

Sudden Unexpected Death in Epilepsy

Is Death by Seizures a Cardiac Disease?

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Results: Sudden unexpected death in epilepsy (SUDEP) gains more and more acknowledgment across the various interdisciplinary fields. Accordingly, we performed in a prospective setting a case-control study of all SUDEP cases in a well-defined part of Denmark (Northern Jutland), between January 1998 and September 2000.

We attempted to look into the cardiopathologic mechanism behind this phenomenon by assessing the degree of myocardial fibrosis in SUDEP patients versus controls.

The histologic evaluation was possible in 65% of the cases (15/23) whose death was attributed to SUDEP and in 71% (15/21) of controls. Forty percent of the SUDEP cases (6/15) presented several foci of fibrotic changes in the deep and subendocardial myocardium in contrast to 1 control (6.6%, $P = 0.03$). None of the subjects from the SUDEP group showed fibrotic changes in their conduction system as compared with 1 control (6.6%). The quantitative evaluation of fibrosis demonstrated a trend toward more fibrosis in the deep and subendocardial myocardium of the SUDEP cases. Forty percent of cases in the SUDEP group were men (6/15), characteristically young at time of death (mean age 38 years) and with a late epilepsy onset (mean age 21 years). Antemortem, 73% of the SUDEP patients (11/15) had experienced infrequent seizures (self-reported).

We conclude that the SUDEP cases displayed significant fibrosis of the myocardium when this was assessed by qualitative means. This fibrosis may be the consequence of myocardial ischemia as a direct result of repetitive epileptic seizures, which, associated with the ictal sympathetic storm, may lead to lethal arrhythmias.

Key Words: epilepsy, SUDEP, infrequent epileptic seizures, seizure concealment, myocardial fibrosis, myocardial ischemia, atherosclerosis, AED, hypoxia

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Sudden unexpected deaths in epileptic persons (SUDEP) are not rare events, most commonly encountered by the forensic pathologists rather than the clinician.^{1,2} SUDEP accounts for 5% to 30% of deaths in epileptic individuals.³ Excluding such causes as drowning, suicide, and aspiration, the ultimate reason for SUDEP is assumed to be cardiac arrhythmia, occurring on a background of myocardial fibrosis and a storm of sympathetic activity caused by epileptic seizures.^{4,5} Of note are the findings from few contemporary studies revealing patchy subendocardial fibrosis in otherwise normal hearts of epilepsy patients.^{4,6} Moreover, this pathologic finding is consistent with the theory that most presumed and actual causes of death are cardiovascular.⁷

Accordingly, the present study assessed for the first time in a prospective setting the occurrence of pathologic fibrosis of the myocardium and of the cardiac conduction system in SUDEP patients, as determined by qualitative and quantitative means.

MATERIALS AND METHODS

In Northern Jutland, Denmark, autopsy cases of sudden deaths among individuals with epilepsy were prospectively studied during the period January 1, 1998, to September 1, 2000. The material was collected sequentially by the Department of Forensic Medicine, Aarhus University.

In the enrollment of our cases, the internationally accepted definition of SUDEP⁸ was employed to ascertain whether or not the SUDEP concept was applicable. Accordingly, SUDEP was considered when a sudden, unexpected witnessed or unwitnessed nontraumatic and nondrowning death occurred in patients with epilepsy, with or without evidence of a seizure and excluding documented status epilepticus, in which postmortem examination did not reveal a toxicological or anatomic cause.⁸

An age- and gender-matched control group was selected from a consecutive nonepileptic material from the same period consisting of persons who had died of accidents, suicides, homicides, or other causes of noncoronary sudden unexpected death (pulmonary embolism, meningitis, pneumonia).

Blood concentrations were categorized as therapeutic, low, or high based on whether the drug levels were within, below, or above the usually recommended clinical target ranges. In Denmark, the accepted ranges are as follows: phenytoin, 40–80 $\mu\text{mol/L}$; carbamazepine, 20–40 $\mu\text{mol/L}$; oxcarbazepine, 75–125 $\mu\text{mol/L}$; valproate, 350–700 $\mu\text{mol/L}$; clonazepam, 50–190 nmol/L ; phenobarbitalone, 65–130 $\mu\text{mol/L}$.

Thirteen tissue blocks from the deep and subendocardial myocardium (left and right) were available. Out of 13, there were 11 transmural blocks containing the endocardium and 2 blocks were longitudinal, 1 from the interventricular septum and 1 from the posterior papillary muscle of the left ventricle.

Tissue blocks from the heart conduction system were obtained according to Davies' method.⁹ They contained at least 5 tissue blocks from the sinus node (S) area, and 5 to 9 from the atrioventricular area (AV), His bundle, and the proximal part of the bundle branches including.

The sections were stained with hematoxylin-eosin, Trichrom-Masson, periodic-acid Schiff, and elastic Van Gieson. Elastic Van Gieson was used for the quantification of collagen tissue in the myocardium.

An experienced cardiovascular pathologist blindly evaluated the myocardial sections. They were classified by qualitative means as being normal or fibrotic. The fibrosis was also quantitatively assessed by a point-counting system in a blinded manner. An average of 6 sections was measured

SUDEP PATIENTS

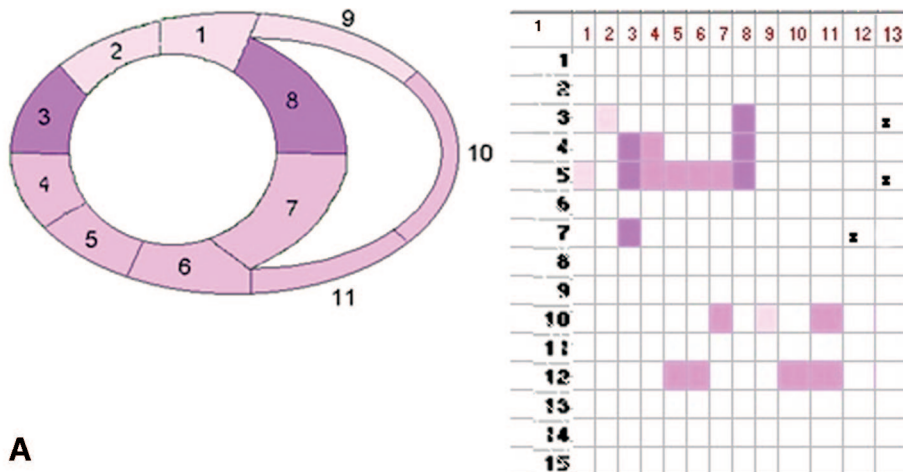
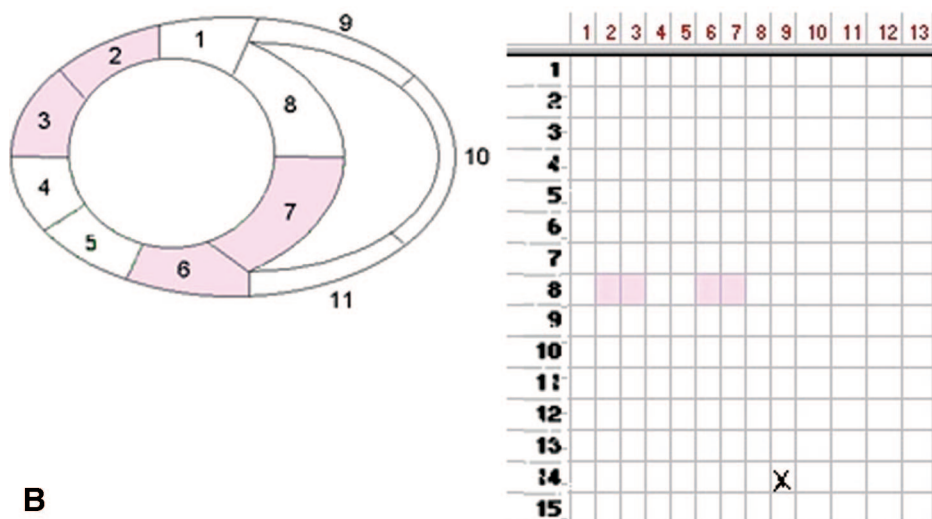


FIGURE 1. Comparison between the distribution of the fibrotic changes of the deep and subendocardial myocardium in SUDEP versus control patients. 1–15 (black), subject's identification number; 1–11 (red), sections from the transmural tissue blocks containing the deep and endocardial myocardium; 12, longitudinal tissue block from intermedial septum; 13, longitudinal tissue block from the papillary muscle of the left ventricle; X, presence of fibrotic changes in singular areas which are not present in the stylized figure. Light violet: slight fibrosis: 1 patient with fibrotic changes confined to 1 area. Darker violet, moderate fibrosis: 2 patients with fibrotic changes observed in the same area. Dark violet, severe fibrosis: 3 patients with fibrotic changes observed in the same area.

A

CONTROLS



B

in each case at a magnification of 160× using an Olympus integrated eyepiece with 100 points.

Statistical Methods

Parametric, 2-tailed unpaired *t* test, and nonparametric Fisher exact test and χ^2 test were performed on the demographic data and histologic features to examine whether there were statistically significant differences between the SUDEP and control groups.

Given the limited number of subjects enrolled in our study and the importance of the possible correlation between the histologic findings and SUDEP, the significance of this association was carefully considered. Therefore, the statistical analysis of the qualitative histology features took into account both anatomic localization and physiological ageing variations.¹⁰⁻¹² Accordingly, obvious fibrotic changes had to be present in each subject in more than 1 singular area of the deep and subendocardial myocardium or conduction system to be considered as abnormal fibrosis (Fig. 1).

We reported any association as significant if the *P* value was less than or equal to 0.05.

RESULTS

Twenty-three SUDEP and 21 control cases were prospectively collected.

Assuming that all SUDEP cases were enrolled in this study, and using an estimate of prevalence of epilepsy in

Denmark of 1%, and an average yearly population of Jutland (excluding the county of Southern Jutland) of 2, 239, 145 (source: Danish Bureau of Statistics), the incidence of SUDEP was of 1:2603 per year. However, this is the minimum estimate of the probable incidence as not all patients with SUDEP can be expected to have been autopsied.¹³

SUDEP Subjects: Demographic and Clinical Data

The overall information is presented in Table 1.

Eight SUDEP cases, out of the 23 initially enrolled, could not be evaluated by histology due to pronounced autolysis.

Seven of the SUDEP patients were found positioned on the abdomen. Two of them had fresh lesions with tongue bite, which represents an indirect sign consistent with an epileptic seizure.¹⁴ Four were lying on their backs, and 4 were found in a sitting position.

Table 2 summarizes the data with regard to the epilepsy course and treatment.

Two of the SUDEP subjects had therapeutic blood concentration of the antiepileptic drugs (AED), 1 had supra-therapeutic concentrations of AED, 7 had subtherapeutic concentrations, and 5 did not have any measurable AED concentrations in the blood. There were no notable differences with regard to the death and finding time between

TABLE 1. The Demographic and Clinical Data of SUDEP Subjects

Variable	Total No. Patients	Mean, SD		P Value
		No. Patients With Fibrotic Changes	No. Patients Without Fibrotic Changes	
Male	6	3	3	0.62
Female	9	3	6	
Age male	6	38 (6)	38 (12)	
Age female	9	52 (8)	37 (17)	
Age (years)	15	45 (10)	37 (15)	0.31
Weight (kg)	15	65.5 (11.0)	67.1 (8.8)	0.52
Height (cm)	15	169.8 (11.4)	167.9 (8.9)	0.72
Age of debut (years)	15	27 (9.4)	14 (9.7)	0.03
Duration of disease (years)	15	18 (15.9)	25 (11.4)	0.39
No. drugs	1	2	4	NA
	2	5	3	
No. seizures	0	0	3	NA
	1-5/month	1	3	
	1-2/year	4	2	
	Myoclonus	1	1	
Atherosclerosis	15	1	0	
Heart weight (g)	15	374.1 (74.3)	317.5 (72.7)	0.16
Lung weight (g)	15	1374 (316.7)	1115 (263.9)	0.31

TABLE 2. Data Regarding the Course, Treatment, and Duration of Epilepsy in the SUDEP Patients

A	B	C	D	E	F	G	H	I	J
32	M	1/M	GP	CZP	29	4	6	0	Yes
39	M	1/Y	GP	OXC + CZP	30	10	5	10 (CBZ)	Yes
45	M	1/Y	GP	CBZ	32	14	2	32	Yes
58	F	MYOC	H	CBZ	33	25	0	97	Yes
42	F	Ca 1/Y	GP	CBZ	30	12	1	1.7	Yes
56	F	2/Y	GP	PRM + CBZ	8	48	4	58 + 33	Yes
53	M	Ca 2/M	GP	CBZ + VPA	23	29	3	0	No
34	M	Ca 5/M	GP	VPA + OXC	2	43	4	64	No
								9 (CBZ)	
29	M	0	H	DZP + OXC	12	18	2	0.5	No
52	F	1 every 2/M	GP	OXC	30	23	3	0	No
45	F	1/Y	GP	VPA	14	35	1	290	No
14	F	1/Y	H	VPA	Birth	14	6	0	No
53	F	0	GP	OXC	20	33	0		No
44	F	0	GP	CBZ	20	24	1	11	No
17	F	MYOC	GP	0	11	6	1	0	No

A indicates age; B, gender; C, numbers of self-reported seizures: /Y = per year, /M = per month, MYOC = myoclonic jerks; D, treatment management: by the hospitals (H), by general practitioner (GP); E, antiepileptic drugs at the point of death: CBZ = carbamazepine, VPA = valproate, OXC = oxcarbazepine, CZP = clonazepam, PHT = phenytoin, PB = phenobarbitone; F, age at the onset of epilepsy; G, epilepsy's duration; H, how many times the drugs have been changed during the course of epilepsy's treatment; I, the postmortem blood concentration of AED: the therapeutic concentrations are underlined; NB, blood concentrations for OXC were not determined; J, the presence of postmortem fibrotic changes.

subjects with detectable and nondetectable AED concentrations in the blood.

Overall, the patients exhibiting fibrotic changes were older at the onset of their epilepsy ($P = 0.03$). The men belonging to this category compared with the women tended to report infrequent seizures and had more frequent changes in the AED therapy. These differences were not noticeable between the 2 groups of women from the SUDEP category.

Control Subjects: Demographic and Clinical Data

Due to pronounced autolysis, 6 controls could not be evaluated by histology. The final analysis included 15 subjects aged 27 to 58 years (mean: 38 years).

The mean weight of the control cases was 70 kg (SD = 16.4) and the mean height was 173 cm (SD = 10.7). There was no significant brain pathology. One patient in the group exhibited significant atherosclerotic changes. The mean weight of the hearts was 356 g (SD = 60.9) and of the lungs was 1.367 g (SD = 455). Six patients had high alcohol concentrations in the blood. Four patients had lethal morphine, 1 paracetamol, and 1 amphetamine concentrations in the blood. Two others had detectable concentrations of cannabis and benzodiazepine.

Comparison of Demographic and Pathoanatomical Postmortem Data Between SUDEP and Control Subjects (Table 3)

A comparison of the 2 groups revealed no detectable statistical difference with regard to age, weight, and height of the subjects.

A significant difference ($P = 0.04$) was present at the comparison between the ages of the SUDEP subjects display-

TABLE 3. Comparison Between the Data on SUDEP and Control Subjects

Variable	SUDEP (Mean, SD)	Controls D (Mean, SD)	P Value
Age (years)	40 (13)	38 (7)	0.54
Weight (kg)	66 (9.4)	69 (15.6)	0.48
Height (cm)	168 (9.9)	173 (9.9)	0.24
Positive alcohol blood test	1	6	0.03
Present			
Brain pathology	8	1	0.01
Atherosclerosis	1	1	
Heart weight (g)	340 (76.2)	369 (65.2)	0.27
Lung weight (g)	1278 (286.7)	1378 (422.6)	0.45

ing fibrotic changes (mean age 45.3 years, SD = 10) versus controls without any fibrotic changes (mean age 37 years, SD = 6).

We observed that the men in the SUDEP group exhibiting fibrotic changes of the heart were younger (mean 38 years, SD = 6) than the women from the SUDEP group presenting the same histologic changes (mean age 52 years, SD = 8).

Significant positive alcohol test in the blood at the time of death was detected in the control group ($P = 0.03$).

Significant gross brain pathology, of note, especially located to the temporal lobe, such as contusions sequels, cortical gliosis, sequels after intracerebral hemorrhage, cortical dysplasia, microcephalia, and heterotopias, was detected in epilepsy patients ($P = 0.01$).

No statistical difference was recorded between the weight of the lungs and hearts of the 2 groups. This was also the case of coronary atherosclerosis changes.

Microscopic Examination of the Hearts of SUDEP and Control Groups (Fig. 1)

Six individuals (40%) in the SUDEP group demonstrated multiple foci of varying degrees of fibrosis in the myocardium (deep and subendocardial myocardium, interventricular septum and the posterior papillary muscle of the left ventricle), as displayed in Fig. 1. This finding is in contrast with the lack of multifocal fibrotic changes in the control group ($P = 0.03$).

None in the SUDEP group showed fibrosis of the conductive system (AV and/or S-node areas), while 1 control (aged 39 years) presented several foci of fibrotic changes of the conduction system. This patient had also a single area displaying fibrotic changes located to the myocardium.

The quantitative evaluations demonstrated a higher percentage of fibrosis both in the deep (7.95%; SD = 3.1) and the subendocardial myocardium (8.34%; SD = 4.1) in the SUDEP subjects compared with 6.5% (SD = 2.4) and 6.5% (SD = 3.1) in the controls. However, the statistical comparison did not reach significance (myocardial fibrosis $P = 0.17$ and subendocardial fibrosis $P = 0.14$).

DISCUSSION

Sudden unexpected death represents a significant cause of death in epilepsy patients.¹⁵ While the exact pathophysiology of SUDEP is unclear, mounting evidence points toward a direct relationship to the seizure activity, especially of generalized tonic-clonic seizures, in patients with drug-refractory epilepsy.^{16,17}

Recently, we have demonstrated that epileptic seizures are associated with ECG changes suggestive of cardiac ischemia in the absence of coronary pathology.¹⁸

In a setting of patients with recurrent seizure activity causing hypoxia and/or apnea,^{19–21} seizures can be expected

to result in scarring, as a by-product of an ischemia-reperfusion injury, which induces cell death with myocardial cell loss and interstitial fibrosis.^{22,23} Interstitial fibrosis, which is known to be the substrate leading to discontinuous propagation and the spatial dispersion of cardiac conduction, henceforth creates a potential substrate for reentrant rhythms.²⁴ These abnormal rhythms, such as ventricular fibrillation, can cause sudden cardiac death.²⁵ Moreover, the severity of abnormal impulse propagation seems to correlate with the amount of increased fibrosis.²⁶

In the light of the above theory, our study adds to the former investigations^{4–6,27–33} the novelty of the first prospective investigation designed to complete a systematic and sequential evaluation of the hearts of SUDEP and age- and gender-matched controls by means of microscopic analysis in a medical examiner setting.

The finding of significant myocardial fibrosis in 40% of the SUDEP patients, confirms the clinical data suggestive of cardiac ischemia found in a previous study on living epilepsy patients.¹⁸

Of note is the concordance of our findings to those from the study of Opeskin et al,²⁸ which neither macroscopically nor microscopically revealed increased prevalence of cardiac pathology in the conduction system of SUDEP patients.

Our data are also amenable with the most recent observations, published by the same author,³² suggesting frequent SUDEP cases among patients with a low rate of self-reported seizures. In this context, a consistent feature is the occurrence of SUDEP in young male patients (mean age 38 years).^{17,33}

Importantly, we found that the women from our SUDEP group were characterized by a higher mean age (52 years). This finding correlates with the data from a prospective cohort study of 121,701 American women proving that the risk of sudden cardiac death in women increased markedly with age.³⁴

This observation stresses the fact that gender differences exist, and SUDEP may be a more heterogeneous disorder in women when compared with men.³⁴

Another finding of importance is the higher age of the patients with fibrotic changes at the onset of their epilepsy. One can speculate if the explanation of this phenomenon may be that patients with early onset of their epilepsy, men and women alike, may have an increased acceptance and awareness of their disease and its consequences, thus being more compliant with their drug treatment and with the report of their seizures. Considering this finding, we are more prone to use the terminology applied by Langan et al³⁵ that SUDEP is a frequent phenomenon in patients with chronic recurrent seizures rather than long-duration, drug-refractory epilepsy.

We consider this finding of special importance as it is supportive for our main theory that it is the recurrence of seizures that damages the heart.

Interestingly, our data show wide variable postmortem levels of AEDs, ranging from the normal clinically targeted therapeutic range to zero. We think our observation is concordant with the hypothesis that low AED levels found in postmortem studies may reflect both variations in drug degradation in the blood after death and noncompliance^{36–40} in patients, which may be feasibly controlled in the subtherapeutic, therapeutic, or supratherapeutic range of AED.⁴⁰ The heterogeneity of these data warrants the overt need of more intense research within this field.

Overall, our study supports the data³² demonstrating increased SUDEP rate in the epilepsy population who generally experiences seizures. Despite the presence of significant myocardial fibrosis, supportive of the theory that most lethal arrhythmias result from structural (fibrosis and scar due to ischemia) abnormalities of the myocardium of the SUDEP subjects, the clarification of SUDEP's pathophysiology still demands joint efforts.

Future studies should include extensive samplings and standardized pathology protocols.

It is also important that future quantification of pathologic fibrosis be viewed in the light of the normal ageing phenomenon,⁴¹ as well as the data regarding the architecture and localization of the interstitial fibrosis, meaning that some of the fibrotic changes would be an expected finding due to normal ageing.^{12,22,23}

Ideally, pathologic fibrosis as a direct consequence of epileptic seizures should be only considered the result between the differences in the observed versus expected fibrosis corroborated with its architectural features in SUDEP patients versus controls of same age at death.^{25,26}

Our findings are also important to be viewed in the light of information showing the role of atherosclerosis in the process of fibrotic transformation.^{41,42} Accordingly, we analyzed our data by looking at the difference between the age of SUDEP subjects displaying fibrotic changes versus controls without any fibrotic changes. Our results are confirmatory for the role played by age ($P = 0.04$). Moreover pathophysiological research in atherosclerosis shows that the production of vascular endothelial growth factor is stimulated by hypoxia.^{43,44} This observation is speculatively thought to be of importance in epilepsy, where the association between epileptic seizures per se and ictal hypoxia^{19–21} thus can stimulate the process of atherosclerosis.

We believe that due to the overall paucity of postmortem data^{4,6,27–33} concerning the cardiac pathology of SUDEP, the acknowledgment of the above core risks is an important key in the future prevention of many deaths.

Moreover, information about the existence and occurrence of SUDEP may ensure that this category of patients does not conceal true seizure rates. Consequently, more

effective prevention of complications, such as SUDEP and, more pragmatically, car accidents,^{13,45} might become a reality.

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