Incidence of cardiac fibrosis in SUDEP and control cases

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Abstract

Objective

Since cardiac fibrosis was previously found more frequently in patients with sudden unexpected death in epilepsy (SUDEP) than control cases, we compared blinded and quantitative reviews of cardiac pathology in SUDEP to multiple control groups.

Methods

We adjudicated causes of death in epilepsy patients as part of consecutive out-of-hospital sudden cardiac deaths (SCDs) from the Postmortem Systematic Investigation of Sudden Cardiac Death (POSTSCD) study. Blinded cardiac gross and microscopic examinations were performed by forensic and cardiac pathologists.

Results

Of 541 SCDs over 37 months (mean age 62.8 years, 69% male), 525 (97%) were autopsied; 25/525 (4.8%) had epilepsy (mean age 56.4 years $\pm$ 15.4, range 27–92; 67% male). The 25 epilepsy patients died of definite SUDEP/definite SUDEP-plus ($n = 8$), possible SUDEP ($n = 10$), or other causes ($n = 7$). Comparison groups included autopsy-defined sudden arrhythmic death (SAD; $n = 285$) and trauma ($n = 104$) and we adjusted for age, sex, HIV, coronary artery disease, congestive heart failure, and cardiomyopathy in the analyses. Compared to SAD cases, SUDEP cases had less gross and histologic evidence of cardiac pathology; significant for cardiac mass ($p < 0.0011$), coronary artery disease ($p < 0.0024$), total cardiac fibrosis (CF) ($p = 0.022$), and interstitial CF ($p = 0.013$). Compared to trauma cases, SUDEP cases had similar cardiac pathology including CF.

Conclusion

Among SUDEP cases, cardiac pathology was less severe than in SAD cases but similar to trauma and epilepsy controls. Our data do not support prior studies finding elevated rates of CF among SUDEP cases compared to controls. Larger studies including molecular analyses would further our understanding of cardiac changes associated with SUDEP.

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Glossary

BMI = body mass index; **CAD** = coronary artery disease; **CF** = cardiac fibrosis; **CHF** = congestive heart failure; **LV** = left ventricle; **MI** = myocardial infarct; **NHLBI** = National Heart, Lung, and Blood Institute; **POSTSCD** = Postmortem Systematic Investigation of Sudden Cardiac Death; **SAD** = sudden arrhythmic death; **SCD** = sudden cardiac death; **SUDEP** = sudden unexpected death in epilepsy.

Sudden unexpected death in epilepsy (SUDEP) is the most common cause of epilepsy-related mortality but the mechanisms of lethality remain poorly understood.^{1,2} In the paradigmatic case, a young adult with chronic treatment-resistant epilepsy has a nocturnal convulsion that leaves him or her prone in a prolonged postictal state with impaired arousal, respiratory, and autonomic functions. Exceptions are common, since SUDEP can (1) afflict children, older adults, and individuals with few lifetime seizures; (2) occur during wakefulness, in the supine or lateral position; and (3) occur after a complex partial seizure or without seizure activity.^{3–5} The mechanisms of SUDEP are likely heterogeneous, and probably differ among and between paradigmatic and atypical cases; yet the pathophysiology has never been well-defined in any case.

Cardiac functional and structural pathology was considered a likely cause of SUDEP by early investigators,^{6–9} although 19th-century clinicians recognized potentially diverse mechanisms and their inability to identify a definite cause in any specific case. Cardiac pathologic abnormalities were reported in SUDEP cases, most commonly focal interstitial myocardial fibrosis. However, none of these studies employed blinded reviews to identify the presence and quantify the severity of cardiac fibrosis (CF). We examined the results of cardiac pathology from the Postmortem Systematic Investigation of Sudden Cardiac Death (POSTSCD) study,¹⁰ which systematically evaluated nearly every incident out-of-hospital sudden cardiac death (SCD) case in San Francisco County between February 2011 and March 2014, including complete autopsies and medical records.

Methods

POSTSCD study

Surveilling all cases referred to the medical examiner, the POSTSCD study identified all incident SCDs, ages 18–90 years.¹⁰ We excluded patients with other known causes of death (e.g., cancer, suicide). All cases underwent systematic and comprehensive evaluation, including full medical record review and autopsy with detailed heart and cranial vault examination. This study was approved by the local institutional review board with a waiver of informed consent.

Cardiac examinations

A standardized, extensive heart examination was performed. Each heart was weighed (cardiac mass) and indexed to body mass index (BMI) (cardiac mass index = cardiac mass/BMI).

Orthogonal dimensions of the atria and ventricles were recorded. Valves were examined for bicuspid aortic valve, aortic leaflet perforation, evidence of endocarditis, and severe aortic leaflet fibrosis/calcification that could indicate aortic stenosis. The thickness of the compact myocardium in the left ventricle (LV) was measured in 4 standard locations: septum 1 cm beneath the aortic valve, as well as posterobasal, lateral, and mid-anterior free wall. Right ventricular free wall thickness was also measured. From each of these 5 regions, hematoxylin & eosin–stained and trichrome-stained slides were studied.

Quantitative analysis of CF was performed on 12/18 SUDEP, 90/285 sudden arrhythmic death (SAD), and 57/104 trauma cases. The lack of quantitative analysis on all samples was based on resource limitations (time to process and analyze samples), and was not based on suspected or known cause of death. CF was quantified by digital image analysis of Masson trichrome-stained sections from standardized septal, anterior, inferior, and lateral LV free wall areas of each heart, using Aperio ImageScope (Leica, Buffalo Grove, IL) software's Positive Pixel Count algorithm. Total CF comprised interstitial, perivascular, replacement, and subendocardial fibrosis, and score was reported as a percentage of total slide tissue area for all sections. Interstitial and perivascular fibrosis was calculated by hand-selecting replacement fibrosis and quantified using Aperio ImageScope. Total replacement fibrosis was subtracted from total fibrosis, and interstitial and perivascular fibrosis score was a percentage for all sections.

Evaluation of coronary arteries and coronary artery disease

The epicardial surface was analyzed and the major extramural coronary arteries examined for abnormalities. Each coronary artery (left main, left anterior descending, left circumflex, right coronary artery) was cut in cross-section every 5 mm to demonstrate narrowed segments; calcification necessitated removal of the intact arteries for fixation and chemical decalcification before cross-sectioning. All segments with thrombi, substantial atherosclerotic plaque, or evidence of dissection were sampled for histology. The narrowest segment of each coronary artery was also sampled. The apical half of the heart was then cut in short axis cross-section to yield 4 to 5 one-centimeter-thick rings of ventricular muscle, and the remaining heart (at the base) was cut to open each chamber along the lines of blood flow. Each ring of ventricular myocardium was examined for acute myocardial infarct (MI) or scar denoting healed MI, and extent of infarction (scar dimensions were measured and classified as subendocardial,

transmural, or epicardial). Internally at the aortic valve, the coronary ostia at the sinuses of Valsalva were inspected for possible malformation. Acute coronary artery disease (CAD) had findings of plaque rupture or coronary thrombus in at least one coronary artery. Chronic CAD was an autopsy diagnosis defined as $\geq 50\%$ stenosis, stent of vessel, or evidence of coronary artery bypass grafting. Congestive heart failure (CHF) was diagnosed premortem, or cardiomyopathy and pulmonary edema on autopsy without known CHF premortem.

Epilepsy and SUDEP classification

We described the case details leading to classification of epilepsy vs acute symptomatic seizures, and epilepsy-related vs other causes of death.¹¹ The determination of probable and definite epilepsy was made independently by 2 epileptologists (O.D., D.F.) using International League Against Epilepsy criteria for epidemiologic studies and surveillance of epilepsy and relied on review of all medical records, family interviews, scene investigation, and autopsy report. SUDEP determination used the criteria of Nashef et al.¹² If there was any disagreement between the reviewers on epilepsy diagnosis or SUDEP determination, they discussed and agreed on a final determination. Details regarding the clinical and pathologic features of the SUDEP cases, including comorbidities of the possible SUDEP cases, were previously reported.²

Statistical analysis

Statistical analyses were performed with Stata (StataCorp LP, College Park, TX). We assessed differences in baseline covariates among the SUDEP, SAD, epilepsy non-SUDEP, and trauma death groups using linear regression for continuous outcomes, followed by *F* and *t* tests for overall and pairwise differences, and Fisher exact tests for categorical outcomes. In examining between-group differences in log-transformed fibrosis scores, we fit 3 linear models: (1) unadjusted, (2) adjusted for age and sex, and (3) adjusted for age, sex, HIV, CAD, CHF, and cardiomyopathy. A 2-tailed *p* < 0.05 was considered statistically significant.

Data availability

The raw data used for this study are part of the NIH R01 HL102090 (National Heart, Lung, and Blood Institute [NHLBI]) POSTSCD study and UCSF-CTSI UL1 TR000004 (National Center for Advancing Translational Sciences). The raw data for the CF findings are currently being analyzed for a separate article on cardiac findings in the overall (nonepilepsy) cohort. These data will be published subsequently and then the entire dataset will be in the public domain through the NHLBI.

Results

Of 541 SCDs over 37 months (mean age 62.8 years, 69% male), 525 (97%) were autopsied; 25/525 (4.8%) had epilepsy (mean age 56.4 years $\pm$ 15.4, range 27–92; 67% male), comprising 10.8% of 231 nonarrhythmic sudden deaths. Of

these, 39 (7.4% of autopsied SCDs) had a history of seizures: 25 with probable or definite epilepsy (6 definite SUDEP, 2 definite SUDEP-plus, 10 possible SUDEP; 7 died from other causes) and 14 with acute symptomatic seizures. Data on blinded quantified CF examinations were available for 5/8 definite SUDEP cases, 7/10 possible SUDEP cases, and 0/7 epilepsy patients who died from other causes. The lack of CF studies in the other cases reflects resource limitations and was applicable to controls as well (see below). We compared the frequency of clinical and cardiac pathologic findings among SUDEP cases (*n* = 18) and 3 comparison groups: epilepsy patients who died from other causes (*n* = 7), autopsy-defined SAD (*n* = 285; 90 had CF studies), and traumatic deaths (*n* = 104; 57 had CF studies). Demographic, clinical, and gross cardiac pathologic findings are summarized in table 1. There were no significant differences between the 18 SUDEP and 7 epilepsy non-SUDEP cases, although the latter group was on average 6 years older and had a nonsignificant increase in CAD (57% vs 22%). Comparing SUDEP cases and SAD cases, the latter group had greater cardiac pathology in almost every measure (table 1 and tables e-1 and e-2, [links.lww.com/WNL/AS48](https://www.lww.com/WNL/AS48)), with significant differences for cardiac mass (*p* < 0.0011), CAD (*p* < 0.0024), interstitial CF (*p* = 0.013; figure 1), and total CF (*p* = 0.022; figure 2). Comparing SUDEP cases and trauma cases, the severity of total and interstitial CF was similar (figures 1 and 2).

Discussion

Our prospective study with systematic blinded cardiac pathology from nearly every sudden death in an entire metro area over a 3-year period found no evidence for an increased frequency of total or interstitial CF among SUDEP cases compared to patients with SAD or traumatic deaths. When adjusted for age and sex, the combined (definite and possible) SUDEP group had a significantly lower frequency of CF and other cardiac pathologies than the SAD group. This contrasts with prior retrospective and unblinded studies that found elevated rates of CF among SUDEP cases.^{13,14} Compared to trauma controls, patients who died from SUDEP had similar degrees of CF and overall cardiac pathology.

Cardiac pathologies reported in SUDEP cases include interstitial fibrosis, mild to moderate myocyte hypertrophy, and arteriolar wall thickening.¹⁵ Although myocardial fibrosis disrupts the normal myocardial structure and may directly affect heart function and normal cardiac electrophysiologic conduction, increasing vulnerability to ventricular arrhythmias and potentially contributing to the cause of death, this histopathologic finding is also observed in diverse settings including normal aging without comorbid hypertension, myocarditis, drug use, and epilepsy.^{15,16} Interpretation of these cardiac findings depends on the methodology to identify and quantify fibrosis, myocyte hypertrophy, and arteriolar wall thickening as well as the selection of the control group. The prevalence of cardiac risk factors in SUDEP and control groups was not matched (e.g., history, duration and severity of

Table 1 Demographic and gross cardiac pathology in sudden unexpected death in epilepsy (SUDEP) cases and controls

	All SUDEP	Autopsy-defined SAD	Trauma death	Overall ANOVA, <i>p</i> value ^a	<i>p</i> Value ^a all SUDEP vs autopsy-defined SAD	<i>p</i> Value ^a all SUDEP vs trauma death
N	12	90	57	—	—	—
Age, y	55.17 ± 17.23	61.73 ± 14.68	51.39 ± 18.65	0.00118	0.20	0.47
Male	8 (67)	74 (82)	42 (74)	0.27	—	—
BMI	26.17 ± 3.03	30.72 ± 9.72	27.22 ± 5.05	0.0174	0.077	0.69
Heart weight, g	446.67 ± 155.41	571.61 ± 158.20	391.93 ± 108.85	<0.0001	0.00484	0.23
Cardiac mass index	17.15 ± 5.35	19.20 ± 4.66	14.53 ± 3.41	<0.0001	0.12	0.058
Cardiac mass index adjusted for age	17.18 ± 2.47	19.15 ± 0.93	14.61 ± 1.16	<0.0001	0.14	0.065
Congestive heart failure	1 (8)	24 (27)	1 (2)	<0.0001	0.29	0.32
Coronary artery disease	2 (17)	52 (58)	7 (12)	<0.0001	0.0115	0.65
Anterior LV compact thickness, cm	1.46 ± 0.33	1.67 ± 0.50	1.62 ± 0.44	0.33	—	—
Posterior LV compact thickness, cm	1.43 ± 0.37	1.57 ± 0.44	1.38 ± 0.34	0.03	0.24	0.75
Lateral LV compact thickness, cm	1.47 ± 0.44	1.58 ± 0.38	1.50 ± 0.40	0.43	—	—
LV septal compact thickness, cm	1.46 ± 0.33	1.67 ± 0.50	1.62 ± 0.44	0.33	—	—
LAD stenosis, %	15.42 ± 30.56	28.1 ± 34.62	4.21 ± 16.14	<0.0001	0.16	0.23
LAD adjusted for age	15.73 ± 16.38	26.83 ± 6.12	5.04 ± 7.70	0.000164	0.21	0.24

Abbreviations: ANOVA = analysis of variance; CHF = congestive heart failure; CMI = cardiac mass index; LAD = left anterior descending coronary artery; LV = left ventricle; SAD = sudden arrhythmic death (no history of seizures).

Values are mean ± SD or n (%).

^a Medical histories were updated to reflect additional records collection since previous publication.

hypertension, hyperlipidemia, smoking). Thus, the increased frequency of cardiac abnormalities in SUDEP cases may relate to the direct or indirect effects of seizures or antiseizure drugs on cardiac tissue, the mechanisms that cause SUDEP, or they may be unrelated to seizures, medications, or SUDEP.

Savelyeva,¹⁷ in a Russian-language article, divided cardiopathologic changes in patients who died during a seizure or status epilepticus into 3 groups: (1) sudden death (acute enlargement of heart chambers, microhemorrhages, stromal edema, muscle fiber fragmentation); (2) diseases accompanying epilepsy (e.g., atherosclerosis); (3) likely seizure-induced (hemocirculation disorders, small foci of necrobiosis and cardiac muscle necrosis, and small fibrous scars). The author attributed necrotic areas to metabolic effects of repeated seizures.

A systematic review of the English-language literature identified 11 pathologic series or case reports over the last 35 years, comprising 288 SUDEP cases: ~25% had gross or microscopic cardiac abnormalities.¹⁵ These studies had multiple methodologic limitations including lack of standardized, systematic methods and diagnostic criteria. Cardiac weights were similar among SUDEP and controls.¹⁸ The most common histopathologic changes were interstitial CF in 44/134

(32.8%; range 11%–57%) cases in which cardiac histopathology was reported.^{9,15,19} Prior studies were limited by the lack of formal criteria used to diagnose SUDEP and cardiac pathologies such as CF, small sample sizes, lack of blinding, and for some, inclusion of possible SUDEP cases among non-SUDEP controls.^{15,18}

Two case-control studies investigated 22 SUDEP cases and 28 controls and found CF more frequently among SUDEP than control cases. In one study,¹³ controls were age- and sex-matched, derived from a mixed group of patients without a history of epilepsy who died from noncardiac causes. It is likely that some possible SUDEP as well as definite SUDEP-plus cases comprised the SUDEP group since the criteria employed did not distinguish subtypes of SUDEP.²⁰ These authors postulated that recurrent seizures cause hypoxia or apnea, and induce scarring via an ischemia–reperfusion injury, which induces myocardial cell loss and interstitial CF. The second study¹⁴ used blinded pathologic reviews and an age-/sex-matched control group of drug overdoses and suicide by hanging. Abundant (n = 67) reversible (myocyte vacuolization) lesions were found in 5/7 epilepsy cases and occasional (n = 22) irreversible (perivascular and less often interstitial fibrosis) lesions were found in 4/7 epilepsy patients. None of the 13 control cases had “reversible or irreversible” cardiac

Figure 1 Total fibrosis

	All SUDEP vs autopsy-defined SAD	All SUDEP vs trauma death
Model 1: Unadjusted	0.0218	0.73
Model 2: Adjusted for age and sex	0.022	0.67
Model 3: Adjusted for age, sex, HIV, CAD, CHF and cardiomyopathy	0.089	0.64

Total cardiac fibrosis in sudden unexpected death in epilepsy (SUDEP) cases and controls. CAD = coronary artery disease; CHF = congestive heart failure; SAD = sudden arrhythmic death (no history of seizures).

Figure 2 Interstitial and perivascular fibrosis

	All SUDEP vs autopsy-defined SAD	All SUDEP vs trauma death
Model 1: Unadjusted	0.0153	0.49
Model 2: Adjusted for age and sex	0.0133	0.45
Model 3: Adjusted for age, sex, HIV, CAD, CHF and cardiomyopathy	0.054	0.42

Interstitial cardiac fibrosis in sudden unexpected death in epilepsy (SUDEP) cases and controls. CAD = coronary artery disease; CHF = congestive heart failure; SAD = sudden arrhythmic death (no history of seizures).

pathology. Thus, 89 lesions were found in 7 epilepsy cases and no lesion was found in 13 controls.

The differences between our CF findings and the prior case-control studies most likely reflect differences in the control groups and criteria to diagnose SUDEP and CF. Although our SUDEP cases were younger than the SAD group, we adjusted for age, sex, HIV, CAD, CHF, and cardiomyopathy.

The frequency of CF in our controls was much higher than in the 2 prior studies, probably because our controls consisted of SAD and trauma deaths, while the other studies used non-cardiac deaths among patients without epilepsy¹³ or drug overdose/hanging deaths.¹⁴ Overall, we found greater cardiac pathology (total and interstitial CF, cardiac mass, CAD) in SAD than SUDEP cases. SAD patients were slightly older (mean, 5.6 years) and had greater BMI (mean, 4.7) than SUDEP cases. This can account for the increased cardiac mass in the SAD group, since the cardiac mass index was non-significantly higher in the SAD than SUDEP cases. The SAD group had greater CF than the SUDEP group when adjusted for age and sex. The greater severity of CAD in the SAD group, as well as arrhythmias leading to hypoxia and cardiac

injury, could have produced a greater CF. However, our trauma controls had similar (nonsignificantly increased) amounts of total and interstitial CF compared to the SUDEP cases. These trauma cases represent a valid control group and more strongly support that SUDEP cases did not have increased cardiac pathology relative to the general population. Notably, other series of drug overdose found cardiac pathology in many cases^{21–23}; in one series, 97% of drug overdose cases had pathologic changes in the heart.²⁴ In another series of 851 autopsies of drug addicts, cardiac lesions were common, especially after age 30, including CF and acute ischemia.²³ Younger average ages of SUDEP cases (25 and 40 years) and controls (25 and 38 years) in the 2 other case-control studies vs our SUDEP cases (55 years) and controls (62 years in SAD and 51 years in trauma cases)^{13,14} may partially account for the lower frequency of CF in controls than our series. However, the absence of CF among the controls differs substantially from other comparable series, suggesting other methodologic issues.

Our SUDEP cases had a nonsignificant increase in higher cardiac mass index than trauma controls but not epilepsy controls. The relatively small number of cases and large SD in the SUDEP group may have contributed to these differences.

Other possible differences include long-term effects of anti-seizure drugs^{25,26} or recurrent sympathetic activation during seizures.²⁷ It would be worthwhile to study cardiac mass index among epilepsy patients and noncardiac controls.

A limitation of our study, like of prior studies, was small sample size. We had quantitative measures of CF for 5 definite and 7 possible SUDEPs while our comparison groups were much larger. It is possible that cardiac pathology is a significant factor in a minority of SUDEP cases. It is possible that convulsive or nonconvulsive seizures with prominent sympathetic activation could induce cardiac structural changes. Seizures often induce electrocardiographic changes²⁸ and rarely can induce Takotsubo cardiomyopathy.¹⁵ Further, terminal hypoxia may contribute to cardiac pathologies in drug overdoses, SAD, trauma, as well as SUDEP cases. However, CF cannot be explained by acute hypoxia. Finally, we did not perform genetic studies in these cases. Some SUDEP cases may have had pathogenic variants in cardiac genes associated with arrhythmia and sudden death (e.g., *RYR2*, *SCN5A*).

A larger group of definite SUDEP and inclusion of diverse controls with other causes of death (e.g., epilepsy from non-SUDEP/noncardiac death, SAD, trauma, and drug overdose) in a prospective, blinded study would greatly contribute to our understanding of cardiac pathology. Nevertheless, our study suggests that the presence and severity of cardiac pathology is not higher among SUDEP cases compared to age- and sex-matched controls who died from SAD or trauma, nor to epilepsy patients who died from causes other than SUDEP.

Author contributions

Orrin Devinsky contributed to study conception and design, analysis and interpretation of data, and critical revision of the manuscript. Anthony Kim contributed to study conception and design, to acquisition of data, drafting the manuscript, analysis and interpretation of data, and critical revision of the manuscript. Annie Bedigian assisted with statistical analysis and preparation of tables and figures. Daniel Friedman assisted in the statistical analysis, interpretation of data, and preparation of tables and figures. Ellen Moffatt contributed to acquisition of data and critical revision of the manuscript. Zian H. 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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