Pathologic Correlation with Autopsy Defined Sudden Arrhythmic Death in the San Francisco Postmortem Systematic Investigation of Sudden Cardiac Death Study

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U.S. Mortality by Death Certificates

![Graph showing mortality by cause, with SCD (Sudden Cardiac Death) being the highest.]

2002 Heart and Stroke Statistical Update, American Heart Association.

Etiology of Sudden Cardiac Death

![Diagram illustrating the etiology of sudden cardiac death.]

RCTs, Registries: Sudden Cardiac Death

- **VALIANT trial:** Valsartan after acute MI and HF
  - “The cause of death was considered as SCD if death occurred suddenly and unexpectedly in a patient in otherwise stable condition, with no prior evidence of progressive circulatory failure, in the absence of premonitory HF, MI, or another clear cause of death. These could have been witnessed (with or without documentation of arrhythmias) or unwitnessed if the patient had been seen within 24 h before death.

- **MERIT-HF trial:** Metoprolol for Heart Failure
  - “Witnessed instantaneous death in the absence of progressive circulatory failure, evidence of progressive circulatory failure, or other cause of death before death.”

- **Hinkle-Thaler, 1982:**
  - “No evidence of circulatory impairment until they collapsed and the pulse disappeared.”

- **SCD-HeFT and MADIT 2**
  - No definition of SCD.

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**ACC/AHA/HRS: Sudden Cardiac Death**

ACC/AHA/HRS, 2006:

“SCA is the sudden cessation of cardiac activity so that the victim becomes unresponsive with no normal breathing and no signs of circulation. If corrective measures are not taken rapidly, this condition progresses to sudden cardiac death.”

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**EMS: Out of Hospital Cardiac Arrest**

2004: CDC established Cardiac Arrest Registry to Enhance Survival (CARES) to precisely define OHCA outcomes in the continuum of emergency cardiac care: 911 dispatch centers, EMS providers, and receiving hospitals.

“OHCA is a cardiac arrest that occurred in the pre-hospital setting, had a presumed cardiac etiology, and involved a person who received resuscitative efforts, including CPR or defibrillation.”
Sudden Cardiac Death: Definition

World Health Organization (WHO), 1969:

- Unexpected death within 1 h of symptom onset if witnessed
- Unexpected death within 24 h of having been observed alive and symptom-free if unwitnessed

- Out of hospital
- Absence of obvious noncardiac condition
- Presumed sudden pulseless condition

Methodological Issues in Population Studies of SCD

- US incidence estimates: 184,000 - 450,000 annually (2.5-fold range)

- Where does the data come from?
  - Death certificate review of listed COD
  - Retrospective review of paramedic/ER narratives
  - Incomplete medical records

- Which definition should we use for SCD?
  - WHO (Hinkle-Thaler) criteria?
  - Documented VF?
  - CARES?
  - Witnessed cases only?

Comprehensive Surveillance of SCD

Oregon – SUDS (Chugh, JACC, 2004)

- WHO criteria
- Portland, OR: population 1,000,000
- Track 50 ambulance services and all area hospitals
- Review of all available records
- SCA+SCD: 53/100,000
- Autopsy rate: 11%
Sudden Arrhythmic Death

- SCA
- CAD
- Tamponade
- Valvular
- Neurologic
- DCM
- HCM
- Hemorrhage
- Ao Dissection
- 1st electrical disease

San Francisco POST SCD Study

- Postmortem Systematic Investigation of Sudden Cardiac Death
- All out of hospital and ER deaths reported by law to ME
- Every incident SCD 2011-2014

San Francisco County

- Single ME office serving 49 mi² (pop: 864,000 (~1.5M business hrs)
- Racially/Ethnically diverse:
  - 33% Asian, 6.1% Black, 15% Hispanic, 48% White
- 8 hospitals, 3 ambulance companies (SFFD responds to ~85% of 911 calls)
- By CA state law, all OOH or ER deaths are reported to the ME
Methods

- Daily AM review of all OOH deaths reported to ME for 37 consecutive months to determine WHO SCDs ages 18-90 y for full autopsy, histology, tox
- All county death certificates retrieved and reviewed quarterly from DPH to cross-check for missed SCDs
- IRBs with all county hospitals and ambulance companies
- Outside medical records obtained by IRB

Case Adjudication

Data reviewed at adjudication
- PMH (active problems, prescriptions, recent visits)
- Medications (Rx, QT-prolonging, methadone)
- EMS runsheets and rhythms
- Witness/family interviews
- Autopsy, tox, histology findings

Adjudication panel

Dr. Phil Ursell
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UCSF
Dr. Ellen Moffatt
Medical Examiner, City and County of San Francisco
Dr. Zian H. Tseng
Study PI
Cardiac Electrophysiologist, UCSF
Dr. Jeff Olgin
Chief of Cardiology, UCSF
Dr. Anthony Kim
Neurologist
Director of UCSF Stroke Center

Deaths in San Francisco
February 1, 2011 – March 1, 2014
N=20441
Not Reported to ME
N= 7769
Deaths Reported to ME:
all ER, OOH, Unexpected Inpatient Death
N= 12672
Non-Natural Deaths
N= 2021
Natural Deaths
N= 10651
Excluded - Age <18 or >90
N= 1998
Excluded - Inpatient/Hospice
N= 3843
OOH Natural Deaths, 18-90 yo, N= 4810
OOH Deaths, Eligible for Autopsy
N= 3690
Under MD Care < 3 weeks Signed Death Certificate, Ineligible for Autopsy
N= 1120
WHO SCD w/o Autopsy
N= 89
Non-Sudden Deaths
N= 1031
Excluded at Initial Presentation (Non-Sudden or Ineligible)
N= 2776
EMS SCD Refused Autopsy
N= 16
Autopsied EMS SCDs
N= 898
Excluded after comprehensive records review (Non-Sudden Death)
N= 268
Adjudicated Autopsied Potential SCDs
N= 630
Excluded at Adjudication (Non-Sudden Death)
N= 105
Adjudicated Autopsied WHO SCDs
N= 525
EMS SCD referred for autopsy
N= 914
(See Table 1A)
(See Table 1B)

POstmortem Systemic Investigation of Sudden Cardiac Death
February 1, 2011 – March 1, 2014

Key for Case Review:
Death Certif. (DC) Only
EMS + Initial ME Investig.
All Records (all medical records, EMS run sheets and ME records)
Adjudication

SCD Criteria
Witnessed: Symptoms <1 hour of death
Unwitnessed: Observed well within 24 hours of death
Excluded: Known metastatic CA, ESRD on HD, Hospice, Hospitalization <1 month

(See Table 1C and 1B)

ME POST SCD Autopsy Rate = 97%
Overall WHO SCD Autopsy Rate = 83%
### POST SCD Demographics

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD</td>
<td>62.8 ± 14.5</td>
<td>73.1 ± 11.6</td>
<td>69.0 ± 6.9</td>
</tr>
<tr>
<td>Age range</td>
<td>18-90</td>
<td>37-89</td>
<td>18-64</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>362 (69%)</td>
<td>74 (70%)</td>
<td>350,179 (51%)</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>279 (53%)</td>
<td>44 (42%)</td>
<td>290,089 (42%)</td>
</tr>
<tr>
<td>Black</td>
<td>87 (16%)</td>
<td>8 (8%)</td>
<td>40,751 (6%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>65 (12%)</td>
<td>8 (8%)</td>
<td>102,913 (15%)</td>
</tr>
<tr>
<td>Other</td>
<td>15 (3%)</td>
<td>3 (3%)</td>
<td>24,174 (3%)</td>
</tr>
<tr>
<td>Median Income</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertile 1</td>
<td>248 (47%)</td>
<td>44 (45%)</td>
<td>266,644 (39%)</td>
</tr>
<tr>
<td>Tertile 2</td>
<td>82 (16%)</td>
<td>14 (13%)</td>
<td>230,900 (33%)</td>
</tr>
<tr>
<td>Tertile 3</td>
<td>171 (32%)</td>
<td>43 (42%)</td>
<td>193,147 (28%)</td>
</tr>
</tbody>
</table>

*Population data from American Community Survey 2011

### Adjusted Etiologies of SCD

- Cardiac, Arrhythmic
- Cardiac, Non-Arrhythmic
- Non-Cardiac

SAD: no extra-cardiac (PE, SAH, lethal tox) or non-arrhythmic (tamponade, acute HF) COD

### Sudden Cardiac Arrhythmic Death

- Is a subset of sudden cardiac arrest
- Requires autopsy with toxicology
- Can only be determined by ruling out all other causes of sudden cardiac death
- Drugs
- Neoplasms
- Sudden Neurologic Death
Pre-Mortem Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>SAD</th>
<th>SAD Non-SAD</th>
<th>Non-SAD</th>
<th>P value SAD vs. non-SAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Failure</td>
<td>22 (6%)</td>
<td>18 (6%)</td>
<td>82%</td>
<td>0.16</td>
</tr>
<tr>
<td>Valvular Disease</td>
<td>9 (2%)</td>
<td>5 (1%)</td>
<td>0.0005</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>58 (17%)</td>
<td>39 (12%)</td>
<td>0.0009</td>
<td></td>
</tr>
<tr>
<td>Chronic Lung Disease</td>
<td>124 (53%)</td>
<td>75 (25%)</td>
<td>0.0005</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>15 (5%)</td>
<td>10 (3%)</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>22 (7%)</td>
<td>16 (5%)</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>Arrhythmic Death</td>
<td>72 (25%)</td>
<td>68 (23%)</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>Cardiac Amyloid</td>
<td>21 (7%)</td>
<td>16 (5%)</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Arrhythmic Death</td>
<td>72 (25%)</td>
<td>68 (23%)</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>Cardiac Amyloid</td>
<td>21 (7%)</td>
<td>16 (5%)</td>
<td>0.10</td>
<td></td>
</tr>
</tbody>
</table>

Coronary Artery Disease is Associated with Sudden Arrhythmic Death
- One vessel coronary disease is more prevalent than multivessel disease
- In one vessel disease and SAD, the right coronary artery involvement is most common
- Multi vessel disease seems to less associated
### Table 1

<table>
<thead>
<tr>
<th>Died OOH/ED (POST SCD)</th>
<th>All UCSF/SFGH SCA Admissions</th>
<th>UCSF/SFGH Inpatient Death</th>
<th>UCSF/SFGH Survival to Hospital Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>62.8</td>
<td>63.8</td>
<td>68.5</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>69%</td>
<td>59%</td>
<td>62%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>279 (53%)</td>
<td>7 (26%)</td>
<td>3 (23%)</td>
</tr>
<tr>
<td>Black</td>
<td>81 (15%)</td>
<td>6 (22%)</td>
<td>4 (31%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>40 (8%)</td>
<td>2 (7%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>White</td>
<td>110 (21%)</td>
<td>9 (33%)</td>
<td>3 (23%)</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>15 (3%)</td>
<td>3 (12%)</td>
<td>2 (15%)</td>
</tr>
</tbody>
</table>

### COD by Initial Rhythm

**Witnessed SCDS**

<table>
<thead>
<tr>
<th>Initial Rhythm</th>
<th>Arhythmic COD N=78</th>
<th>Non-Arhythmic COD N=42</th>
<th>P value Fisher's Exact</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agonal/Idioventricular</td>
<td>3 (60%)</td>
<td>2 (40%)</td>
<td>1.0</td>
<td>5</td>
</tr>
<tr>
<td>Asystole</td>
<td>26 (63%)</td>
<td>15 (37%)</td>
<td>0.84</td>
<td>41</td>
</tr>
<tr>
<td>NSR</td>
<td>3 (60%)</td>
<td>2 (40%)</td>
<td>1.0</td>
<td>5</td>
</tr>
<tr>
<td>Sinus Brady</td>
<td>2 (13%)</td>
<td>13 (87%)</td>
<td>&lt;0.0001</td>
<td>15</td>
</tr>
<tr>
<td>VT/VF</td>
<td>20 (91%)</td>
<td>4 (9%)</td>
<td>&lt;0.0001</td>
<td>43</td>
</tr>
<tr>
<td>Other</td>
<td>1 (33%)</td>
<td>1 (33%)</td>
<td>1.0</td>
<td>3</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (33%)</td>
<td>2 (67%)</td>
<td>0.61</td>
<td>3</td>
</tr>
</tbody>
</table>

### COD by Presenting Symptom

**Witnessed SCDS**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Arhythmic COD N=78</th>
<th>Non-Arhythmic COD N=42</th>
<th>P value Fisher's Exact</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>None Known</td>
<td>40 (65%)</td>
<td>18 (35%)</td>
<td>0.70</td>
<td>58</td>
</tr>
<tr>
<td>Multiple</td>
<td>18 (62%)</td>
<td>11 (38%)</td>
<td>0.70</td>
<td>29</td>
</tr>
<tr>
<td>Other</td>
<td>10 (33%)</td>
<td>2 (67%)</td>
<td>0.18</td>
<td>12</td>
</tr>
<tr>
<td>Shortness of Breath</td>
<td>3 (57%)</td>
<td>5 (43%)</td>
<td>0.09</td>
<td>8</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>2 (67%)</td>
<td>4 (33%)</td>
<td>0.10</td>
<td>6</td>
</tr>
<tr>
<td>Syncope</td>
<td>2 (66%)</td>
<td>2 (34%)</td>
<td>0.82</td>
<td>4</td>
</tr>
<tr>
<td>Hoisting / Nauseous</td>
<td>2 (100%)</td>
<td>0 (0%)</td>
<td>0.30</td>
<td>2</td>
</tr>
<tr>
<td>GI</td>
<td>1 (100%)</td>
<td>0 (0%)</td>
<td>0.45</td>
<td>1</td>
</tr>
<tr>
<td>Pallor</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cough</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>78 (65%)</td>
<td>42 (35%)</td>
<td>-</td>
<td>120</td>
</tr>
</tbody>
</table>
Implications

- Reliance on EMS records and/or death certificates is insufficient for accurate determination of SCD incidence, and by implication, SAD
- Further investigation in minority groups and women
- To reduce overall public health burden of SCD/SAD, in addition to CAD, efforts also should be directed towards screening, treating and preventing OD, neurologic diseases, hypertrophy, cardiomyopathy
- SCD cohorts for genetic and molecular association studies will need refinement of phenotype

Next Steps

- Precise phenotypes for future molecular association studies
  - with “humanized” risk factors
  - Predictive modeling for true SAD in existing SCD cohorts
  - Evaluation of myocardial fibrosis, cardiac mass, CAD, MVP as risk factors
  - Precision EMS protocols
  - SND, SuDEP, hemorrhage risk with anticoagulants, anti-platelets
  - Determine the burden and cardiac pathologic substrate of HIV+ SCDs
  - Determine the role of immunopathology in HIV+ SCD
  - HIV tissue reservoirs for cure?
  - FDA postmortem pathologic surveillance: all deaths, perimortem remote transmissions in VANCOF

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