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EEG and ECG in Sudden Unexplained Death in Epilepsy

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Summary: *Purpose:* Sudden unexpected death in epilepsy (SUDEP) is a major cause of mortality for patients with epilepsy. Cardiac factors may be involved and were evaluated in this study.

Methods: EEG and ECG data for 21 patients with definite (n = 6) or probable (n = 15) SUDEP were compared with data from a group of 43 patients with refractory partial epilepsy. ECG abnormalities and heart rate (HR) changes were correlated with clinical data.

Results: Fourteen patients died in their sleep; two were awake. Ictal maximal HR (90 seizures from 16 of 21 patients) was significantly higher in SUDEP (mean, 149 beats/min, BPM) than in comparison patients (mean, 126 BPM; $p < 0.001$). Greater increases in HR were associated with seizures arising from sleep (78 BPM increase) than from wakefulness (47 BPM; $p < 0.001$) in SUDEP, as compared with the non-SUDEP group (52 BPM in sleep, 43 BPM in wakefulness; $p = 0.27$). Ictal cardiac repolarization and rhythm abnormalities occurred in 56% of SUDEP (including two atrial fibrillation, two ventricular premature depolarizations, two marked sinus arrhythmia, two atrial premature depolarizations, one junctional escape, one ST-segment elevation), and 39% of comparison patients ($p = 0.39$). No specific seizure onset (laterality or lobe) was associated with SUDEP.

Conclusions: This study reveals, for the first time, evidence of increased autonomic stimulation (as measured by HR) associated with seizures, particularly in sleep, in patients with SUDEP, as compared with a clinically similar group of patients with refractory epilepsy. **Key Words:** SUDEP—EEG—ECG.

Sudden unexplained death in epilepsy (SUDEP) is a major cause of mortality in patients with epilepsy (1–4). Although SUDEP has been associated with generalized tonic–clonic (GTC) seizures, young adult age, mental retardation, low antiepileptic drug (AED) levels, use of multiple AEDs, and refractory epilepsy (5–12), no specific data can identify which patients are at greatest risk for SUDEP. Therefore targeted prophylactic interventions cannot be implemented.

The etiology for SUDEP remains elusive and may be multifactorial. Both cardiac rate and rhythm disturbances and respiratory-pattern abnormalities have been identified during seizures (13–25). Cardiopulmonary autonomic abnormalities have also been identified interictally in patients with epilepsy (26). However, whereas autonomic derangements have been identified in patients with epilepsy, they have not been identified in actual victims of SUDEP. Studies on SUDEP have evaluated historical data regarding cardiac and pulmonary status, including interictal 12-lead ECG data, but no specific abnormalities have been identified. Many SUDEP victims are found in bed (6,19), suggesting that the risk for specific etiologic mechanisms directly responsible for death may increase during sleep. Nonetheless, strong evidence implicates seizures as being directly responsible for SUDEP. Seizures have been noted shortly before death in many people with SUDEP, suggesting that seizures and their resulting systemic effects have a direct role in causing death. Additionally, surgical series (27,28) report that mortality due to SUDEP declines when epilepsy surgery is successful in eliminating seizures, also supporting an etiologic role of seizures in SUDEP.

No detailed analyses are found in the medical literature regarding the ictal EEG and ECG from patients who subsequently died with a diagnosis of SUDEP. This study examines these data and whether specific clinical features such as location or laterality of the epileptogenic zone, timing of seizures, or patterns of seizure activity are related to SUDEP. Identification of any such abnormalities before death may help to elucidate the etiology of SUDEP, aid in identification of those at greatest risk, and lead to strategies for its prevention.

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METHODS

Definitions

Definite SUDEP was defined as sudden death in a patient with a confirmed history of epilepsy, who was otherwise in good health, whose death remains unexplained after autopsy. Probable SUDEP was defined as sudden death with all the same criteria as for definite SUDEP, except that autopsy evidence is unavailable.

Subjects

Twenty-one subjects with definite (n = 6) or probable (n = 15) SUDEP who had undergone video-EEG monitoring for epilepsy between 1990 and 1999 were identified at three tertiary care epilepsy centers (Jefferson Comprehensive Epilepsy Center, Philadelphia, PA; Vanderbilt University Medical Center, Nashville, TN; Beth Israel Deaconess Medical Center, Boston, MA).

For comparison, interictal and ictal ECG data from 43 consecutive subjects with refractory partial seizures were analyzed for heart rate and rhythm. Details regarding this population are available in a previous article (20). These patients were evaluated in a previous study, and at the time of reevaluation in February 2003, none subsequently had SUDEP since data collection in 1997 and 1998. Raw data obtained prospectively for that study were reanalyzed for the current study as described later. Only GTC and complex partial seizures were evaluated from this group.

Data

All available inpatient and outpatient EEG and ECG data for each subject were reviewed. At least one seizure per patient in the comparison group was analyzed. EEG data were obtained by using the international standard 10–20 system electrode placement and sphenoidal or anterior temporal electrodes with one lead of ECG monitoring. Continuous video-EEG data were obtained by using commercially available equipment.

Video-EEG data evaluated for each recorded seizure are (a) location of ictal onset zone, (b) seizure duration, (c) seizure type, (d) location of interictal epileptiform abnormalities, (e) presence or absence of seizure clusters, and (f) state (wakefulness or sleep) during which the seizure arose.

Continuous ECG data recorded simultaneously with the video-EEG data (available for 16 of 21 SUDEP patients) were reviewed for (a) any repolarization or rhythm abnormality (any rhythm other than sinus rhythm) occurring interictally, during seizures, or postictally; (b) preictal heart rate (averaged over a 20-s baseline 1 min before seizure onset); and (c) maximal heart rate during each seizure (determined from the shortest RR interval). Marked sinus arrhythmia was defined as a ≥50% change in the RR interval. Abnormalities were correlated with specific factors noted during monitoring: (a) seizure clusters, (b) specific seizure types, and (c) state (wakefulness or sleep) during which seizures arose. All ECG data were reviewed by a board-certified cardiologist and electrophysiologist (R.H.). All available interictal (during wakefulness and sleep) and ictal ECG data were reviewed. AEDs were tapered in a similar fashion, as needed, in both control and SUDEP patients during video-EEG monitoring.

Additional data for each patient were obtained from review of the medical records: (a) autopsy data, (b) time and circumstances of death, (c) history of seizure clusters, (d) timing of seizures (wakefulness or sleep), (e) comorbid medical problems, (f) all medications at the time of death, (g) magnetic resonance imaging (MRI) of the brain, (h) seizure frequency before death, (i) seizure types, and (j) type and outcome of epilepsy surgery.

Data analysis

ECGs were classified as abnormal if any abnormalities of rhythm or conduction were found during the ictal or immediate postictal period. Isolated sinus tachycardia (heart rate, ≥100 BPM) was not considered an abnormality and was analyzed separately. χ^2, *t* tests, paired *t* tests, and Fisher's exact tests were used, as appropriate, for statistical analyses.

RESULTS

Patients

Twenty-one patients (10 men, 11 women; mean age, 34.8 years; range, 20–46 years, at time of death) were identified with probable (n = 15) or definite SUDEP (n = 6). Mean duration of epilepsy was 23.1 years (range, 6–38 years). No patients had a history of cardiac or pulmonary problems. Monitoring was performed a mean of 20.8 months before death (range, 2 to 78 months).

Data from 43 comparison patients (25 men, 18 women; mean age, 34 years at time of video-EEG; range, 14–55 years) were analyzed. None had cardiac or pulmonary disease. All patients were from one institution (Jefferson) and had partial epilepsy.

Epilepsy data

Seizure types

Seventeen patients had symptomatic or cryptogenic partial epilepsy (81%), three had idiopathic generalized epilepsy (14.2%), and one had symptomatic generalized epilepsy (4.8%). Nine patients had complex partial and GTC seizures, seven patients had complex partial seizures (CPSs) but no GTC seizures, three patients had only GTC seizures, and three patients had GTC and absence seizures (see Table 1 for details). For the comparison patients, 18 had CPSs and GTC seizures, 22 had only CPSs, and three had only GTC seizures.

Seizure frequency

At time of death, seizure frequency was one or more per week for 38% (daily in two), one or more per month but fewer than one per week for 19%, one or more per year but fewer than one per month for 10%, and fewer than one per

TABLE 1. *SUDEP patients*

Patient	Age	Epilepsy type	Seizure frequency at death	Duration (yr) of epilepsy	Time found	Last clinical data
1	45	P	CPS unclear frequency	N/A	N/A	Last sz unknown
2	20	P	CPS ≥1/wk; GTC N/A	10	2:40 pm	Found in bed (nap after sz in afternoon)
3	30	P	GTC ≥1/yr	27	N/A	Found in bed; last known sz 9 mo before death
4	41	P	CPS ≥1/wk; GTC >1/mo	15	7 am	CPS 2 am; GTC 3 am
5	22	IGE	GTC ≥1/wk; absence N/A	6	N/A	Found in bed after a sz
6	43	IGE	GTC ≥1/6 mo; absence daily	30	9am	Daily szs: unclear when last sz occurred
7	36	P	CPS, GTC unclear frequency	35	N/A	N/A
8	42	P	CPS ≥1/wk; GTC ≥1/wk	7	am	Daily szs: unclear when last sz occurred
9	41	P	CPS ≥1/mo	36	Night	Last sz unknown
10	38	P	CPS, GTC: postoperative seizure frequency unknown	37.25	N/A	Found by EMS unconscious -> ventricular fibrillation-> asystole; soft tissue injury frontal region
11	27	P	CPS ≥1/6 mo; GTC ≥1/wk	25.25	5:30 pm	Found in bed; prone
12	42	IGE	GTC ≤1/yr; absence ≥1/6 mo	38	N/A	GTC sz just before death
13	25	P	GTC ≥1/mo	12	12 noon	Found unresponsive 12 noon: Code for 1 h, 41 min
14	35	P	CPS unclear frequency	33.5	6:30 pm	Unknown sz; recent tongue laceration
15	44	P	CPS unclear frequency	37	Night	Found in bed; prone; blood on pillow
16	46	P	CPS ≥1/6 mo; SPS ≥1/wk	19	N/A	Found at home on ground
17	21	P	CPS ≤1/yr; GTC ≤1/yr	12	am	Found in bed; no injury or evidence of sz
18	39	P	CPS ≥1/mo	10	6 am	Sz during dinner, went to bed and found in am
19	32	SGE	GTC ≥1/wk; tonic/atonic >2/mo	22.5	N/A	Last sz unknown
20	34	P	CPS ≤1/yr, GTC N/A	33.98	6:15 am	2 GTC szs (12:35 am, 1:35 am)
21	27	P	CPS ≥1/mo; GTC ≥1/6 mo	16	N/A	Found in bed

P, partial; IGE, idiopathic generalized epilepsy; SGE, symptomatic generalized epilepsy; CPS, complex partial seizure; GTC, generalized tonic–clonic; sz, seizure; N/A, not available.

year for 14%. Seizure frequency was unknown for 19% of patients. (See Table 1 for details.)

MRI data and anticonvulsant medications

Six SUDEP patients had a normal MRI of the brain, and 11 had abnormal scans (see Table 2 for details). MRI data were not available for the other four patients. AED data were available for 17 patients. Of these patients, the mean number of AEDs used by each patient at time of death was 1.8 (range, 0–3). Twenty-nine percent were taking phenytoin (PHT), and 35% were taking carbamazepine (CBZ). All other AEDs were each used by ≤18% of patients. For the comparison group, 35% were taking PHT, 39% were taking CBZ, and 30% were taking topiramate (TPM). All other AEDs were each used by ≤19% of patients. The mean number of AEDs used by each patient was 1.8. No significant differences in AED use were seen between SUDEP and comparison subjects.

TABLE 2. *MRI of brain, SUDEP patients*

Patient	MRI of brain
1	N/A
2	Dilated right lateral ventricle
3	Normal
4	Left hippocampal atrophy; left parietal lesion
5	Normal
6	Normal
7	N/A
8	Empty sella
9	Mild left frontoparietal cortical atrophy
10	Right mesial temporal sclerosis; right anterior temporal cortical dysplasia
11	S/p left temporal tumor resection; no residual tumor
12	Normal
13	N/A
14	Normal
15	Left mesial temporal sclerosis
16	Normal
17	Right frontal old contusion
18	N/A
19	Cerebellar atrophy
20	Cerebellar hypoplasia
21	1-cm mass adjacent to pineal gland

Epilepsy surgery

Eleven SUDEP patients had undergone epilepsy surgery (four, left temporal lobectomy; one, right temporal lobectomy; one, right frontal lobectomy; four, anterior corpus callosotomy; and one, left temporal lobectomy and anterior corpus callosotomy). Five of these patients had Engel class IV outcome (<80% seizure reduction), one patient had a class I outcome (the last seizure occurred 9 months before death, only after medication withdrawal), two had a class II outcome (rare seizures or purely nocturnal seizures), and one patient had a class III outcome (>80% seizure reduction). Seizure frequency before death was not certain in the other two patients. All video-EEG/ECG data for the SUDEP and comparison patients were obtained before any epilepsy surgery.

Twenty-eight patients in the comparison group underwent epilepsy surgery (14, right anterior temporal lobectomy; five, left anterior temporal lobectomy; one, multilobar resection; one, complete corpus callosotomy; one, complete corpus callosotomy and right frontal resection; one, anterior corpus callosotomy; one, anterior corpus callosotomy and right frontal resection; one, anterior corpus callosotomy and vagal nerve stimulator; one, left frontal resection; one, right frontal resection; one right parietal

resection) after ECG data were obtained. Engel class outcome was class I in 11, class II in seven, class III in seven, and class IV (no worthwhile improvement) in three. No significant difference in outcomes was seen in those individuals who underwent surgery in each group.

Timing of seizures

SUDEP patients were more likely to experience seizures during sleep than were those in the comparison group. Seizures occurred in both wakefulness and sleep in the majority of SUDEP patients (67%), only during sleep in 19%, and only from wakefulness in 9%. This information was unavailable in one patient. For the comparison group, 42% had seizures during wakefulness and sleep, 16% only during sleep, and 42% had seizures arising from wakefulness only ($p = 0.028$).

Seizure frequency and seizure clusters

Fifty-seven percent of SUDEP patients had a history of seizures that were known to cluster over one to a few days. Two patients had daily seizures (20 absence seizures/day in one patient; four CPSs/day in one patient). Three patients had a catamenial pattern of seizures. Other patients were not noted to have seizure clusters in medical record review. Seizure frequency and cluster data were not available from comparison patients.

Circumstances of death

State before death. Of those whose last state before death was available (16 patients), the majority of patients were last known to be asleep (14 of 16). Two patients were seen to be awake before death. Eleven patients were found dead in bed. Of these, two patients were known to be found in the prone position. Positioning for other patients was not known.

Last seizure. There was evidence of a seizure within 8 h of death in seven patients. Two patients had daily seizures, but the timing of the last seizure in relation to death was not known. Two patients had at least two witnessed seizures within 6 h of death (Table 1). The last seizure was not known for all other patients.

Postmortem data. Six SUDEP patients underwent autopsies. A cardiac microscopic examination was performed in two cases and discovered diffuse myocardial injury consisting of hypereosinophilia, fragmentation, hypertrophy, and myocardial fiber disarray in one patient (patient 5) and normal findings in another patient (patient 13). Bronchial fluid or pulmonary edema was noted in four patients. Acute cerebral edema was noted in one case, and acute congestion of the leptomeninges was noted in one patient. Organomegaly (spleen, liver) was noted in two patients. All patients had low or undetectable AED levels. One additional patient who did not undergo a full autopsy also had low AED levels.

Cardiac data

Baseline ECG. Five SUDEP patients had 12-lead ECGs available for review. Two had nonspecific ST-T wave changes, and three were normal. Interictal ECG data from video-EEG monitoring were available from 20 patients (see Table 4). Interictal ECG abnormalities (four of 20 patients) were not significantly more commonly seen than in the comparison patients (three of 43) (20).

Video-EEG data

Seizures and ictal onset. A total of 90 seizures (and additional frequent absence seizures in one patient) with ictal ECG data available ($n = 16$) were reviewed in SUDEP patients; the mean number of seizures per patient (whose seizures were recorded and not including absence seizures) was 5.6. (See Table 3 for details.) Seizure localization varied, and no specific lateralization or lobe of onset was identified for those with partial epilepsy (Table 3). Seizure onset also varied in the comparison population (20).

Ictal ECG

Maximal heart rate. Of the 16 SUDEP patients with ictal ECGs, 15 (94%) had sinus tachycardia during or shortly after seizures. The other patient had only brief absence seizures and had a maximal heart rate of 96 BPM associated with seizures. Although this patient had GTC seizures as well, none were recorded in the hospital. The majority (84%) of the comparison group also had sinus tachycardia associated with their seizures (mean maximal HR, 126 BPM); however, the maximal HR was significantly higher for those with SUDEP (mean, 149 BPM for SUDEP; SD, 15.8; $p < 0.001$). Because of the differences in epilepsy types between the two groups, the maximal HR also was calculated for those in the SUDEP group with partial epilepsy only. These patients also had a significantly higher mean maximal HR (143 BPM; $p < 0.001$).

Rhythm and repolarization. Sixteen SUDEP patients had ictal ECGs available for review. Of these, nine (56%) patients had ictal rhythm or repolarization abnormalities (see Table 4). The types of abnormalities and frequency of abnormalities were similar to those of the control population (39%; $p = 0.39$). Two had an increased frequency of ventricular premature depolarizations; atrial fibrillation (and atrial flutter in one) occurred in two patients; marked or moderate sinus arrhythmia was seen in four patients; and ST-segment elevation occurred in one patient. A rate-related right bundle branch block (considered normal) occurred in three patients. Two patients' data were normal throughout. Movement artifact severely limited ECG evaluation in four patients, but no abnormalities were noted in the portions of ECG that were not obscured by artifact.

Seizure clusters and heart rate response. Eight SUDEP patients had seizure clusters consisting of three or more

TABLE 3. *Patient data*

Clinical data	SUDEP	Controls
Men	10	25
Women	11	18
Mean age (range)	34.8 yr (20–46 yr)	34 yr (14–55 yr)
Duration of epilepsy	23.1 yr (6–38 yr)	24 yr (1–54 yr)
Last known state	14, sleep (11 found in bed) 2, awake 5, unknown	N/A
Time of last seizures	7, evidence of/witnessed recent seizure 2, daily seizures; unknown last seizure 12, unknown	N/A
Timing of seizures (history and video-EEG data) ($p = 0.028$)	67% awake and asleep 9% only asleep 9% only awake 5% unknown	42% awake and asleep 16% only asleep 42% only awake

Seizures (recorded in 16 patients) in SUDEP patients[a]

Total: 90 seizures (not including frequent absence seizures recorded in 1 patient)

Mean seizures recorded per patient: 5.6

Seizure duration: Mean, 89 s for generalized tonic–clonic and complex partial; range, 10–208 s

Seizure onset: (Localization for determined by video-EEG and clinical data)

Localization		Probable lobe of onset[b]
Left hemisphere	29%	43% temporal
Right hemisphere	14%	19% frontal
Generalized	14%	
Multifocal	5%	
Nonlateralized	24%	
No seizures recorded	14%	

[a] Seizure data for comparison patients described previously (20).

[b] Several patients' seizures could not be lateralized but were thought to be of temporal or frontal lobe onset based on EEG and other clinical data.

seizures occurring within 6 h of each other during video-EEG monitoring. A tendency was noted for incremental increases in HR to occur when seizures occurred within a cluster. Both preictal and maximal HRs increased in the majority of patients (six of eight patients). This effect was seen more frequently when seizures clustered together closely, as in patient 3 (Fig. 1); however, this could also be seen when seizures occurred within a few hours of each other, as in patient 9 (Fig. 2). Cluster data were not available for the comparison group.

Seizure types and heart rate and rhythm type. GTC seizures in SUDEP patients were generally associated with a greater maximal HR than were other seizure types. For GTC seizures, the mean maximal HR was 169 BPM; for CPS, 140 BPM; $p < 0.001$. Tonic seizures were associated with maximal HRs between 120 and 133 BPM (HR increase during seizures between 6 and 31 BPM). Absence seizures were associated with minimal HR changes. Rhythm abnormalities occurred in both CPSs and GTC seizures and were not more commonly seen in a specific state. Seizure duration was not analyzed separately.

State and cardiac rate and rhythm. In SUDEP patients, a greater degree of HR increase was seen during CPSs and GTC seizures arising from sleep than during those from wakefulness (mean increase in HR, 78 BPM in sleep, 47 BPM in wakefulness, $p < 0.001$). This difference was seen independently with CPSs (mean increase, 70 BPM in sleep, SD = 22.4; 48 BPM in wakefulness, SD = 22.9; $p = 0.019$) and also tended to be seen with GTC seizures (mean increase, 87 BPM in sleep, SD = 16; 63 BPM in wakefulness, SD = 21; $p = 0.058$). Because of the relatively small number of patients with generalized epilepsy, it is difficult to determine whether timing of seizures differed between those with generalized epilepsy and partial epilepsy (see Table 4 for details).

For the comparison population, no significant difference was noted in HR change during seizures associated with sleep (52 BPM) as compared with wakefulness (43 BPM), $p = 0.27$. In this group, no significant difference occurred in percentages of CPSs and GTC seizures occurring during the two states.

DISCUSSION

Although studies to date have revealed that seizures can cause respiratory and cardiac abnormalities, this study reveals, for the first time, evidence of increased autonomic activity associated with seizures in patients who later died of SUDEP, as compared with a clinically similar comparison population. Seizure-associated HR increases were

TABLE 4. *SUDEP patients: ECG and seizure data*

Patient	State	Sz type	Sz duration (s)	Interictal ECG	Ictal ECG	EEG data	
						Interictal	Ictal
1	1A	CPS	65	Normal	Normal	None	R frontal
2	11A	GTC	90–114	Mild sinus arrhythmia	Marked sinus arrhythmia postictally; junctional escape	Sp1>Sp2	Non-loc
3	1A, 5S	GTC	114–208	VPD (6/100 s); ventricular quadrigeminy	RBBB (postictal); VPDs increase in frequency	F3,F4,C3, Sp1, Sp2	?R frontal
4	5A, 3S	CPS	44–100	Normal	Limited data (artifact); heart rate variability noted	None	L temp
5	2S	GTC	97–105	Normal	Postictal rate-related RBBB; atrial fibrillation >110 s; atrial flutter	GSW	gen
6	9A:1S[a]	Absence	7–31	Normal	Normal	GSW	gen
7	2A	1 CPS, 1 GTC	60–69	N/A	Only EEG available	Sp1, rare Sp2	L temp
8	2A	CPS	55–94	Normal	Initial sinus arrhythmia with 1-s sinus pause; limited (artifact)	R>L temp	R temp
9	5A, 4S	CPS	50–90	VPDs (1/4 beats)	VPDs increase in frequency	L temp	L temp
10	—	—	—	Normal	No ictal ECG	R temp	R temp
11	2S	CPS	72–87	1 APD	ST-segment elevation postictally	L temp; L f-ctrl	Non-loc
12	—	—	—	Normal	No szs recorded	GSW	
13	1S	GTC	105	Normal	Artifact	None	Non-loc
14	6S	CPS	30–160	Normal	Artifact	None	?frontal
15	4A	CPS	67–90	Normal	Artifact	L>R temp	L temp
16	—	—	—	Normal	No szs recorded	None	
17	—	—	—	Normal	No szs recorded	Bilat frontal	
18	—	—	—	Normal	No szs recorded	F8	
19	3A, 8S	7 GTC 4 tonic	13–75	Normal	Rate-related RBBB	None	Non-loc
20	4A, 1S	CPS	55–77	Normal	Sinus arrhythmia; atrial bigeminy/tachycardia; atrial fibrillation (55 s)	None	L temp
21	10S	6 CPS, 2 GTC, 1 SCS 1 SPS	50–65	APDs, VPDs; 2nd degree AVB in sleep, high-grade (paroxysmal) AVB in S (1.7-s pause)	39–50% sinus arrhythmia; sinus exit block; frequent APDs	Sp1, Sp2	L fronto-temp

Sz, seizures; A, awake; S, sleep; CPS, complex partial seizure; GTC, generalized tonic–clonic; SCS, subclinical seizure; SPS, simple partial seizure; APD, atrial premature depolarization; VPD, ventricular premature depolarization; RBBB, right bundle branch block; AVB, atrioventricular block; L, left; R, right; temp, temporal lobe; Non-loc, nonlocalizable; f-ctrl, frontal-central; bilat, bilateral; Sp, sphenoidal; GSW, generalized spike–wave; gen, generalized onset.

[a]Numerous brief absence seizures were recorded in this patient; these numbers represent the ratio of seizures occurring in wakefulness and sleep.

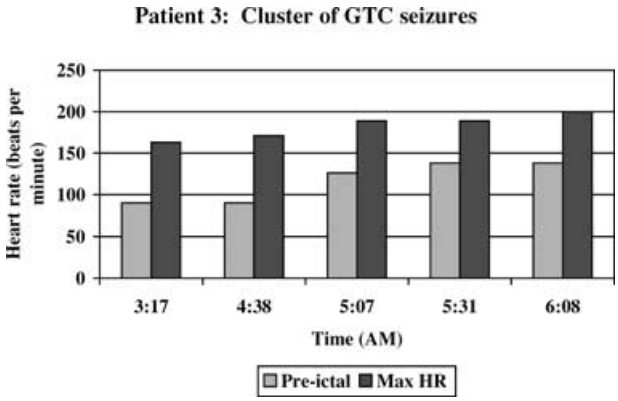

FIG. 1. A cluster of generalized tonic–clonic seizures. The first four seizures occurred directly from sleep, and the last occurred from wakefulness. Note the incremental increase in preictal heart rates, as well as maximal heart rates (Max HR) associated with seizures.

more marked in this group, particularly when seizures arose from sleep. Increases in HR were particularly notable and sustained during seizure clusters. In addition, half of the SUDEP patients in whom seizures were recorded also had an abnormality of cardiac rhythm or repolarization, including atrial fibrillation, marked sinus arrhythmia, and ST-segment elevation during the ictal or immediate postictal period, although the frequency of

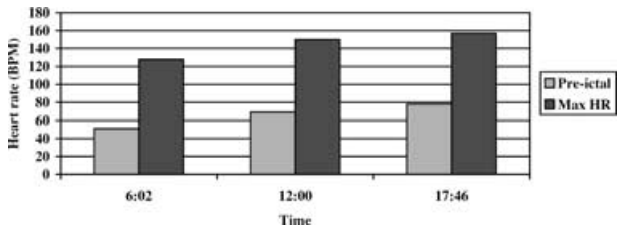

FIG. 2. A cluster of complex partial seizures in patient 9. The first seizure occurred in sleep. The others occurred in wakefulness.

abnormalities was not significantly higher than in the comparison group. These abnormalities offer further evidence of the extreme autonomic stimulation that occurred during seizures in this population. Additionally, whereas previous studies revealed evidence of postmortem myocardial injury in SUDEP patients (29,30), the present study reveals such injury associated with evidence of a clinically significant cardiac arrhythmia (atrial fibrillation and flutter) before death in one patient.

As previously noted, patients with SUDEP were young, most had a history of GTC seizures, were last known to be asleep before death, and were often found in bed. At least one third had a recent seizure before death. All patients with postmortem examinations had low AED levels, suggesting that they may have been at elevated risk for having seizures at the time of death. Alternatively, the low levels seen may represent an artifact of postmortem detection. Because AEDs were tapered in a similar fashion in both control and SUDEP patients during video-EEG/ECG monitoring, significant differences in the number of AEDs at any given time during monitoring is unlikely, particularly because both groups were taking similar numbers and types of AEDs. Thus it is unlikely that AED differences contributed to HR or rhythm differences between the two groups. Additionally, seizure clusters were seen in approximately half of the SUDEP patients, and some had known seizure clusters just before death. However, neither location nor lateralization of the epileptogenic zone appeared to be associated with a heightened risk of death. Although the majority of patients had abnormal MRI brain scans, no common pathologic substrate was found.

These data suggest several factors that may be related to SUDEP: (a) the sleep state, which may produce physiological conditions increasing the likelihood of SUDEP; (b) seizures (particularly GTC seizures) might directly precipitate death; and (c) seizure clusters. The majority of patients died during sleep, supporting that these patients had greater vulnerability to SUDEP during this state. These patients additionally had evidence of marked sympathetic tone during seizures arising from sleep. This increased autonomic instability during seizures arising from sleep may be a key factor in SUDEP. Sleep is generally associated with increased vagal tone (causing relative bradycardia) (29–31). SUDEP may be related to mechanisms similar to those of sudden cardiac death, which is associated with a peak incidence in the morning. Death in these cases is thought to be related to sudden surges in catecholamines associated with awakening (32,33). In a similar but perhaps even more striking manner, seizures from sleep could cause sudden and extreme fluctuations in autonomic tone (from predominant vagal tone to sudden and extreme sympathetic tone), which might precipitate lethal cardiac arrhythmias. This change from vagal to sympathetic stimulation would be expected to be greatest in younger individuals, because their baseline vagal tone is higher (36), and may explain why most SUDEP patients die at a relatively young age. GTC seizures and seizure clusters may increase the risk of SUDEP further in these individuals because of more sustained and even greater degrees of autonomic stimulation. These data suggest that seizure clusters occurring during sleep in a young person with uncontrolled epilepsy may be particularly dangerous. Additional autonomic evaluation, such as HR variability assessment in wakefulness and sleep in this population, may further define whether these patients have significant differences in autonomic tone as compared with a non-SUDEP population.

Sudden death due to a cardiac arrhythmia is more likely when underlying structural disease exists (35). In SUDEP, postmortem studies have not shown gross abnormalities (6). However, myocardial injury has been identified at a microscopic level. This may be sufficient to result in significant arrhythmias, particularly during catecholamine surges associated with seizures. Such a mechanism may explain SUDEP in some individuals. Although this study was not able to identify any specific common rhythm abnormality in these patients, it is intriguing that many patients had evidence of a cardiac arrhythmia or ST-segment elevation in association with seizures and that two had atrial fibrillation, which is not a common seizure-induced arrhythmia. Video-EEG monitoring captures only a brief period in the course of a patient's epilepsy, and longer recordings would likely have revealed an even greater incidence of arrhythmias. A greater number of patients also may have had myocardial injury identified with microscopic cardiac examinations. Perhaps the catecholamine surges associated with repeated seizures could cause such injury in a similar manner as in other catecholamine-rich states, including pheochromocytoma (36). In a destructive cycle, seizures could first cause this injury, which would later serve as the substrate for lethal arrhythmias during further seizures. However, this now remains speculative.

As with any retrospective study of mortality, limitations exist in the data available. Information regarding respiratory patterns might shed additional important clues regarding the mechanism of SUDEP. This study focused on cardiac data because pulmonary data were lacking. The postmortem data revealed bronchial fluid or pulmonary edema in four of six cases, and it is possible that the increased autonomic stimulation associated with seizures in SUDEP seen in this study may contribute to pulmonary changes that may be important in SUDEP. Other factors that might affect the results include the availability of only one channel of ECG and baseline HR taken 1 min before each seizure. As with any mortality study, it is difficult to determine an ideal control population for comparison. Although our comparison group was not a matched sample, we assured that they were similar in that all had a history of refractory epilepsy, were young, used similar AEDs, and had similar seizure types. Because of these

very similarities, some of the control subjects may eventually die of SUDEP. However, it is likely that the majority of these control subjects will not die of SUDEP, and thus it is likely that their data reflect this majority influence. Of note, the control group did differ in that all patients had partial epilepsy, whereas the SUDEP group included individuals with generalized epilepsy. However, when only those SUDEP patients with partial epilepsy were compared with the comparison group, similar findings were observed. Thus it is unlikely that epilepsy type alone can explain differences seen between the two groups.

In conclusion, this study suggests that patients with evidence of a great degree of change in autonomic tone during seizures might be at increased risk for SUDEP. Although the precise mechanism of death remains elusive, these data nevertheless suggest that prevention of nocturnal seizures and seizure clusters may be important in reducing the risk for SUDEP. Accurate diagnosis of nocturnal seizures and evaluation of their frequency, with either long-term ambulatory or inpatient EEG monitoring, may be more important than has been generally considered. Aggressive treatment, even when seizures are only nocturnal, might help reduce the risk of SUDEP. Elimination of seizures is ideal, but when this cannot be accomplished, it is possible that other measures to reduce autonomic instability specifically in selected patients, such as use of β-blockers, might aid in preventing SUDEP. However, further investigation is needed to evaluate the role of such potential therapy, with caution regarding other possible mechanisms of SUDEP, including increased parasympathetic activity or bronchoconstriction.

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