LAD: TOTAL OCCLUSION

VF during STEMI
CHRONIC ISCHEMIC HEART DISEASE

LV Ejection Fraction: 30 %

VENTRICULAR TACHYCARDIA IN A PATIENT WITH CHRONIC MI
Hypertrophic Cardiomyopathy

ARRHYTHMOGENIC RV DYSPLASIA
Genetic Loci Responsible for Long QT Syndrome

<table>
<thead>
<tr>
<th>Arrhythmia</th>
<th>Chromosome</th>
<th>Gene</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>11p15</td>
<td>KCNQ1</td>
<td>~50%</td>
</tr>
<tr>
<td>LQT2</td>
<td>7q35</td>
<td>KCNH2</td>
<td>30%–40%</td>
</tr>
<tr>
<td>LQT3</td>
<td>3p21</td>
<td>SCNSA</td>
<td>5%–10%</td>
</tr>
<tr>
<td>LQT4</td>
<td>4q25</td>
<td>ANK2</td>
<td>Rare</td>
</tr>
<tr>
<td>LQT5</td>
<td>21q22</td>
<td>KCNIE</td>
<td>Rare</td>
</tr>
<tr>
<td>LQT6</td>
<td>21q22</td>
<td>KCNE2</td>
<td>Rare</td>
</tr>
<tr>
<td>LQT7</td>
<td>17</td>
<td>KCNJ2</td>
<td>Rare</td>
</tr>
</tbody>
</table>

Recessive (and Deafness)

<table>
<thead>
<tr>
<th>Arrhythmia</th>
<th>Chromosome</th>
<th>Gene</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>11p15</td>
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</tr>
<tr>
<td>LQT2</td>
<td>21q22</td>
<td>KCNQ2</td>
<td>Rare</td>
</tr>
</tbody>
</table>

GENES IDENTIFIED TO DATE IN LQT SYNDROME

<table>
<thead>
<tr>
<th>Nomenclature, gene names, and proteins associated with LQTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>LQT1</td>
</tr>
<tr>
<td>LQT2</td>
</tr>
<tr>
<td>LQT3</td>
</tr>
<tr>
<td>LQT4</td>
</tr>
<tr>
<td>LQT5</td>
</tr>
<tr>
<td>LQT6</td>
</tr>
<tr>
<td>LQT7</td>
</tr>
<tr>
<td>LQT8</td>
</tr>
</tbody>
</table>
ECG in Long QT Syndrome

A.

BRUGADA 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)
- QTc DURATION
- CARDIAC EVENT AT PRESENTATION
- RESTING HEART RATE

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

Risk Stratification in the Long QT Syndrome

**Figure 1.** Kaplan–Meier Estimates of Survival Free of Cardiac Events among the 580 Patients with the Long QT Syndrome in the Risk-Stratification Analysis, According to the Genomic Locus of the Mutation. The difference among the groups was significant (P=0.007 by the log-rank test).
Risk Stratification in the Long QT Syndrome

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

<table>
<thead>
<tr>
<th>Risk Groups</th>
<th>Percentage of Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher Risk</td>
<td></td>
</tr>
<tr>
<td>→ HR: 6.4 Syncope AND Spont. pattern</td>
<td>10%</td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td></td>
</tr>
<tr>
<td>→ HR: 2.1 Spontaneous ECG pattern</td>
<td>41%</td>
</tr>
<tr>
<td>Lower Risk</td>
<td></td>
</tr>
<tr>
<td>Negative baseline ECG with or without syncope</td>
<td>49%</td>
</tr>
</tbody>
</table>

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

Silvia G. Pirro, MD, PhD; Carlo Napolitano, MD, PhD; Natasca Tiso, PhD; Mirella Menini, PhD; Gabriele Vignati, MD; Raffaella Blesse, MD; Vincenzo Sorrentino, MD; Giust Antonio Duneli, BS

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 after-depolarizations observed during digoxin 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 arrhythmia 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 unaffected 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;103:199-206.)

Key Words: arrhythmia • genetics • tachycardia • ryanodine receptor calcium release channel
Familial catecholaminergic polymorphic VT: Bidirectional VT in a Child

MAJOR ARRHYTHMIC EVENTS DURING F/U IN IDIOPATHIC VF
ACQUIRED LONG QT ION CHANNEL FOR $I_{Kr}$

Drug-related Repolarization Abnormality
CAUSES OF ACQUIRED LONG QT

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Drugs that frequently cause torsade de pointes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Disopyramide</td>
</tr>
<tr>
<td></td>
<td>Dofetilide</td>
</tr>
<tr>
<td></td>
<td>Ibutilide</td>
</tr>
<tr>
<td></td>
<td>Procainamide</td>
</tr>
<tr>
<td></td>
<td>Quinidine</td>
</tr>
<tr>
<td></td>
<td>Sotalol</td>
</tr>
<tr>
<td>Drugs</td>
<td>Drugs clearly associated with torsade de pointes but with low incidence</td>
</tr>
<tr>
<td></td>
<td>Amiodarone</td>
</tr>
<tr>
<td></td>
<td>Arsenic trioxide</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
</tr>
<tr>
<td></td>
<td>Droperidol</td>
</tr>
<tr>
<td></td>
<td>Haloperidol</td>
</tr>
<tr>
<td></td>
<td>Thioridazine</td>
</tr>
<tr>
<td></td>
<td>Methadone</td>
</tr>
</tbody>
</table>

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

N = 799
MEAN EF = 46%

% ONE-YEAR CARDIAC MORTALITY
GISSI-2
SURVIVAL

Non-sustained VT, Sustained VT, and VF during Holter Monitor Recording
Better Non-Invasive Risk Predictors Needed

Example: in post MI patients

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Source</th>
<th>Sens</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF &lt; 0.4</td>
<td>Pedretti, 1993</td>
<td>79%</td>
<td>26%</td>
</tr>
<tr>
<td>LVEF &lt; 0.4</td>
<td>Bourke, 1991</td>
<td>73%</td>
<td>6%</td>
</tr>
<tr>
<td>LVEF &lt; 0.4</td>
<td>Farrell, 1991</td>
<td>48%</td>
<td>10%</td>
</tr>
<tr>
<td>SAECG</td>
<td>Pedretti, 1993</td>
<td>79%</td>
<td>17%</td>
</tr>
<tr>
<td>SAECG</td>
<td>Farrell, 1991</td>
<td>64%</td>
<td>17%</td>
</tr>
<tr>
<td>HRV</td>
<td>Pedretti, 1993</td>
<td>89%</td>
<td>15%</td>
</tr>
<tr>
<td>HRV</td>
<td>Farrell, 1991</td>
<td>92%</td>
<td>17%</td>
</tr>
<tr>
<td>HRV</td>
<td>Bigger, 1996</td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>NSVT</td>
<td>Pedretti, 1993</td>
<td>42%</td>
<td>25%</td>
</tr>
<tr>
<td>NSVT</td>
<td>Farrell, 1991</td>
<td>56%</td>
<td>15%</td>
</tr>
</tbody>
</table>

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

ECG

TIME SERIES

SPECTRUM

0 2 04 06 08 10 12 14 16 18 20
0 2 04 06 08 10 12 14 16 18 20

Beat Number

T Wave Level (μV)

100 120 140 160 180 200

0 2 04 06 08 10 12 14 16 18 20
0 2 04 06 08 10 12 14 16 18 20

Frequency (Cycles/Beat)

0.0 0.1 0.2 0.3 0.4 0.5

Resp
Alternans

Spectral Method Detects Microvolt T Wave Alternans


Alternans-Induced VT

S1 VPB VT VT

VPB

VT

MGH / MIT Results
Arrhythmia Free Survival


Survival in Congestive Heart Failure

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

Total number of subjects at risk:

<table>
<thead>
<tr>
<th>Group</th>
<th>TWA -</th>
<th>TWA+</th>
<th>TWA IND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>186</td>
<td>161</td>
<td>195</td>
</tr>
<tr>
<td>Survival</td>
<td>95</td>
<td>83</td>
<td>66</td>
</tr>
<tr>
<td>70-79</td>
<td>41</td>
<td>49</td>
<td>38</td>
</tr>
<tr>
<td>80-89</td>
<td>95</td>
<td>83</td>
<td>66</td>
</tr>
<tr>
<td>90-99</td>
<td>38</td>
<td>41</td>
<td>38</td>
</tr>
</tbody>
</table>

Frankfurt CHF Study Results

107 consecutive patients
NYHA class II and III heart failure
No recent MI (6 weeks)
No prior history of VT or VF
TWA, EF, SAECG, Mean RR, HRV,
NSVT, BRS tests performed
End-point Ventricular Tachyarrhythmic
Events (VTE = VT, VF or SCD)
Sensitivity 100%
PPV 21%
TWA: the only statistically significant predictor


POST-MI SURVIVAL: LVEF & HRV INTERACTIONS

SCD TREATMENT & PREVENTION

I) IMPLANTABLE CARDIOVERTER DEFIBRILLATOR (ICD) THERAPY

II) ANTIARRHYTHMIC DRUG THERAPY

III) CATHETER ABLATION

IV) SURGERY

AF TRANSFORMING TO VF IN A PATIENT WITH WPW SYNDROME
WPW Syndrome: Disappearance of Ventricular Pre-excitation during RF Application

Current 0.51 Am
Voltage 53 V
Power 27 W

ANOMALOUS LEFT CORONARY ARTERY
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
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: 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 Metaanalysis

SCD: Difficulties with Primary Prevention

- Large numbers of patients at risk
  - need for simple, inexpensive, non-invasive testing
- Low incidence of sudden cardiac death among patients with known heart disease
  - post myocardial infarction mortality rates ~5%
  - ‘needle in a haystack’
PVC Hypothesis:

PVC ➔ VT ➔ VF

CAST-I

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

SCD: PRIMARY PREVENTION

ANTIARRHYTHMIC DRUG (AAD) TRIALS

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

DETECTION & TERMINATION OF VT BY ICD

Ventricular Tachycardia

atrial electrogram
ventricular electrogram

Sinus Rhythm
SCD: PRIMARY PREVENTION
ICD THERAPY

• 4 randomized, prospective trials showed survival benefit with ICD in:
  – Ischaemic heart disease and non-sustained VT
  – Ischaemic heart disease and depressed LV function
  – CHF and depressed LV function (ischaemic or non-ischaemic)

• ICD-related survival benefit not established in:
  – Patients undergoing surgical coronary revascularization
  – Implantation immediately after acute MI

PRIMAR Y PREVENTION OF SCD
MADIT-II SURVIVAL RESULTS

P = 0.007

Efficacy of ICD for Prevention of Sudden Death in Patients with HCM

Retrospective Multicenter Study; n=128


Risk Profile & Treatment Algorithm in Brugada Syndrome
ICD THERAPY IN REPOLARIZATION ABNORMALITIES: INDICATIONS

LQTS PRESENTING WITH CARDIAC ARREST

LQTS WITH RECURRENT SYNCOPE ON BETA BLOCKER Rx AND
  POSITIVE FAMILY Hx FOR SUDDEN DEATH
  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