Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study

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Summary

Background Sudden unexpected death in epilepsy (SUDEP) is the leading cause of death in people with chronic refractory epilepsy. Very rarely, SUDEP occurs in epilepsy monitoring units, providing highly informative data for its still elusive pathophysiology. The MORTEMUS study expanded these data through comprehensive evaluation of cardiorespiratory arrests encountered in epilepsy monitoring units worldwide.

Methods Between Jan 1, 2008, and Dec 29, 2009, we did a systematic retrospective survey of epilepsy monitoring units located in Europe, Israel, Australia, and New Zealand, to retrieve data for all cardiorespiratory arrests recorded in these units and estimate their incidence. Epilepsy monitoring units from other regions were invited to report similar cases to further explore the mechanisms. An expert panel reviewed data, including video electroencephalogram (VEEG) and electrocardiogram material at the time of cardiorespiratory arrests whenever available.

Findings 147 (92%) of 160 units responded to the survey. 29 cardiorespiratory arrests, including 16 SUDEP (14 at night), nine near SUDEP, and four deaths from other causes, were reported. Cardiorespiratory data, available for ten cases of SUDEP, showed a consistent and previously unrecognised pattern whereby rapid breathing (18–50 breaths per min) developed after secondary generalised tonic-clonic seizure, followed within 3 min by transient or terminal cardiorespiratory dysfunction. Where transient, this dysfunction later recurred with terminal apnoea occurring within 11 min of the end of the seizure, followed by cardiac arrest. SUDEP incidence in adult epilepsy monitoring units was 5·1 (95% CI 2·6–9·2) per 1000 patient-years, with a risk of 1·2 (0·6–2·1) per 10 000 VEEG monitorings, probably aggravated by suboptimum supervision and possibly by antiepileptic drug withdrawal.

Interpretation SUDEP in epilepsy monitoring units primarily follows an early postictal, centrally mediated, severe alteration of respiratory and cardiac function induced by generalised tonic-clonic seizure, leading to immediate death or a short period of partly restored cardiorespiratory function followed by terminal apnoea then cardiac arrest. Improved supervision is warranted in epilepsy monitoring units, in particular during night time.

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Introduction

Sudden unexpected death in epilepsy (SUDEP) is a frequent cause of non-accidental, non-suicidal sudden death in young adults in general, and one of greatest concern for the epilepsy community. SUDEP most often affects patients with drug-resistant epilepsy, with an average incidence of four deaths per 1000 patient-years.[1] This incidence translates to a 12% cumulative risk over 40 years for patients with uncontrolled childhood-onset epilepsy.[2] Although most cases of SUDEP are believed to be peri-ictal, their pathophysiology remains unclear.[1] Recordings from patients who died suddenly while undergoing long-term video electroencephalogram monitoring (VEEG) provide a unique opportunity to improve our understanding of terminal events.[3] However, only a handful of case reports have so far been reported, sometimes with incomplete data or data interpretation.[4–7] We undertook the MORTality in Epilepsy Monitoring Unit Study (MORTEMUS) to gain further insight into the mechanisms of SUDEP by identifying deaths during VEEG on an international scale. A secondary objective was to assess the risk of death and SUDEP in epilepsy monitoring units.

Methods

Participants

For this retrospective study we identified epilepsy monitoring units doing VEEGs for longer than 24 h in Europe, Israel, Australia, and New Zealand through national chapters of the International League Against Epilepsy. 160 units were invited to participate in January, 2008. The survey sought the following information: start and end dates of mortality census for each unit, number of VEEGs done during this period, proportion of adult patients and epilepsy surgery assessments, average length of hospital stay, average duration of monitoring during presurgical VEEG, and number of cardiorespiratory arrests occurring in the units during the census. Census start date, which ranged from Jan 1, 1968, to Dec 31, 2007, was the start of each unit's activity with the exception of a

few centres, for which the start date was the time when a reliable database was implemented. Census stop date was Dec 31, 2007, for the 108 centres completing the survey during the first half of 2008. For the 39 remaining centres that responded later, census stop dates were between June 30, 2008, and Dec 29, 2009. The median duration of census per unit was 8 years (IQR 4–13, range 1–40).

Data collected during the survey were used to explore mechanisms of SUDEP and investigate the risk of SUDEP in epilepsy monitoring units in participating countries. We also invited epilepsy monitoring units from any other country to report monitored cardiorespiratory arrests. These reports, however, were not incorporated in the epidemiological analyses. Centres reporting cardiorespiratory arrests completed a questionnaire detailing patients' characteristics, circumstances of these arrests, and all relevant observations regarding mechanisms. Spontaneously reversible ictal asystole and ictal apnoea or laryngospasm without cardiac arrest were not considered in this study.

This retrospective survey of anonymous patient data was done according to the ethics and legal regulations of countries involved in the study coordination and data management (France) and from where data were collected. Wherever needed, patients or family provided written informed consent for the use of the clinical and VEEG data reported in this study.

Procedures

Cardiorespiratory arrests were classified as either SUDEP (definite or probable), near SUDEP (fatal or non-fatal), or non-SUDEP (panel 1).[8] Available VEEG or electrocardiogram (ECG) recordings were analysed by members of the expert panel (LN, PR, TT) to establish the sequence of events leading to SUDEP or near SUDEP, including the characteristics of the preceding seizure, postictal electroencephalogram (EEG) flattening, as well as respiratory and heart rate abnormalities. Postictal generalised EEG suppression was defined as the generalised absence of EEG activity greater than 10 μV in amplitude, allowing for muscle, movement, breathing, and electrode artifacts.[5] Respiration was assessed by visual inspection on video recordings and digitally optimised respiration-induced EEG artifacts. Each detected respiratory movement was tabulated and used to calculate the time separating two consecutive movements (T), and a respiratory rate of 60/T. Apnoea was defined as a recording segment longer than 10 s without respiratory movement. Cardiac activity was extracted from ECG recordings as well as from postictal flat EEGs, where using an appropriate gain and filters showed reliable ECG or pulse artifacts. For each consecutive sequence of 5 s, the mean time separating all QRS complexes during that period (M) was tabulated and used to calculate a heart rate of 60/M. All data were initially tabulated by the principal investigator (PR) and then checked and confirmed by the investigator reporting the corresponding case.

Panel 1: **Glossary of terms**

SUDEP
Sudden unexpected death in epilepsy is a sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death, occurring in benign circumstances in an individual with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus.

Definite SUDEP
A SUDEP for which post-mortem examination failed to reveal a cause of death.

Probable SUDEP
A SUDEP for which no post-mortem examination is available and the victim died unexpectedly while in a reasonable state of health, during normal activities, and in benign circumstances, without a known structural cause of death.

Near SUDEP
A sudden, unexpected, non-traumatic, and non-drowning cardiorespiratory arrest with no structural cause identified after investigation, occurring in benign circumstances in an individual with epilepsy, with or without evidence for a seizure excluding documented status epilepticus, where the patient survived resuscitation for more than 1 h after the cardiorespiratory arrest.

Fatal near SUDEP
A near SUDEP in which the cardiorespiratory arrest was responsible for irreversible major brain damage directly leading to death more than 1 h after the cardiorespiratory arrest.

Non-SUDEP
A sudden death in an individual with epilepsy with a clear cause of death other than SUDEP (eg, myocardial infarction, brain haemorrhage).

Statistical analysis

The incidence in epilepsy monitoring units of death, cardiorespiratory arrest, pooled SUDEP and near SUDEP, and SUDEP was calculated on the basis of an estimation of total patient-years spent in units. This calculation was done for the entire population, as well as in subgroups defined by age (adults *vs* children aged <18 years) and clinical indication for VEEG (presurgical *vs* other diagnostic purposes). We incorporated units not responding to the survey in our conservative estimation by ascribing to them the average duration of stay reported by responding units and assuming they had not encountered cardiorespiratory arrests. To calculate the 95% CI for all above incidences, we first estimated the 95% CI for the number of observed events. The denominator of the incidence rate (ie, the number of patient-years) can be regarded as a non-random quantity, whereas the number of events is a random variable that follows the Poisson distribution for rare events. The resulting CI limits were then divided by the patient-years spent in

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	Sex/age (years)	Age of onset of epilepsy (years)	Epilepsy		GTCS during past 3 months	Characteristics of triggering seizure and CRA						Delay from end of seizure to CPR (min)
			Brain area	Side		AED tapering	VEEG ongoing	At night*	Seizure type	Duration of seizure (s)	Sequence of events until CRA	
Monitored SUDEP												
1	M/41	24	Temporal	Right	Yes	100%	Yes	No	GTCS	87	Unknown	18 min
2[4]	M/47	19	Temporal	Right	No	100%	Yes	Yes	GTCS	124	EPINVB→early terminal CRA	No CPR
3[5]	M/39	28	Temporal	Right	Yes	Unknown	Yes	No	GTCS	248	EPINVB→apnoea→asystole	13 min
4	F/42	20	Temporal	Left	No	>50%	Yes	Yes	GTCS	98	EPINVB→apnoea→asystole	No CPR
5[6]	F/42	35	Temporal	Left	No	>50%	Yes	Yes	GTCS	102	EPINVB→apnoea→asystole	20 min
6[7]	F/35	19	Temporal	Right	No	100%	Yes	Yes	GTCS	120	EPINVB→apnoea→asystole	>30 min
7	M/40	7	Unknown	Right	No	100%	Yes	Yes	GTCS	87	EPINVB→early terminal CRA	>15 min
8	F/35	25	Temporal	Right	Yes	100%	Yes	Yes	GTCS	95	EPINVB→apnoea→asystole	20 min
9	F/58	55	Frontotemporal	Right	No	100%	Yes	Yes	GTCS	Unknown	EPINVB→apnoea→asystole	180 min
10[6]	M/62	6	Temporal	Left	No	100%	Yes	Yes	GTCS	120	EPINVB→early terminal CRA	>15 min
11	M/19	8	Parietal	Right	Yes	>50%	Yes	Yes	GTCS	65	EPINVB→apnoea→asystole	No CPR
Non-monitored SUDEP												
12	M/39	24	Unknown	Unknown	Yes	0%	No	Yes	Unknown	Unknown	Unknown	No CPR
13	F/39	11	Temporal	Bilateral	Yes	>50%	No	Yes	Unknown	Unknown	Unknown	Unknown
14	F/62	45	Temporal	Bilateral	Yes	>50%	No	Yes	Unknown	Unknown	Unknown	Unknown
15	F/25	18	Temporal	Right	Yes	<50%	No	Yes	Unknown	Unknown	Unknown	Unknown
16	F/28	9	Temporal	Left	No	<10%	No	Yes	Unknown	Unknown	Unknown	Unknown
Near SUDEP												
17†	M/61	51	Temporal	Left	Yes	>90%	No	Yes	GTCS	90	Unknown	Unknown
18†	F/36	35	Temporal	Bilateral	Yes	0%	No	Yes	GTCS	Unknown	Unknown	Unknown
19[9]	F/20	1	Frontal	Bilateral	Yes	>50%	Yes	No	GTCS	56	EPINVB	<2 min
20	F/10	7	Insula	Right	Yes	0%	Yes	No	CPS	82	Immediate postictal CRA	<1 min
21	F/43	16	Temporal	Left	No	>50%	No	No	GTCS	Unknown	Unknown	<1 min
22	M/32	23	Generalised	NA	Yes	<50%	No	No	GTCS	Unknown	Unknown	<1 min
23	M/42	9	Frontal	Right	Yes	100%	Yes	No	GTCS	90	EPINVB	<1 min
24[10]	F/51	3	Temporal	Right	No	>50%	Yes	Yes	GTCS	270	Ictal ventricular fibrillation	3 min
25[11]	F/54	19	Insula	Right	No	<50%	Yes	No	CPS	60	Ictal asystole	<1 min

Corresponding reference numbers for published case reports are shown alongside patient numbers. SUDEP=sudden unexpected death in epilepsy. GTCS=generalised tonic-clonic seizure. CRA=cardiorespiratory arrest. CPR=cardiopulmonary resuscitation. AED=antiepileptic drugs. VEEG=video electroencephalogram. M=male. EPINVB=early postictal neurovegetative breakdown. F=female. CPS=complex partial seizure. NA=not applicable. *Between 2200 h and 0600 h. †Fatal near SUDEP.

Table 1: **Patient characteristics and observations at the time of SUDEP or near SUDEP, by patient number**

epilepsy monitoring units to provide 95% CIs for all incidence rates.

To ensure the robust assessment of respiratory movements in patients with monitored SUDEP, two investigators (SR, PR) did an independent evaluation of the video and EEG data from eight patients. They reported the occurrence and timing of each detected respiratory movement, using the time of expiration onset as a reference. The observed proportion of agreement was first calculated and the corresponding parameter of a non-conditional logistic regression model estimated. In a second step, we fitted a mixed-effect logistic regression model, including a random effect for inter-patient variability, using the glmmPQL function of R software (version 3.0.1). The two investigators then compared their disagreement to see whether they could reach a consensus.

See Online for appendix

Role of the funding source

The funding source had no role in the study design, data collection, analysis, or interpretation, writing of the Article, or the decision to submit for publication. The authors have not been paid to write this Article. PR had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

147 (92%) of the 160 identified epilepsy monitoring units in Europe, Israel, Australia, and New Zealand completed the survey. During the census, an estimated 133788 VEEGs were done, 93751 in adults (70%) and 65556 for presurgical evaluation (49%). Presurgical VEEG had a mean duration of 9 days, translating into 1771 patient-years (appendix). However, VEEG data were not recorded during 41% of the time spent in monitoring units because of in-hospital

	Relevant history	Epilepsy cause	GTCS		Pre-surgical VEEG	Days of VEEG	Awake or sleep stage	Number of GTCS in past 12 h	Available respiratory data	Available cardiac data	Observations at time of event	Autopsy findings	SUDEP
			In past history	Number during VEEG									
Monitored SUDEP													
1	None	Unknown	Yes	3	Yes	2	Awake	1	..	..	Cyanosis	Mild pulmonary oedema	Definite
2	None	Unknown	Yes	5	Yes	4	Unknown	5	VEEG	PA on icEEG	Prone	Mild pulmonary oedema	Definite
3	None	HA	Yes	5	Yes	5	Awake	5	VEEG	ECG	Prone	No abnormality	Definite
4	None	Unknown	No	1	Yes	4	Awake	1	VEEG	ECG on EEG	Prone	Not done	Probable
5	None	Unknown	Yes	2	Yes	4	2	2	VEEG	ECG	Prone	Not done	Probable
6	None	Unknown	Yes	1	Yes	4	2	1	VEEG	ECG	Prone	Not done	Probable
7	None	Unknown	Yes	5	Yes	5	3–4	4	VEEG	ECG	..	Not done	Probable
8	None	HA	Yes	1	Yes	1	3–4	1	VEEG	ECG	Prone	Not done	Probable
9	None	Unknown	Yes	1	Yes	2	1	1	VEEG	ECG	Prone	Subendocardial fibrosis	Definite
10	None	Unknown	Yes	2	Yes	4	REM	1	VEEG	ECG	Prone	Coronary atherosclerosis	Definite
11	None	Unknown	Yes	2	Yes	2	3	1	VEEG	ECG on EEG	Prone	Not done	Probable
Non-monitored SUDEP													
12	None	Unknown	Yes	0	Yes	5	Unknown	1	..	..	Prone	No abnormality	Definite
13	Postictal apnoea	Encephalitis	Yes	1	Yes	10	Unknown	Unknown	..	..	Prone, cyanosis	Not done	Probable
14	Mild HBP	Unknown	Yes	0	No	2	Unknown	Unknown	..	..	Fell down	Mild pulmonary oedema	Definite
15	None	Unknown	Yes	0	Yes	3	Unknown	Unknown	..	..	Prone	Not done	Probable
16	None	Unknown	No	0	Yes	4	Unknown	Unknown	..	..	Prone	No abnormality	Definite
Near SUDEP													
17	Postictal apnoea	Ganglio-glioma	Yes	3	Yes	7	Unknown	3	..	..	Cyanosis	Not done	-
18	Postictal apnoea	Encephalitis	Yes	5	No	5	Unknown	2	..	..	Prone, cyanosis	Not done	Probable
19	Postictal CRA	Unknown	Yes	4	Yes	3	Awake	4	Observer report	ECG	..	..	..
20	None	Unknown	Yes	1	Yes	2	Awake	1	VEEG	Pulse	..	..	..
21	None	Unknown	Yes	1	No	2	Awake	1	..	..	Neck stuck	..	..
22	AVB1	JME	Yes	1	No	3	Awake	1	..	..	..	..	..
23	Postictal apnoea	DNET	Yes	1	Yes	7	Awake	1	Observer report	Observer report	..	..	..
24	HBP, PE	HA	Yes	1	Yes	5	2	1	VEEG	ECG	..	..	..
25	Ictal asystole	Cavernoma	Yes	0	Yes	1	Awake	0	VEEG	ECG	..	..	..

SUDEP=sudden unexpected death in epilepsy. GTCS=generalised tonic-clonic seizure. VEEG=video electroencephalogram. EEG=electroencephalogram. PA=pulse artefact. icEEG=intracerebral electroencephalogram. HA=hippocampal atrophy. ECG=electrocardiogram. REM=rapid eye movement. HBP=high blood pressure. CRA=cardiorespiratory arrest. AVB1=atrioventricular block stage 1. JME=juvenile myoclonic epilepsy. DNET=dysembryoplastic neuroepithelial tumour. PE=pulmonary embolism. ..=no data.

***Table 2*: Additional patient characteristics, by patient number**

antiepileptic drug withdrawal before recording, in-hospital surveillance after recording and resumption of antiepileptic drugs, or lack of supervising staff in the evening, at night, or during weekends. Organisational issues varied greatly between units. Six units from the USA and India did not participate in the survey, but reported a monitored cardiorespiratory arrest.

29 cardiorespiratory arrests were reported by 27 units from 11 countries. These were classified as follows: 16 SUDEP, half definite and half probable, including five previously reported (patients 2, 3, 5, 6, and 10);[4–7] nine near SUDEP including two eventually fatal (patients 17 and 18) and three previously reported (patients 19, 24, and 25);[9–11] and four deaths from other causes (two subarachnoid haemorrhage, one myocardial infarction, and one brain oedema complicating subdural grids). Tables 1 and 2 show circumstances of SUDEP and near SUDEP. 28 (97%) of the 29 patients with cardiorespiratory arrest, and all those who died, were adults. The epileptic focus in the 25 cases of SUDEP or near SUDEP was temporal in 16 (64%), insular in two (8%), right-sided in 13 (52%), left-sided in six (24%), and bilateral or generalised in five (20%). Generalised tonic-clonic seizure (GTCS) within the preceding 3 months was reported in 14 (56%) of the

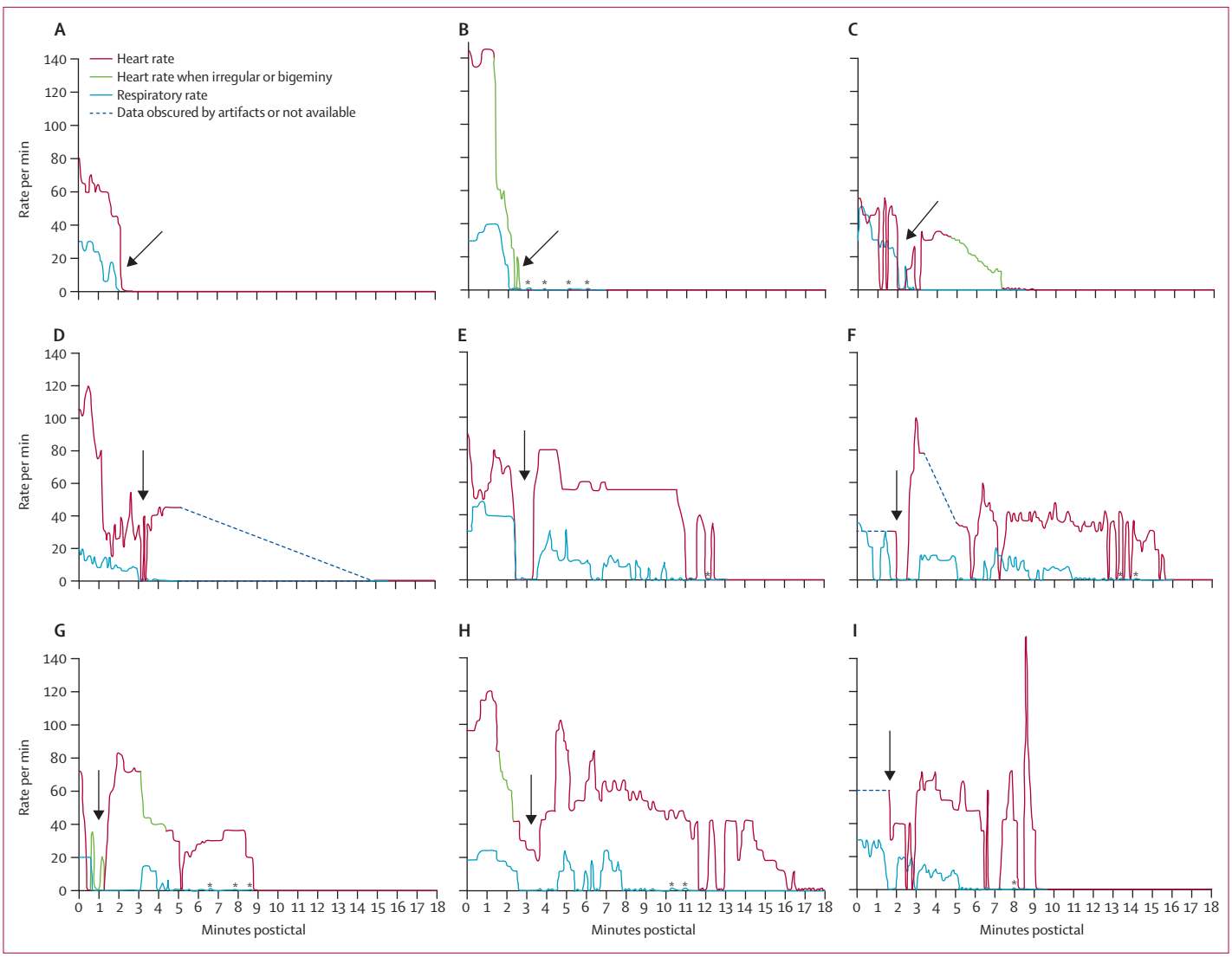

Figure 1: **Individual patterns of postictal cardiorespiratory functions, starting from the end of seizure, in the nine patients with monitored SUDEP for which both respiration and heart rates could be measured by the expert panel**

(A) Patient 10, (B) patient 7, (C) patient 8, (D) patient 9, (E) patient 6, (F) patient 4, (G) patient 3, (H) patient 5, (I) patient 11. When the time separating two QRS complexes was longer than 5 s, heart rate was quoted as 0 for each consecutive 5 s period of asystole, and as 1 for an isolated beat. Similarly, when the time separating two respiratory movements was longer than 10 s, respiratory rate was quoted as 0 for periods of apnoea longer than 10 s, and as 1 for respiratory movements, with the latter usually corresponding to terminal gasps (<1 breath per 30 s, asterisks on abscissa). Black arrows indicate the early postictal parallel collapse of respiratory and cardiac rates, which was observed in every patient during the first 3 min postictally, leading to immediate death in three patients (A–C). A similar pattern was observed in a fourth patient for whom transient arrest of recording hampered firm conclusion (D). In the other patients, cardiorespiratory functions were transiently and partly restored, until terminal apnoea followed by terminal asystole (E–I). SUDEP=sudden unexpected death in epilepsy.

25 cases of SUDEP or near SUDEP, and six (21%) had a documented history of postictal apnoea, postictal cardiorespiratory arrest, or ictal asystole.

All non-monitored SUDEP and fatal near SUDEP occurred at night in a unit where nocturnal staff resources and level of supervision were similar to that of a standard neurological ward, precluding nocturnal VEEG recording. Monitored SUDEP occurred between 1930 h and 0600 h in all but one patient. Cardiorespiratory resuscitation (CPR) was undertaken in 11 of the 16 cases of SUDEP and all fatal near SUDEP with, where known, a delay always exceeding 10 min after initial apnoea. By contrast, CPR was started within 3 min in all seven non-fatal near SUDEP, six of which occurred during the daytime, with one needing defibrillation (patient 24).

In all assessable cases, a seizure occurred immediately before the cascade of events that led to cardiorespiratory arrest. This event was a GTCS in all SUDEP cases, and in seven of the nine near SUDEP cases. Half of the 18 patients who had a GTCS-induced cardiorespiratory arrest either never had GTCS in the past or were free of such seizures for at least 3 months before VEEG.

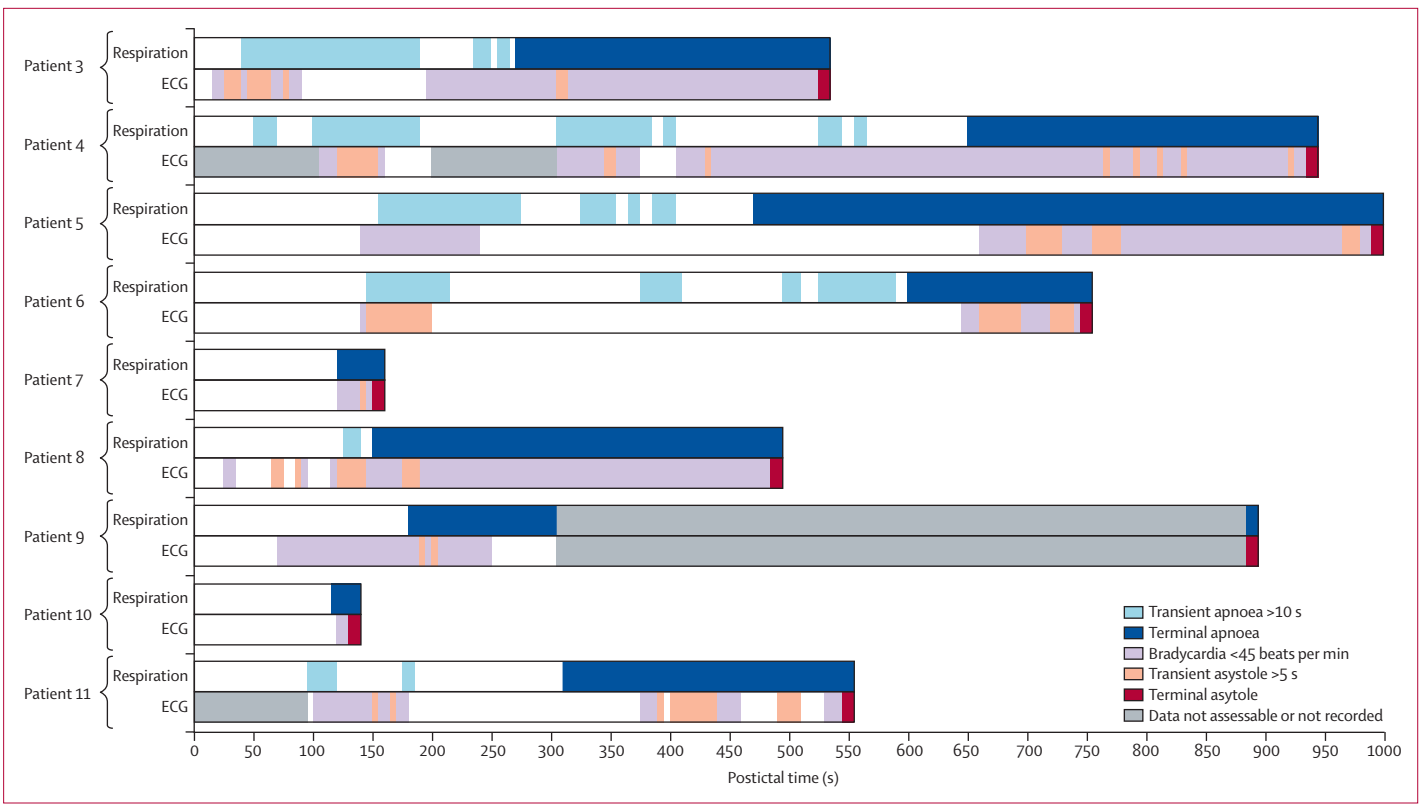

Figure 2: **Patterns of postictal cardiorespiratory functions, starting from the end of seizure, in the nine patients with monitored SUDEP for which both respiration and heart rates could be measured by the expert panel**

Transient episodes of apnoea (>10 s), asystole (>5 s), and bradycardia (<45 beats per min) are shown, together with terminal apnoea and asystole. Cardiorespiratory abnormalities were always observed during the first 3 min postictally, often concomitantly. Terminal apnoea always preceded terminal asystole. SUDEP=sudden unexpected death in epilepsy.

Antiepileptic drugs were reduced by more than 50% in all these nine patients, and completely withdrawn in five, suggesting a role of such withdrawal in promoting the terminal seizure and associated cardiorespiratory arrest. Among the 16 SUDEP and fatal near SUDEP cases in which the position of the patient could be assessed, 14 were prone at the time of cardiorespiratory arrest, often with the face partly tilted to one side.

SUDEP was monitored in 11 patients, with various levels of data available. All video (patients 1–11) and digital EEG or ECG data (patients 4–11), as well as one set of analogue EEG and ECG data (patient 3), could be reviewed by the expert panel (figures 1–3 and appendix). Analogue EEG data from patient 2 were analysed and reported in detail by the corresponding investigator, but were not available for review by the panel. Video and analogue EEG data were not informative in patient 1, who fell out of bed during his seizure. Respiratory movements could be reliably detected in patients 2–11, owing to stereotyped trunk and head movements reflecting inspiratory efforts followed by brisk expiration. These were responsible for equally stereotyped EEG artifacts that proved readily detectable in most patients (2–7, 9–11; appendix), including during the late postictal stage when respiration faded (appendix). In the eight patients used to calculate inter-rater variability of respiration assessment, 601 respiratory movements were detected by either one of the two independent raters. Their reports agreed for 586 events, and disagreed for 15, leading to a probability of agreement between raters of 97·5%. The corresponding estimated agreement parameter fitting a logistic regression model was log(586/15)=3·67, and that fitting a mixed-effect logistic regression model with a random effect for inter-patient variability was 3·77, corresponding to an estimated probability of agreement of 97·7%. The two investigators reached a consensus on each of their disagreements.

Overall, the sequence of respiratory and cardiac events that led to terminal cardiorespiratory arrests could be ascertained in ten patients with monitored SUDEP (2–11), despite missing sections of recording in three patients (4, 9, and 11). Four consistent features were observed in all informative monitored SUDEP. First, the immediate postictal phase was characterised by rapid breathing between 18 and 50 breaths per min (median 30 per min, IQR 21–30), while heart rate varied from 55 to 145 beats per min (median 90 per min, IQR 76–101). Second, postictal generalised EEG

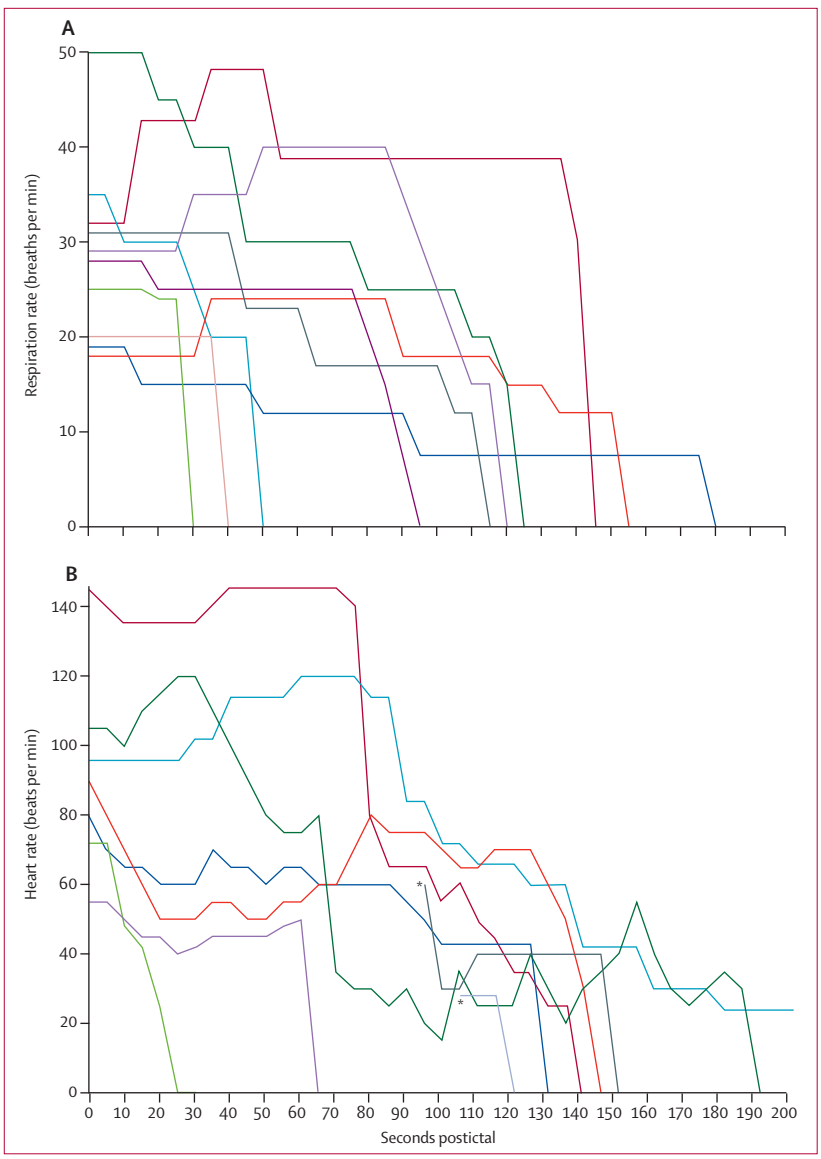

Figure 3: **Patterns of respiratory rate and cardiac rate during the first 3 min postictally in patients who had a monitored SUDEP**

(A) Respiratory rates in the ten patients with monitored SUDEP for which these data were available. Each line represents a patient and stops at the beginning of the first apnoea longer than 10 s. All patients had a respiratory rate of 18 breaths per min or higher at the end of GTCS, which rapidly deteriorated until transient or terminal apnoea. (B) Cardiac rates in the nine patients with monitored SUDEP for which these data were available. Each line represents a patient and stops at the beginning of the first asystole longer than 5 s if occurring during the first 200 s postictal. In two patients (4 and 11) for whom heart rate was extracted from electrocardiogram artifact observed on EEG traces, data are missing until the first 100 s and 105 s postictal (*) because of respiratory movement artifacts obscuring EEG traces. Heart rate varied between 55 and 145 beats per min at the end of GTCS, and deteriorated in parallel with respiration until asystole or major bradycardia in one patient (5). SUDEP=sudden unexpected death in epilepsy. GTCS=generalised tonic-clonic seizure. EEG=electroencephalogram.

suppression was observed in all monitored SUDEP cases once EEG was no longer obscured by respiratory-related artifacts. Third, an early cardiorespiratory dysfunction developed in all patients during the first 3 min postictally (figures 1, 2). This dysfunction was characterised by bradycardia (<45 beats per min) starting between 15 and 140 s postictally (median 100 s, IQR 48–130) and culminating in asystole in nine patients (90%) between 20 and 190 s postictally (median 135 s, IQR 106–146; figure 3), periods of apnoea with onset varying between 25 and 180 s postictally (median 118 s, IQR 61–136; figure 3), and a parallel worsening of cardiac and respiratory dysfunction that usually peaked together between the first and third minutes postictally (appendix). Fourth, terminal apnoea always preceded terminal asystole (figure 2).

Two distinct patterns of evolution were noted. In three patients (2, 7, and 10), the early cardiorespiratory arrest described above was terminal. A similar pattern was observed in a fourth patient (9) for whom transient arrest of recording hampered firm conclusion. In the six others, cardiorespiratory arrest spontaneously reversed after a median duration of 13 s of asystole (IQR 7–30, range 5–55) and 50 s of apnoea (IQR 28–116, range 15–150). In these patients, restored respiration progressively deteriorated with reduced frequency and amplitude of respiratory movements, including transient apnoeic episodes of 10–120 s duration in four patients, until terminal apnoea, which occurred 2·5–10·8 min postictally (median 5·2, IQR 3·8–8·6). Restored heart rate showed persistent bradycardia until terminal asystole in two patients, while in the other four, bradycardia resumed only after the onset of terminal apnoea. Five of these six patients also showed further transient asystole of 5–40 s duration. Terminal asystole always followed terminal apnoea with a delay of 2·4–8·8 min (median 4·5, IQR 4·0–5·5).

Near SUDEP was monitored in five cases and presented with variable patterns, including: GTCS followed by early postictal apnoea followed by asystole, reproducing the most common pattern observed for SUDEP (n=2; postictal EEG showed diffuse suppression after 20 s in one patient, and was not available in the other); ictal asystole (n=1) and ventricular fibrillation (n=1) progressing to cardiorespiratory arrest, triggered by partial seizure of insular origin and GTCS, respectively; and postictal cardiorespiratory arrest after partial seizure of insular origin (n=1).

Seven (24%) of the 29 cardiorespiratory arrests, including five SUDEP and two near SUDEP, were reported outside the epidemiological survey and were not considered in the calculation of incidence (six from units in the USA or India, and one in Europe occurring after the census stop date). Table 3 shows the incidence of cardiorespiratory arrest, pooled SUDEP or near SUDEP, death from all causes, and SUDEP for the overall population and relevant subgroups (adults, children, presurgical VEEG, other diagnostic VEEG). The incidence of definite or probable SUDEP per 1000 person-years was 7·5 (95% CI 3·6–13·8) in adults undergoing presurgical evaluation, versus 1·2 (0·0–6·9) in those undergoing VEEG for other diagnostic purposes. The risk of definite or probable SUDEP per 10 000 VEEGs was 1·2 (0·6–2·1) in adults, 2·1 (1·0–3·8)

	Adults			Children, all presurgical VEEG (436 patient-years)	Total (3008 patient-years)
	Presurgical VEEG (1334 patient-years)	Other VEEG (812 patient-years)	Total VEEG (2146 patient-years)		
Incidence of all cardiorespiratory arrests	12·7 (7·4–20·4; n=17)	4·9 (1·3–12·6; n=4)	9·8 (6·1–15·0; n=21)	2·3 (0·1–12·8; n=1)	7·3 (4·6–11·1; n=22)
Incidence of SUDEP or near SUDEP	9·7 (5·2–16·7; n=13)	4·9 (1·3–12·6; n=4)	7·9 (4·6–12·7; n=17)	2·3 (0·1–12·8; n=1)	6·0 (3·5–9·5; n=18)
Incidence of death	11·2 (6·3–18·5; n=15)	2·5 (0·0–6·9; n=2)	7·9 (4·6–12·7; n=17)	No data	5·7 (3·3–9·0; n=17)
Incidence of SUDEP	7·5 (3·6–13·8; n=10)	1·2 (0·0–6·9; n=1)	5·1 (2·6–9·2; n=11)	No data	3·7 (1·8–6·5; n=11)

Data are events per 1000 patient-years (95% CI; number of patients). SUDEP=sudden unexpected death in epilepsy. VEEG=long-term video electroencephalogram monitoring (>24 h). *The five SUDEP and two near SUDEP cases reported by centres outside the MORTEMUS study list or after census stop date were not taken into account for calculation of incidence.

Table 3*: Incidence of cardiorespiratory arrest, SUDEP or near SUDEP, death, and SUDEP in epilepsy monitoring units

in those undergoing presurgical evaluation, versus 0·2 (0·0–1·2) in those undergoing VEEG for other diagnostic purposes.

Discussion

Although rare, VEEG-recorded cardiorespiratory arrests occurring in epilepsy monitoring units provide crucial insights into SUDEP pathophysiology.[1,3] Our findings shed light on a previously unrecognised pattern common to all monitored SUDEP, whereby the triggering GTCS is followed by a short period of normal or increased heart and respiratory rates, after which a combination of central apnoea, severe bradycardia, and most often transient asystole occurs together with postictal generalised EEG suppression, typically peaking between 1 and 3 min postictally. This cardiorespiratory collapse is terminal in a third of patients. In the remainder, it is followed by transient restoration of cardiac function associated with abnormal and possibly ineffective respiration probably aggravated by the prone position. Respiration then progressively deteriorates until terminal apnoea, which always precedes terminal asystole.

Thus, our data suggest that the main mechanism leading to SUDEP starts with an early, centrally mediated, severe alteration of both respiratory and cardiac functions after GTCS, which we propose to refer to as an early postictal neurovegetative breakdown. Depending on its intensity, this mechanism might lead to immediate death or delayed terminal cardiorespiratory arrest after several minutes of altered cardiorespiratory function, most likely aggravated by profound hypoxia. A hypothesis is that intrinsic mechanisms leading to or associated with seizure termination cause this centrally mediated neurovegetative breakdown and postictal generalised EEG suppression. The contribution of ictal hypoxia in determining the occurrence and severity of this pattern as discussed below is unknown. The timescale involved suggests a potential window for life-saving intervention, in as much as all patients in whom CPR was started within 3 min after cardiorespiratory arrest were successfully resuscitated.

We have found no previous study investigating the incidence and mechanisms of SUDEP and near SUDEP in epilepsy monitoring units on an international level (panel 2). 11 monitored SUDEP and five monitored near SUDEP cases were collated in MORTEMUS and analysed with a systematic assessment by an expert panel independent of the reporting units. All eight previously published case reports with detailed information were included in this reviewing process,[4–7,9–11] reducing case selection bias, and allowing for the identification of a previously unrecognised consistent pattern. We are aware of only two other monitored SUDEP cases reported in abstract form more than 15 years ago,[12,13] with no further data available. The small amount of information in these abstracts is consistent with our observations. Another SUDEP was captured during ambulatory EEG with no available respiratory or ECG data.[14] A monitored death was also reported in a patient with previous myocardial infarction and angina who had seizures in the context of chest pain with ECG changes, cyanosis, and cardiac arrest with terminal ventricular fibrillation, suggesting ischaemic coronary artery disease, rather than SUDEP.[15] Similarly, the few cases of ictal respiratory distress without cardiac arrest,[16] as well as the numerous cases of spontaneously reversible ictal asystole,[17] represent different concerns. Overall, our series offers a comprehensive assessment of respiratory and cardiac data currently available worldwide for patients who have a monitored SUDEP or near SUDEP. Although some caution is needed in extrapolating these observations to out-of-hospital SUDEP, both share similar patient profiles and circumstances of death, including age, GTCS and nocturnal seizures, prone position, and lack of supervision.[18,19]

Limitations of this study include the small number of cases reported, despite the comprehensive survey undertaken, the absence of pathological data in half the cases of SUDEP that fulfilled the criteria of probable SUDEP, and missing or suboptimum ECG and respiratory data. In the nine SUDEP cases for which heart rate could be calculated, ECG data were extracted

from flat EEG in two patients and were recorded through a single precordial derivation in the others. Although such data enable precise measures of heart rate and detection of bigeminy or irregular cardiac rhythm, they cannot provide reliable information about the morphology of QRS complexes. The assessment of postictal respiration through video and EEG data also raises substantial concern, despite its very high inter-rater agreement. Some respiratory movements might have been too subtle to be detected on video or through movement-related EEG artifacts. However, this possibility seems unlikely according to the very stereotyped and readily detectable pattern observed across patients until terminal gasps.

A more important limitation is the lack of data on blood pressure, cerebral perfusion, oximetry, and partial pressure of CO_2. Respiration, even if well ascertained, cannot provide information about the timing and level of hypoxia. There are very likely to be periods of clinically significant hypoventilation due to inadequate respiration, neurally mediated pulmonary oedema[20] (a pathological hallmark of SUDEP), mismatch, or internal or external obstruction to airflow, which we could not assess. Hypoxia could have been promoted by the prone position noted in most SUDEP cases, even though most patients had their face slightly tilted to the side and not strictly down in the pillow. However, they were not seen to take any corrective action to optimise their position and remained in the same position from seizure end until death. Finally, respiration is withheld during GTCS, resulting in ictal hypoxaemia in 33% of cases.[21] Thus, brain oxygenation might well be already compromised before postictal apnoea in GTCS-induced SUDEP, possibly leading to a self-aggravating process whereby cerebral hypoxia promotes breakdown of central neurovegetative functions and vice versa.[9] The rapid breathing observed immediately postictally might reflect such hypoxia. Similar respiratory rates have been recently reported after GTCS,[22,23] with mean values between 22 and 27 breaths per min, reflecting an average increase of 12 breaths per min from preictal baseline.[24]

The role and interpretation of postictal EEG suppression observed in all cases in this series also remains uncertain. Postictal generalised EEG suppression has been reported to occur in 27–82% of GTCS,[5,23–29] whereas it seems to be rare in partial seizures.[25,29] Its underlying mechanism is unknown and possibly multifactorial. Seizure-induced neuronal exhaustion seems unlikely to represent a primary factor in view of the absence of correlation between duration of GTCS and the presence or duration of postictal generalised EEG suppression.[5,24–29] Alternative hypotheses include a dysfunction of subcortical and brainstem network controlling electrogenesis,[30] mechanisms involved in seizure termination including release of neurotransmitters such as adenosine,[31] seizure-associated cortical spreading depression, major hypoxia, or acute hypercapnia.[32] A scenario whereby the ictal respiratory dysfunction discussed above could promote postictal generalised EEG suppression is supported by several observations: an association between the occurrence of ictal hypoxaemia and postictal generalised EEG suppression,[24,29] with the nadir of oxygen de-saturation always preceding the onset of suppression;[24] a correlation between the duration of the tonic phase of GTCS, in which breathing is withheld, and the later occurrence of postictal generalised EEG suppression;[23] and the association between early nurse intervention during GTCS and reduced ictal hypoxaemia and risk of postictal generalised EEG suppression.[32] In fact, GTCS associated with postictal generalised EEG suppression were characterised by longer postictal immobility and

Panel 2: Research in context

Systematic review

We searched the PubMed database from Jan 1, 1950, to June 30, 2013, using the terms "epilepsy" and "sudden death". A secondary search for missed references was done by review of the bibliographies of review articles and meta-analyses identified in the primary search. We identified 740 articles. Our search was not limited by language. We did not set any criteria for assessment of quality. We did not find any previous report estimating the incidence of sudden unexpected death in epilepsy (SUDEP) and near SUDEP in patients undergoing long-term video electroencephalogram (EEG) monitoring. Our search identified six reports of a total of five cases of SUDEP and two near SUDEP that had occurred during EEG monitoring with or without video. The reports suggested different primary mechanisms for the fatal outcome including ictal hypoventilation, postictal central apnoea, positional airway obstruction, ictal cardiac malignant arrhythmia, and postictal generalised EEG suppression. However, the sequence of events leading up to SUDEP or near SUDEP has not previously been analysed in a systematic, standardised manner, which is likely to have contributed to the divergent conclusions.

Interpretation

Our systematic international survey of cardiorespiratory arrests in epilepsy monitoring units identified 16 cases of SUDEP and nine cases of near SUDEP. SUDEP rates in the units were similar to out-of-hospital rates in patients with refractory epilepsy. The circumstances surrounding death suggest a need for reassessment of safety protocols in epilepsy monitoring units with the aim of reducing the risks. Our review of all available video EEG and electrocardiogram recordings showed a consistent and previously unrecognised pattern of terminal events, in which SUDEP in epilepsy monitoring units primarily resulted from an early postictal neurovegetative breakdown induced by generalised tonic-clonic seizure leading to immediate death or a short period of partly restored cardiorespiratory function followed by terminal apnoea and then cardiac arrest.

prompted more frequent nurse intervention than did GTCS without this suppression.[27,32] Finally, postictal generalised EEG suppression was associated with peri-ictal autonomic dysfunction,[23,26] including reduced postictal tachycardia,[23] again arguing against it being an independent factor, although the peri-ictal autonomic finding was not reproduced in another study.[28] Similarly, the relation between postictal generalised EEG suppression and risk of SUDEP remains controversial. The duration of suppression predicted the risk of SUDEP in one case-controlled study,[5] but this finding was not confirmed in another.[25] During SUDEP, interpretation of postictal generalised EEG suppression is further complicated by the occurrence of early transient or terminal postictal apnoea and asystole, both of which can influence the EEG suppression observed thereafter. Furthermore, the immediate postictal EEG activity is obscured by prevalent respiratory artifacts, an observation previously reported by others leading to the first 30 s postictally often being disregarded,[5,25] and hampering interpretation of postictal generalised EEG suppression in this context.

Non-fatal near SUDEP might be due to effective resuscitation or differ pathophysiologically from fatal cases. Our observations support both these possibilities. Close analysis of the monitored near SUDEP cases strongly suggests that patients would have died without prompt CPR. However, the sequence of events differed in some cases from that usually observed in monitored SUDEP, with GTCS not always implicated and cardiorespiratory arrests triggered by ictal rather than postictal cardiac disorder (ie, asystole or ventricular fibrillation) in two patients. Another distinctive feature of non-fatal near SUDEP was its daytime occurrence in 86% of cases versus 11% in SUDEP and fatal near SUDEP. The preferential occurrence of SUDEP at night out of hospital is well known.[33,34] Accordingly, the occurrence of nocturnal seizures was found to be a risk factor for SUDEP.[35] This finding could reflect circadian differences in the brain response to GTCS during sleep, with greater risk of neurovegetative dysfunction during the night. Indeed, a case-control study of SUDEP showed greater increase in postictal heart rate in cases compared with controls, selectively at night,[36] while another series reported reduced heart-rate variability during sleep in epilepsy surgery candidates.[37] Postictal generalised EEG suppression was also found to be more common at night.[28] However, two other recent studies failed to confirm this finding,[22,29] and one also found no difference in peri-ictal autonomic dysfunction between diurnal and nocturnal GTCS.[22]

The distinct circadian occurrence of SUDEP and near SUDEP is also likely to reflect more effective supervision and timely CPR during the day than at night, as suggested by our data. Indeed, CPR was started within 3 min in all but one of the daytime cardiorespiratory arrests occurring before 1930 h, but in none of those occurring later or at night. In fact, none of the 16 SUDEP cases had CPR within 10 min of apnoea. This observation provides indirect support for the previously reported protective effect of nocturnal supervision, including outside hospital.[38,39] It also clearly points to suboptimum supervision of patients in epilepsy monitoring units, especially at night. In fact, more than half of SUDEP and fatal near SUDEP cases, either monitored or not, occurred under a similar level of supervision to that of a standard neurological ward where the patient's clinical status is checked a few times per night. In the other cases, constant nocturnal supervision was organised but with reduced staff compared with daytime monitoring, possibly accounting for the delayed interventions. These observations suggest that more intensive nocturnal supervision and education of staff regarding the risk of GTCS-induced cardiorespiratory arrest might reduce the occurrence of SUDEP in epilepsy monitoring units.

The estimated risk of SUDEP in epilepsy monitoring units was 2·1 per 10 000 presurgical monitorings in adults, translating into SUDEP incidence (7·5 per 1000 patient-years) in the same order as that among ambulatory patients contemplating or having failed epilepsy surgery (between 6 and 9 per 1000 patient-years).[3] Some might argue that the risk of SUDEP in these units is too low to prompt a change in practice. We disagree with this view for the following reasons. Most affected patients are healthy young adults with potentially surgically remediable epilepsy in whom such a tragic outcome, if avoidable, is unacceptable. The failure to use readily available solutions to ensure timely detection of cardiorespiratory arrests and CPR, such as effective constant supervision or standard oximetry and ECG or pulse alarm systems, is indefensible. Furthermore, staff often choose to instigate drug withdrawal to facilitate the seizure occurrence necessary for patient evaluation. Drug withdrawal raises the risk of GTCS,[40] and potentially SUDEP, as suggested by our data. This potential causality is supported by the complementary observation that addition of another antiepileptic drug during randomised controlled trials of refractory epilepsy was found to decrease by seven fold the risk of SUDEP compared with placebo.[41] Although rare, SUDEP and near SUDEP in epilepsy monitoring units were encountered by more than 10% of surveyed units in our study. Accordingly, a recent survey of 70 US-based units showed that 7% of centres have encountered a cardiac arrest, and 3% a death, within the past 12 months.[42] Finally, patients in these units face other important risks, such as seizure clusters, status epilepticus, and GTCS-induced vertebral compression,[40,43–46] all of which might be reduced by improved safety protocols.[40,43]

Existing guidelines for long-term VEEG monitoring offer little information about safety measures.[47–49] The guidelines of the North American association of epilepsy centres recommend around the clock VEEG with continuous supervision,[49] a policy followed by only 78%

of units surveyed in our study and 74% of US-based units.[50] The routine use of oximetry and ECG or pulse alarm systems is not regarded as a current standard of care in epilepsy monitoring units, by contrast with other medical departments where patients face substantial risk of cardiorespiratory arrest. This policy deserves to be challenged, and in particular nocturnal monitoring and supervision should be improved. Finally, no controlled data are available regarding the risk–benefit balance of current practices of antiepileptic drug withdrawal in epilepsy monitoring units, translating into absence of precise recommendation. Overall, our findings should prompt reassessment of safety protocols in epilepsy monitoring units with the aim of reducing the risk of GTCS-induced cardiorespiratory arrests and allowing their timely detection and effective CPR.

Contributors

The three scientific coordinators of the study, PR, LN, and TT, conceptualised, designed, and ran the study. They, as well as SR, reviewed and analysed the data. All other authors reported a patient who had a SUDEP or a near SUDEP in an epilepsy monitoring unit, and analysed the corresponding data. All authors contributed to the preparation of the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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