

Sudden neurologic death masquerading as out-of-hospital sudden cardiac death



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ABSTRACT

Objective: To characterize the frequency of and risk factors for out-of-hospital sudden neurologic deaths.

Methods: During the initial 25 months (February 1, 2011–March 1, 2013) of the San Francisco Postmortem Systematic Investigation of Sudden Cardiac Death Study, we captured incident WHO criteria sudden cardiac deaths (SCDs) through active surveillance of consecutive out-of-hospital deaths, which must be reported to the medical examiner by law. All cases were referred for full autopsy with detailed examination of the heart and cranial vault, toxicology, and histology. A multidisciplinary committee adjudicated a final cause of death.

Results: Of 352 incident SCDs, 335 (95%) underwent systematic evaluation including full autopsy. Of these 335 cases, 18 (5.4%) were sudden neurologic deaths (mean age 60.6 years [SD 17.6, range 27–87]; 67.7% female), which accounted for 14.9% of the 121 noncardiac sudden deaths. The risk of sudden neurologic death compared to non-neurologic SCD was lower in male and white participants ($p < 0.01$). Neurologic causes included intracranial hemorrhage (8), sudden unexpected death in epilepsy (6, including 2 with juvenile myoclonic epilepsy), aneurysmal subarachnoid hemorrhage (2), acute ischemic stroke (1), and aspiration from Huntington disease (1). Most deaths were unwitnessed (16; 89%) with asystole at presentation (17; 94%). Prior stroke/TIA was not associated with risk of stroke (odds ratio [OR] 1.4 [95% confidence interval (CI) 0.18–11.8], $p = 0.73$), but antithrombotic medication use was (OR 3.9 [95% 1.01–15.5], $p = 0.05$).

Conclusions: Sudden neurologic death is an important cause of out-of-hospital apparent SCDs. Low prevailing autopsy rates may result in systematic misclassification of apparent SCDs and underestimation of the incidence of sudden neurologic death. *Neurology*® 2016;87:1669–1673

GLOSSARY

CI = confidence interval; OR = odds ratio; SCD = sudden cardiac death; SUDEP = sudden unexpected death in epilepsy.

Sudden cardiac death (SCD) is defined as a sudden unexpected death occurring within 1 hour of symptom onset for witnessed events, or within 24 hours of being observed symptom-free for unwitnessed events.¹ By this definition, there are 184,000 to 450,000 sudden cardiac deaths in the United States annually and more than 90% occur out of the hospital.² Since complete autopsies are uncommon and investigations for these natural deaths are limited, a cardiac cause is often assumed and cerebrovascular deaths or sudden unexpected death in epilepsy (SUDEP) could be missed. Therefore, we conducted complete autopsies and systematically evaluated consecutive out-of-hospital SCDs as part of the Postmortem Systematic Investigation of Sudden Cardiac Death (POST SCD) Study.³

METHODS From February 2011 to March 2013, through active, real-time surveillance of all medical examiner cases, we identified all incident SCDs within the city and county of San Francisco.³ State law mandates reporting all out-of-hospital deaths to the medical examiner.¹ All cases were referred for systematic and comprehensive evaluations, including full autopsies, toxicology, and detailed heart and cranial vault examinations. A multidisciplinary committee of cardiologists and cardiac electrophysiologists, anatomic and forensic

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Table 1 Characteristics of sudden cardiac deaths (SCD), sudden neurologic deaths (SND), non-neurologic sudden deaths, and adult San Francisco population

	All SCD	SCD non-neurologic	SND	p Value, ^a SND vs non-neurologic	Adult San Francisco population
No.	336	318	18		725,225
Age, y, mean ± SD	62.9 ± 14.6	63.0 ± 14.4	60.6 ± 17.6	0.50	—
Male, n (%)	233 (69.4)	227 (71.4)	6 (33.3)	0.001	369,865 (51)
Race, n (%)					
Asian	81 (24.1)	74 (23.3)	7 (38.9)	0.16	253,829 (35)
Black	52 (15.5)	48 (15.1)	4 (22.2)	0.50	43,514 (6)
Hispanic	26 (7.7)	23 (7.2)	3 (16.7)	0.15	108,783 (15)
White	171 (50.9)	167 (52.5)	4 (22.2)	0.01	304,595 (42)
Other	6 (1.8)	6 (1.9)	0 (0)	0.99	14,504 (2)

^aFor age, t test assuming unequal variance; for categorical, Fisher exact test.

pathologists, and a neurologist adjudicated the causes of death by consensus. Stata (StataCorp LP, College Station, TX) was used for all statistical analyses.

Standard protocol approvals, registrations, and patient consents. Local institutional review board approval with a waiver of informed consent was obtained for this study.

RESULTS Of 352 consecutive SCDs identified during the 25-month study period, 335 (95.2%) underwent a systematic evaluation and full autopsy (table 1). Of these 335 cases, 18 (5.4%) had an acute neurologic cause of death (table 2). Sudden neurologic death

accounted for 15% (18 of 121) of all noncardiac deaths, and was the most common noncardiac cause of sudden death after drug overdose. The risk of sudden neurologic death compared to non-neurologic sudden cardiac death was lower in male ($p = 0.001$) and white participants ($p = 0.01$). Sudden neurologic deaths were typically unwitnessed (16; 89% vs 74%; $p = 0.26$) and had asystole at initial presentation (15; 83% vs 79%; $p = 0.14$).

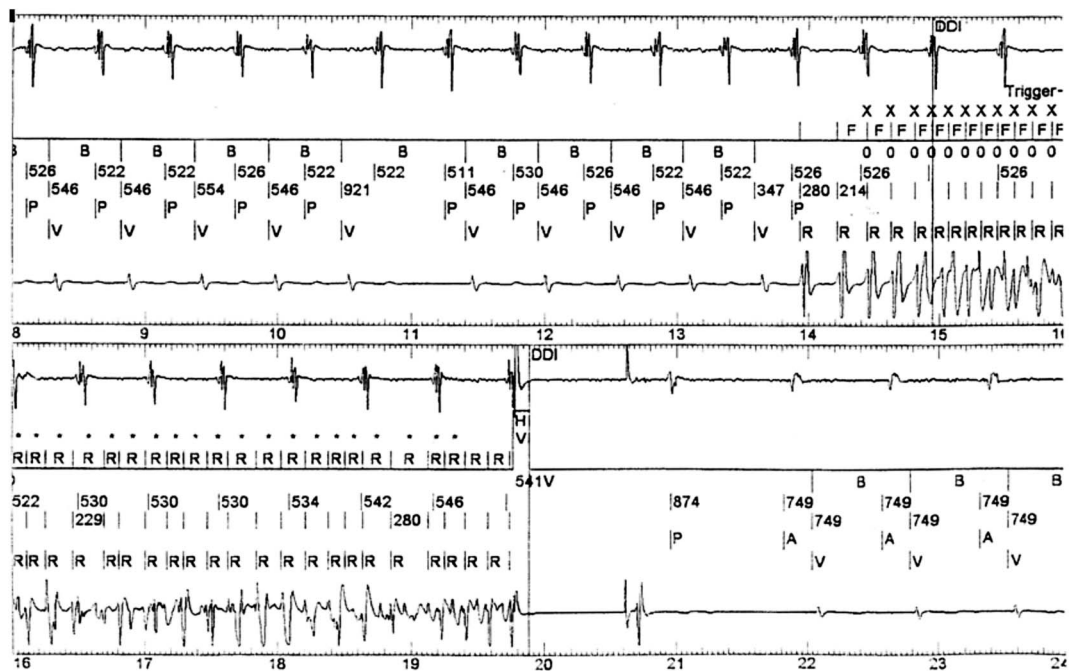
Most intracerebral (6/8) and subarachnoid (1/2) hemorrhage deaths occurred while on antiplatelet or

Table 2 Consecutive cases of sudden neurologic death in San Francisco (February 1, 2011–March 1, 2013)

Case no.	Age, y	Sex	Ethnicity	Cause of death	Location of lesion	Witnessed event	Initial presenting rhythm
1	59	M	White	Aneurysmal subarachnoid hemorrhage	Left anterior communicating artery	No	Ventricular fibrillation
2	77	F	Asian	Aneurysmal subarachnoid hemorrhage	Left anterior communicating artery	No	Asystole
3	60	F	Black	Intraventricular hemorrhage	Lateral ventricle	No	Asystole
4	70	F	Black	Intracerebral hemorrhage	Pons	Yes	Asystole
5	47	M	Asian	Intracerebral hemorrhage	Right basal ganglia	No	Pulseless electrical activity
6	87	F	White	Intracerebral hemorrhage	Right basal ganglia	No	Atrial fibrillation
7	75	F	Asian	Intracerebral hemorrhage	Right basal ganglia	No	Asystole
8	72	F	Asian	Intracerebral hemorrhage	Left basal ganglia	No	Asystole
9	58	M	Hispanic	Intracerebral hemorrhage	Left basal ganglia	No	Asystole
10	81	F	Asian	Intracerebral hemorrhage	Right basal ganglia	No	Asystole
11	85	F	Asian	Acute ischemic stroke	Left middle cerebral artery	No	Asystole
12	49	M	Asian	Huntington disease		No	Asystole
13	48	F	Hispanic	SUDEP		No	Asystole
14	31	F	White	SUDEP		No	Asystole
15	54	M	Black	SUDEP		Yes	Asystole
16	67	F	Black	SUDEP		No	Asystole
17	27	F	White	SUDEP		No	Asystole
18	43	M	Hispanic	SUDEP		No	Asystole

Abbreviation: SUDEP = sudden unexpected death in epilepsy.

Figure Postmortem interrogation of an implantable cardioverter-defibrillator (ICD) from a 59-year-old man with history of heart failure and unwitnessed sudden death found to have aneurysmal subarachnoid hemorrhage on autopsy



This representative intracardiac ECG demonstrates intrinsic sinus (P) with paced ventricular (V) rhythm degenerating to ventricular fibrillation (R), which was recognized by the ICD and treated with a 35 J shock, restoring atrial-ventricular (AV) paced rhythm. Ventricular fibrillation recurred shortly thereafter and was treated with >30 ICD shocks until the battery of the device was depleted.

anticoagulant therapy. One ischemic stroke death occurred in an 85-year-old woman with atrial fibrillation with an unwitnessed left middle cerebral artery stroke. Antiplatelet or anticoagulation use was associated with intracranial hemorrhage among noncardiac deaths (odds ratio [OR] 6.0 [95% confidence interval (CI) 1.5–24.8], $p = 0.01$) and overall (OR 3.9 [95% CI 1.01–15.5], $p = 0.05$). A history of stroke or TIA was not associated with hemorrhagic or ischemic stroke among noncardiac deaths (OR 1.1 [95% CI 0.13–9.8]; $p = 0.92$) or overall (OR 1.4 [95% CI 0.18–11.8], $p = 0.73$). In one case, postmortem interrogation of an implantable cardioverter defibrillator demonstrated that the patient had been repeatedly shocked for ventricular fibrillation, but the full autopsy revealed that aneurysmal subarachnoid hemorrhage was the cause of death that secondarily led to neurogenic ventricular fibrillation (figure).

Of the 6 SUDEP cases, 3 had nonspecific cardiac findings (minor thickening of septal and posterior left ventricle and interstitial fibrosis) and 1 case had a witnessed seizure followed by asystole and apnea. Two cases were in young women with juvenile myoclonic epilepsy, including 1 who had recently stopped taking seizure medications. SUDEP cases were significantly younger than other sudden neurologic deaths and the cohort overall (mean age 45 years; SD 14.8;

range 27–67; $p = 0.001$ and $p = 0.002$, respectively).

A history of epilepsy was identified in 15 of 335 (4.5%) sudden deaths; 6 (40%) were SUDEP. Of the remaining 9 sudden deaths in epilepsy patients, 7 died of cardiac causes (2 hypertrophy, 2 cardiomyopathy, 1 chronic coronary artery disease, 1 acute coronary artery disease, 1 heart failure) and 2 had noncardiac deaths (1 intracranial hemorrhage, 1 incarcerated hernia). A history of epilepsy was associated with a substantially higher relative risk of sudden neurologic death compared to sudden cardiac death (relative risk 10.6, 95% CI 4.6–25.5; $p < 0.0001$). Similarly, 7.5% (25 of 335) sudden deaths had a history of at least 1 seizure, often in the setting of alcohol withdrawal; 24% (6 of 25) were SUDEP. For the 10 cases with history of seizure but not epilepsy, 5 died of cardiac causes, 1 had a pulmonary embolism, 1 had hemorrhage, and 3 had an overdose.

DISCUSSION In this comprehensive, population-based study of consecutive out-of-hospital apparent SCDs, 5.4% were due to an acute neurologic cause. These sudden neurologic deaths represented the largest group of noncardiac sudden deaths after drug overdose. The lower risk of sudden neurologic death compared to sudden cardiac death among male and

white participants and a corresponding trend toward increased risks in women and the fast-growing population of Asians and Hispanics may justify follow-up studies to evaluate whether greater vigilance is warranted for specific demographics. Prior estimates of out-of-hospital sudden death were derived from ethnically homogeneous populations with low autopsy rates (typically <15%) or were based on retrospective review of records from incomplete or selectively applied investigations.⁴ Moreover, in the rare cases when they are performed, autopsies for natural out-of-hospital deaths often exclude cranial vault or neuropathologic examination, thereby increasing the risk for misclassification.^{5,6}

Given that the case fatality rate for stroke is high, cerebrovascular deaths were not unexpected. Although stroke can cause death through direct mass effect, hydrocephalus, and herniation, especially when unwitnessed and untreated, neurocardiogenic pathways can also be involved. For instance, subarachnoid hemorrhage can cause characteristic electrocardiographic changes and a Takotsubo pattern of apical hypokinesis and cardiac injury (voodoo death) and increased intracranial pressure can cause autonomic changes and arrhythmias.⁷ For SUDEP, the mechanism of death may also include neurocardiogenic and neurorespiratory mechanisms.

Assuming that 5.4% of apparent SCDs are sudden neurologic deaths, as we found, then there are 10,000 to 25,000 sudden neurologic deaths in the United States annually.² Similarly, if half of the 2.3% of intracerebral hemorrhage deaths we observed were missed without a full autopsy, this would translate into 2,000 to 5,000 fatal intracerebral hemorrhages annually (a 30% increase in incidence).⁸ For aneurysmal subarachnoid hemorrhage, similar assumptions would result in an additional 500 to 1,300 fatal subarachnoid hemorrhages annually (a nearly 25% increase in incidence).⁹ For SUDEP, assuming a 1% prevalence of epilepsy among San Francisco adult population of 725,225, the 3.4 out-of-hospital cases per year we observed represents about half of the expected SUDEP cases, though our methods only capture out-of-hospital deaths.¹⁰

A failure to identify sudden neurologic deaths, particularly among those at high risk for SCD, has potential implications for interpreting the results in large cardiovascular trials. Those at high risk for SCD are often on antithrombotic therapy, which increases the risk of hemorrhage. Yet identifying intracerebral hemorrhage adverse outcomes among these clinical trial participants typically relies on the overburdened medical examiner and coroner's infrastructure, low prevailing autopsy rates, and unreliable death certificates. Although the limited number of outcomes in our study precludes a precise characterization of associated risk

factors, overall misclassification of these outcomes in cardiovascular clinical trials could shift balance of the relative risks and benefits of antithrombotic therapy.

Sudden neurologic death accounts for a substantial proportion of sudden deaths that would otherwise meet the widely applied epidemiologic definition of out-of-hospital SCD. Systematic autopsies of nearly every SCD in San Francisco over a 2-year period allowed for the accurate recognition of these neurologic causes and provide a framework for revising estimates of the incidence of acutely fatal neurologic events. These data may change public health estimates of disease burden and mortality attributed to SCD and to neurologic disorders in the general population, for women and certain race-ethnic subgroups in particular, and among high-risk participants in cardiovascular clinical trials.

AUTHOR CONTRIBUTIONS

Anthony Kim contributed to study conception and design, acquisition of data, drafting the manuscript, analysis and interpretation of data, and critical revision of the manuscript. Ellen Moffatt contributed to acquisition of data and critical revision of the manuscript. Philip Ursell contributed to acquisition of data and critical revision of the manuscript. Orrin Devinsky contributed to critical revision of the manuscript. Jeffrey Olgin contributed to acquisition of data and critical revision of the manuscript. Zian Tseng contributed to acquisition of study funding, study conception and design, acquisition of data, analysis and interpretation of data, and critical revision of the manuscript.

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DISCLOSURE

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Calcium supplementation and risk of dementia in women with cerebrovascular disease (see p. 1674)

This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the October 18, 2016, issue of *Neurology*. In the second segment, Dr. Jeff Burns talks with Dr. Silke Kern about her paper on whether calcium supplementation was associated with the development of dementia in women with cerebrovascular disease. Dr. Sarah Wesley reads the e-Pearl of the week about *MGMT* promoter methylation in glioblastoma. In the next part of the podcast, Dr. Ted Burns focuses his

interview with Dr. Matthew Glasser on a *Neurology Today*[®] story about a new brain map identifying previously unidentified brain areas and what it means for neurology.

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