Redefining Sudden Cardiac Death: Insights from the San Francisco Postmortem Systematic Investigation of Sudden Cardiac Death Study

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U.S. Mortality by Death Certificates

Etiology of Sudden Cardiac Death

Background

- Traditional SCD definitions are based on:
  - Death certificates
  - EMS records (CARES)
  - Epidemiologic criteria (ACC/AHA/HRS, WHO, Hinkle-Thaler) which all presume cardiac cause
- Therefore, incidence of SCD estimates vary widely
- WHO criteria:
  - Witnessed: unexpected death within 1 h symptom onset
  - Unwitnessed: unexpected death within 24 h of having been observed alive and free of symptoms

RCTs, Cohorts: Sudden Cardiac Death

- ARIC, CHS:
  - “A sudden pulseless condition from a cardiac origin in a previously stable individual occurring OOH or in the ED. For unwitnessed deaths, the participant must have been seen within 24h of arrest in a stable condition and without evidence of a noncardiac cause.”
- MERIT-HF trial: Metoprolol for Heart Failure
  - “Witnessed instantaneous death in the absence of progressive circulatory failure lasting for 60 min or more, unwitnessed death in the absence of pre-existence progressive circulatory failure or other causes of 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

Emperor’s New Clothes?

- ~ 90% of SCDs occur out of hospital (OOH)\(^1\) in jurisdiction of coroner or medical examiner (ME)
- Investigation after such natural deaths is not routine ME practice. Autopsy rates
  - OOH deaths: ~10% (U.S.),\(^2\) 23% (Finland)\(^3\)
  - Hinkle-Thaler: 27%\(^4\)
- Exemplar autopsy studies demonstrating CAD as cause of > 80% of SCDs\(^5,6\) therefore limited by referral bias

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1. Nichol JAMA 2008
2. Shojania NEJM 2008
3. Lunetta Inj Prev 2007
4. Hinkle, Thaler Circulation 85, 1992
5. Virmani Circulation 85, 1992

The death of Antonin Scalia: Chaos, confusion and conflicting reports

MARFA, Tex. — 14 February 2016

In the cloistered chambers of the Supreme Court, Justice Antonin Scalia's days were highly regulated and predictable. He met with clerks, wrote opinions and appeared for arguments in the august courtroom on a schedule set months in advance.

Yet as details of Scalia's sudden death trickled in Sunday, it appeared that the hours afterward were anything but orderly. The man known for his elegant legal opinions and profound intellect was found dead in his room at a hunting resort by the resort's owner, who grew worried when Scalia didn't appear at breakfast Saturday morning.

It then took hours for authorities in remote West Texas to find a justice of the peace, officials said Sunday. When they did, Presidio County Judge Cinderela Giavara pronounced Scalia dead of natural causes without seeing the body — which is permissible under Texas law — and without ordering an autopsy.
Comprehensive Surveillance of SCD
▪ Oregon–SUDS (Chugh, JACC, 2004)
▪ WHO criteria
▪ Portland, OR: population 1,000,000
▪ Track dozens of ambulance companies and area hospitals
▪ Review of all available records
▪ SCA+SCD: 53/100,000

Autopsy rate: 11%

Sudden Cardiac Arrest vs. Sudden Cardiac Death
SCA
SCD?

Sudden “Cardiac” Death
SCA
CAD
Tamponade
Valvular
Neurologic
DCM
HCM
Ao Dissection
Hemorrhage
1° electrical disease
Sudden Arrhythmic Death

SCA
CAD
Tamponade
Valvular
Neurologic
DCM
DCM
Hemorrhage
Aortic Dissection
1st electrical disease

Case Adjudication

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

Adjudication panel

Dr. Phil Ursell
Chief Cardiac Pathologist
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

Reported to ME
All out of hospital and ER deaths reported by law to ME

Every Incident SCD
2011-

N = 12,671

Attended Deaths Ineligible for Autopsy
Active MD care < 3 wk, MD signed DC
N = 1,120

Non-Sudden Deaths
N = 1,031

Adjudicated Autopsied WHO-Defined SCDs 
N = 525

OHCA Deaths Referred for Autopsy
N = 912

Adjudication

Death Certificate Review

WHO-Defined SCDs w/o Autopsy
N = 105

Death in San Francisco County
N = 20,440

WHO-Defined SCDs (Suppl Table II)

Non-Natural Deaths
N = 3,330

CHD Deaths
N = 129

OHCA Deaths Referral Autopsy
N = 202

SAHD Deaths
N = 202

Non-Sudden Deaths
N = 5,135

Death Certificate

Death in San Francisco County
N = 20,440

WHO-Defined SCDs
N = 2,744

OHCA Deaths Excluded Deaths (Suppl Table I)

Non-Sudden Deaths
N = 5,135

Death Certificate

Death in San Francisco County
N = 20,440

WHO-Defined SCDs
N = 2,744

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Death Certificate
SCD Case Study #1

- 74 yo Filipino gentleman
  - 4 V CABG 2002
  - EF 22%, fixed defect anterior, inferior walls
  - Diabetes
- Admitted for fever and bronchitis, receiving IV antibiotics
- Troponin negative, slightly fluid overloaded
- Called to consult on several asymptomatic runs of NSVT (5-7 beats) and to consider primary prevention ICD

SCD Case Study #1

- Recommended uptitration of ß blocker, ICD implant as an outpatient after completing antibiotic treatment
- ICD scheduled for 1 month after discharge
- 2 weeks later patient found dead in the morning by wife
- Pt had returned to usual state of health, no complaints the night before

“Non-Cardiac SCD”

- Autopsy: 2.5 L fresh blood in stomach and duodenum
- Heart: no acute coronary lesions
- Cause of death: exsanguination
- ICD would not have prevented SCD, pt may not have survived procedure

Adjudicated Etiologies of SCD

- N=525
  - Cardiac, Arrhythmia (143) N=248 (47.5%)
  - Cardiac, Non-Arrhythmia N=122 (46%)
  - Non-Cardiac N=23 (42%)

- Acute Myocardial Infarction
  - N=134 (26%)
- Cardiac, Non-Arrhythmia
  - N=122 (46%)
- Non-Cardiac
  - N=23 (42%)

- Other Non-Cardiac
  - N=11 (2%)
- Other
  - N=17 (3.3%)

- Acute CHF
  - N=5 (1%)
3 hours later wife found him unresponsive

Primary prevention ICD implanted 3 years ago, no shocks

Asystole on arrival, no shocks

Paramedics called, asystole on arrival, no resuscitation attempted

SCD Case Study #2

- 78 yo Asian man
  - Dilated cardiomyopathy, stable EF 25%
  - Paroxysmal AF, on warfarin
  - Primary prevention ICD implanted 3 years ago, no shocks

- In usual state of health when wife went shopping
- 3 hours later wife found him unresponsive

In review...
**ICD Interrogation**

- VF ≠ Sudden Arrhythmic Death
  - At autopsy
    - Massive subarachnoid hemorrhage (requires perfusing rhythm)
    - Heart 760 g
  - Neurocardiogenic injury
    - VF due to acute adrenergic surge
  - Despite rhythm documentation of VF, cause of death was neurologic

**Sudden Neurologic Death: 2nd largest Non-cardiac Cause**

- Risk of SND higher in women and non-whites (p<0.01)
- Mostly intracranial hemorrhages but also stroke and SUDEP
- Antiplatelet or AC associated with ICH among noncardiac deaths (OR 6.0 [95% CI 1.5–24.8], p = 0.01) and overall (OR 3.9 [95% CI 1.01–15.5, p = 0.05)
- Up to 25,000 SNDs missed annually in U.S.
- 50% increase in fatal ICH incidence in U.S. annually
SCD Case Study #3

• 46 yo Hispanic man with well-controlled HIV disease (CD4 1000, VL <50)
• Compliant with HAART and statins
• Without complaint, found dead by his roommate 1 hour after last seen well

HIV Increases Risk of Fibrosis and SCD

• 760 g heart
• Pulmonary edema
• 2V CAD
• 50% LAD, 60% LCx
• Dense transmural and interstitial fibrosis
SCD Case Study #4

- 74 yo Caucasian man with CAD, PPM for CHB
- Gen change scheduled for 5 weeks after ERI
- Did not show up to UCSF EP lab morning of procedure: died in sleep

Autopsy negative (no acute MI, PE, or bleed)

**Battery Status**

<table>
<thead>
<tr>
<th>Estimated remaining longevity: 6 months, &lt; 1-13 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Based on Past History</td>
</tr>
<tr>
<td>Voltage/Impedance</td>
</tr>
<tr>
<td>AS - VS 2.2%</td>
</tr>
<tr>
<td>AS - VP 0.7%</td>
</tr>
<tr>
<td>AP - VS 2.3%</td>
</tr>
<tr>
<td>AP - VP 94.9%</td>
</tr>
</tbody>
</table>

Ventricular High Rate Episodes: 0

Current Postmarket Surveillance of CIEDs

- >3 million in U.S. alone have a PPM or ICD
- Manufacturer and User Facility Device Experience (MAUDE) is mandatory for manufacturers, voluntary for healthcare providers
  - Major limitation is that it generally captures patients under active care who by definition are alive
  - No mandatory surveillance of devices exists for patients who die to determine the role of CIED failure
  - Vast majority of SCDs with CIEDs do not get investigated

Sudden Death in Patients with CIEDs

- SCD without CIED (17%, 95.5%)
- SCD with CIED (22.43%)
- CIED Concern (11, 50%)
- No CIED Concern (11, 50%)
Sudden Death in Patients with CIEDs

- 1% SCDs w/ device malfunction
- 50% CIED Concern (11, 55%)
- 4.3% SCD w/o CIED
-~1% SCDs w/ device malfunction

Tseng ZH, Hayward R, Clark N et al

JAMA - IM 2015

- Improper device selection
- VT programming: delayed VF detection, ATP in VF zone
- Opportunities for MD practice improvement: device selection, programming

Tseng ZH, Hayward R, Clark N et al

JAMA - IM 2015

ICD Lead Fracture During Shock

- Improper device selection
- VT programming: delayed VF detection, ATP in VF zone
- Opportunities for MD practice improvement: device selection, programming

Tseng ZH, Hayward R, Clark N et al

JAMA - IM 2015

Missed VF on Postmortem ICD Interrogation

- 76 M ischemic CM, AF
- Autopsy: Anterior LV scar, no acute MI

Tseng ZH, Hayward R, Clark N et al

JAMA - IM 2015
Reframing the World Health Organization Definition
Predicting Autopsy-Defined Sudden Arrhythmic Deaths Among
Presumed Sudden Cardiac Deaths in the POST SCD Study

BACKGROUND: Conventional definitions of sudden cardiac death (SCD) assume cardiac cause. We studied the World Health Organization defined SCDs autopsied in the POST SCD study (Postmortem Systematic Investigation of SCD) to determine whether premonition characteristics could identify autopsy-defined sudden arrhythmic death (SAD) among presumed SCDs.

CONCLUSIONS: Our models identify premonition characteristics that can better specify autopsy-defined SAD among presumed SCDs and support the World Health Organization definition can be improved by restricting witnessed SCDs to ventricular tachycardia/ventricular fibrillation or non-sustained electrical activity rhythms and unwitnessed cases to <1 hour since last normal, at the post-mortem.

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Teng, ZH…., Vittinghoff E.
Circ A&E 2019

https://ucsfhealthcardiology.ucsf.edu/sites/ucsfhealthcardiology.ucsf.edu/files/2018-08/SADCalculation.xlsx

Magnitude of Sudden Cardiac Death in the U.S.

Teng, ZH…., Vittinghoff E.
Circ A&E 2019

https://ucsfhealthcardiology.ucsf.edu/sites/ucsfhealthcardiology.ucsf.edu/files/2018-08/SADCalculation.xlsx
Conclusions

- Half of conventionally defined SCDs in an entire metro area were autopsy-defined SAD
  - PPV WHO criteria for SAD: 55.8%, OHCA: 48.6%
  - <50% SAD in women
  - >50% had no cardiac history
  - 98% of SADs had structural heart disease
  - SAD incidence rates vary widely by sex and race
    - Black males highest risk, Hispanic females lowest
  - Most common non-SADs: Occult OD, neurologic, CIEDs
  - CAD 1/3 overall SCD and 58% of SADs
  - Cardiomyopathy and hypertrophy: 1/3 of SADs
  - Cardiac mass increased risk for non-SAD and SAD

Implications

- The emperor is half naked: Conventionally defined SCDs should be considered “presumed SCDs”
- Further investigation in minority groups and women
- To reduce overall public health burden of SCD, in addition to CAD, efforts also should be directed towards screening, treating, and preventing non-arrhythmic causes (OD, neurologic diseases), hypertrophy, cardiomyopathy, and CIED problems
- SCD cohorts for genetic and molecular association studies need refinement of phenotype
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• All victims of SCD and their families in San Francisco County

Next Steps

• Molecular association studies and family risk stratification

• Precision EMS protocols

• SND: SUDEP, hemorrhage risk with anticoagulants, anti-platelets

• HIV tissue reservoirs for cure?

• FDA postmortem postmarket surveillance: all deaths, other municipalities

• Workup occult renal failure in infants

Incident SCDs in the San Francisco POST SCD Study, 1/1/11 - 11/30/13
N=517
SCDs with CIEDs*
N=22 (22/517, 4.3%)
PPM SCDs
N=14
ICD SCDs
N=8
Device concern
N=7 (7/8, 87.5%)
Device concern
N=4 (4/14, 28.6%)
No device concern
N=10
Terminal rhythms:
VF (N=3)
PEA (N=2)
Unknown (N=2)
Other (N=3)
Hardware Failure
N=3
Improper Device Selection
N=1
No device concern
N=1
Patient with an Indication for an ICD died from VF
Rapid battery depletion with presumed asystole or profound bradycardia (N=1)
Rise in RV lead impedance prior to death with polymorphic VT/VF on device interrogation (N=1)
Rapid rise in lead impedance prior to death in a patient with pneumonia. Lead fracture or a global pacemaker circuit issue could not be excluded (N=1).
Terminal rhythm: VF; COD: Subarachnoid hemorrhage
N=1
Hardware Failure
N=1
Undersensing/failure to detect VF
N=5
Programming issue
N=1
RV lead fracture while delivering shock for VF
Undersensing/failure to detect VF only (N=3)
Delay to shock due to unsuccessful ATP in VF zone (device algorithm issue) and undersensing of VF (N=2)
VT slower than lower limit of VT zone

SCDs without CIEDs
N=495 (495/517, 95.7%)
San Francisco ICD Population, 1/1/11 - 11/30/13
N=712
ICD Deaths
N=109 (109/712, 15.3%)
Survived
N=603 (603/712, 84.7%)
Non-Sudden Deaths
N=101
Tseng ZH, Hayward R, Clark N et al
JAMA-IM 2015
Sudden Cardiac Death in Patients With Human Immunodeficiency Virus Infection
Zuo X, Tseng, MD*, Eric A. Swanson, MD, David Doocy, MD, PhD, Sc.M.
Eric Vittinghoff, PhD, MPH, et al
San Francisco, California, and Baltimore, Maryland
In Vivo Ventricular tachycardia and fibrillation
Lead placement in patients with severe fibrosis and dilated cardiomyopathy
In Vivo Assessment of Ventricular Tachycardia and Fibrillation in Patients With Severe Cardiac Fibrosis

Heart Rhythm Disorders
Heart Trouble Early and Often in H.I.V. Patients

Health
Mortality Rates by Cause and Year

- 230 deaths over 3.7 median years' follow-up.
- 13% SCDs, 86% (30/35) of all cardiac deaths.
- Mean HIV SCD rate: 2.6/1,000 PY (95% CI 1.8-3.8), 4.5-fold higher than background HIV-SCD rate.

Tseng ZH et al. JACC 2012 59(21):1891-6