

Sudden unexpected death in epilepsy

FERGUS J. RUGG-GUNN

Department of Clinical and Experimental Epilepsy, The National Hospital for Neurology and Neurosurgery, Queen Square, London

SUDEP is defined as the sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death in patients with epilepsy with or without evidence for a seizure, and excluding documented status epilepticus, in which postmortem examination does not reveal a structural or toxicological cause for death¹. Where autopsy is not performed, and for the purpose of epidemiological studies, sudden death occurring in benign circumstances with no known competing cause for death is classified as ‘probable SUDEP’. Despite an applicable definition, and clear guidance where there is uncertainty, significant variability in use has hampered efforts to integrate findings from multiple studies on epidemiological and risk factor data and hence establish common relevant factors^{2,3}.

Epidemiology

Sudden unexpected death in the general population is extremely rare in young adults with an incidence of 5–10/100,000 person-years, while the rate climbs steeply with advancing age to approximately 300/100,000 person-years in the elderly⁴. The incidence of sudden death in patients with epilepsy is significantly higher and varies markedly with the population studied⁵. For example, in population-based studies the incidence has been reported to be 0.35 and 2.7/1000 person-years depending on the methodologies employed^{6,7}. This increases to between 2 and 5.9/1000 person-years in cohorts of patients attending specialist epilepsy clinics^{8–10}, 3.4/1000 person-years in pupils with epilepsy enrolled in a special residential school¹¹ and up to 9.3/1000 person-years in epilepsy surgery candidates^{12,13}. The incidence of sudden death in young adults with intractable epilepsy is therefore many times that of the general population, with a peak between the ages of 20 and 40 years¹⁴. In older age groups the relative increased incidence of SUDEP is too small to measure, and is confounded by the occurrence of co-morbidity such as cardiovascular, respiratory or cerebrovascular disease.

Risk factors

There is significant debate regarding risk factors for SUDEP. Relevant and independent risk factors are difficult to establish given the non-independence of patient, syndrome, seizures and treatment characteristics. Multiple logistic regression analyses require large cohorts of patients to achieve statistical significance for each of the variables evaluated and this is difficult to attain¹⁵. Furthermore, the high variability between studies in terms of patient cohorts, definition, choice of control group, methodology and overall study quality precludes not only a valid meta-analysis, but even a simple meaningful comparison.

Demographics

Descriptive studies have almost universally reported that patients with SUDEP are young adults^{6,7,9,10,16–20}. A number of biases exist however, including, by definition, the exclusion of patients with significant co-morbidity associated with increasing age, such as ischaemic heart disease or cerebrovascular disease, identified on postmortem examination^{9,16,20}. Other examples of bias include case identification through self-referral by bereaved relatives, most commonly parents¹⁸, and studies with only small numbers of patients^{6,9}. Case-control studies

are less conclusive. Some studies only included defined age groups and can draw no conclusions regarding other age groups. Nevertheless, it is interesting to note that 70–80% of the studied population in a number of case-control studies were less than 45 years old^{14,21}. Data regarding age, however, is not available from a number of large studies due to age-matching of control subjects^{14,21,22}.

Of the remaining studies, the use of a cohort of non-SUDEP deaths as a control group may bias the patient group towards a younger age due to exclusion of co-morbid conditions more commonly associated with advancing age^{23–26}, although young age as an independent risk factor has not been universally reported^{27,28}. The likelihood of selection bias is corroborated by finding significantly less co-morbidity in the SUDEP group than the non-SUDEP group²⁶. In studies using living control subjects, younger age was not seen more frequently in the SUDEP group, although numbers of SUDEP patients were small⁸.

Although a large number of descriptive studies have suggested that male gender is a significant risk factor for SUDEP^{7,9,17,20,29}, this has not been confirmed by the vast majority of case-control studies^{21–23,26–28,24,30,34}. In addition, a small number of both descriptive and case-control studies have reported a significantly increased standardised mortality rate in female patients, which may be attributable to a lower background rate of death in the female non-SUDEP control group^{6,25}.

Epilepsy characteristics

A number of case-control studies have suggested that early onset of epilepsy is a significant risk factor for SUDEP^{21,24,26,27}. For example, an eight-fold higher SUDEP risk in patients with an onset of epilepsy between the ages of 0 and 15 years has been reported, when compared to patients with seizure onset after 45 years of age²¹. However, while this may reflect a different aetiological basis for the epilepsy, it may also merely be a surrogate marker for an increased cumulative lifetime risk of having seizures for a longer period of time, as suggested by other studies^{14,19,20}. Conversely, there are several reports of a shorter duration of epilepsy being associated with an increased risk of SUDEP although this is most likely as a result of comparison with an older control population^{23,24,26}. Furthermore, following conditional multiple logistic regression analysis, a long duration of epilepsy (>30 years) was no longer a risk factor after adjustment for seizure frequency²⁸.

One would expect epilepsy syndrome to be a key factor in defining the risk of SUDEP. Yet there is only limited evidence to support the association of epilepsy syndrome with an increased risk of SUDEP^{21,27}. Discordant results from the relatively few case-control studies that assessed this risk factor and low numbers of patients in each group preclude detailed evaluation or definitive conclusions²⁵. In one study, 7 out of 57 (12%) SUDEP cases had primarily generalised epilepsy compared to 12 out of 171 (7%) control subjects. Statistical comparison revealed that there was a higher risk of SUDEP in patients with primary generalised epilepsy compared to patients with focal, symptomatic epilepsy, although this was only significant in men²¹. Nevertheless, although idiopathic primary generalised epilepsy (IGE) is usually less refractory to treatment, individuals with IGE are well represented in SUDEP cohorts. It is possible that specific epilepsy syndrome subtypes carry an increased risk of sudden death due to phenotypic expression in other cerebral and possibly cardiac structures.

Less controversy exists as to whether high seizure frequency is an independent risk factor for SUDEP. Several descriptive and large case-control studies have reported an increased risk of SUDEP in patients experiencing frequent seizures^{19,21,22,24,28,29}. This increased risk is most marked for convulsive seizures^{6–8,18,19,22,28} rather than non-convulsive episodes, such as complex partial seizures²⁴. Moreover, on logistic regression analysis, it was noted that only the frequency of convulsive seizures was relevant, and not the frequency of all seizures

combined²⁸. Conversely, high seizure frequency was not an independent risk factor in a number of other reports although a number of methodological issues exist^{8,20,25,27}. For example, in a retrospective case-control study of 42 patients with SUDEP there was no reported difference in seizure frequency between the SUDEP and non-SUDEP control groups. The study was undertaken at a tertiary referral centre, with both groups having chronic refractory epilepsy and frequent seizures²⁷. Other negative studies may have been similarly influenced²⁵. Intuitively, the *severity* of convulsive seizures may also be important in SUDEP, but this is more challenging to quantify and hence has not been evaluated as a risk factor.

Antiepileptic medication

The number of antiepileptic drugs (AEDs) taken concomitantly has been reported to be an independent risk factor for SUDEP²⁹, even after correction for seizure frequency^{21,28}. This is not universally reported however^{8,14,25-27}, although small numbers of patients and a high frequency of polytherapy in control subjects may be contributory in these negative studies. It has been shown that the risk of SUDEP increases with the number of AEDs previously taken despite correction for seizure frequency, perhaps a surrogate for epilepsy severity. Risk of SUDEP is also increased in those whose treatment history was unclear, which may reflect the risk associated with the lack of treatment and uncontrolled seizures, although the reason for this was not objectively assessed²².

Despite several descriptive studies suggesting that subtherapeutic levels of AEDs are a risk factor for SUDEP^{6,7,16,20}, this has not been corroborated by the majority of case-control studies^{25,31,32}, most likely because this is difficult to study as an independent factor. Of note is that postmortem levels of AEDs may not accurately reflect antemortem levels possibly due to, for example, redistribution and continuing metabolism³³. Compliance with AED treatment was proposed as a risk factor for SUDEP in an uncontrolled study which found 'subtherapeutic' AED levels in 68% of SUDEP cases¹⁶. Therapeutic drug monitoring has traditionally been considered a surrogate for medication adherence although, due to the existence of a number of confounding factors, it is clear that the two terms are not interchangeable. For example, in patients with uncontrolled seizures, changes of dose and type of medication are commonplace and serum levels will not be stable and may frequently be sub-therapeutic despite excellent compliance. The issue of variability of AED use was recently addressed in a study comparing hair AED concentration variability in patients with SUDEP, non-SUDEP epilepsy-related deaths, epilepsy outpatients and epilepsy inpatients. The SUDEP group showed greater hair AED concentration variability than either the outpatient or the inpatient groups, reflecting variable AED ingestion over time. However, this cannot distinguish prescribed changes from poor compliance, or identify consistent non-compliance over time. Secondly, it does not provide information on drug taking behaviour immediately before death as it takes about five days for drug sequestered into the follicle to appear at the scalp; therefore short-term non-compliance immediately before death is not assessed by this study and may have been overlooked³⁴.

Despite a number of descriptive and controlled studies, no specific AED has been clearly associated with an increased risk of SUDEP^{14,20,23,27,28,31,35}, although a small number of studies have implicated treatment with carbamazepine as an independent risk factor^{22,36,37}. For antiepileptic medication in general, proposed mechanisms include perturbed heart rate variability, lengthening of the Q-T interval on the electrocardiogram combined with a mild pro-arrhythmic effect of epileptic seizure discharges, or excessive post-seizure brainstem inhibition producing a blunting or transient abolition of the central hypoxic and hypercarbic respiratory drive, with consequent post-ictal respiratory arrest³⁶⁻³⁸. Elevated serum levels of carbamazepine have been associated with an increased risk of SUDEP even after adjustments for seizure frequency have been made. Frequent drug changes and multiple concomitant AEDs, conventional markers of severe and unstable epilepsy, increased this risk

synergistically³². On this basis, it is difficult to know whether a high carbamazepine level is an independent risk factor or is merely representative of challenging epilepsy.

Perimortem features

There is evidence from both descriptive and controlled studies that a terminal convulsive seizure^{7,10,16,18,20,25,27,39}, being found alone in bed^{10,17-19,25,27} and in the prone position^{20,27} are independent risk factors for SUDEP. Whereas a small number of descriptive studies have not found an association, all case-control studies that have evaluated these factors have found a positive relationship with the risk of SUDEP. In a published report of interviews with bereaved relatives, evidence for a terminal seizure was found in 24 out of 26 cases but it is of interest that only two were witnessed. The observation that, in most studies, unwitnessed cases far outnumber those witnessed suggests that enhanced surveillance of patients with epilepsy may be protective¹⁸. This is corroborated by a study of young patients with epilepsy at a special residential school. All sudden deaths during the period of the study occurred when the pupils were not under the close supervision of the school and most were unwitnessed¹¹. Similar findings of a protective effect of enhanced supervision at night were also found in a large controlled study, where supervision was defined as the presence in the bedroom of an individual of normal intelligence and at least 10 years old or the use of special precautions, such as checks throughout the night or the use of a listening device²².

In some cases where a prone position was not observed, other factors which might compromise breathing were identified. For example, in one study only five out of 26 people were found face down in the pillow, and a sixth with the head in carpet pile. In total however, there were 11 out of 26 cases in which an extrinsic or intrinsic positional obstruction to breathing amenable to intervention may have contributed¹⁸. Moreover, it is possible that this may be an underestimate as obstructive apnoea can occur in an apparently benign position⁴⁰.

Other features

There is limited evidence for an independent relationship between learning disability and an increased risk of SUDEP. Early descriptive and population-based studies, in which learning disability was determined by observer impressions rather than by formal IQ examination, provided only weak support for this association^{7,41}. Most recent studies have found no clear correlation^{18,25-27,30} although others have reported an IQ of less than 70 to be a risk factor for SUDEP, even after accounting for seizure frequency²⁸. It has been postulated that patients with learning disability are more susceptible to central apnoea and positional asphyxia that may cause SUDEP as a result of prolonged post-ictal encephalopathy⁴², decreased post-ictal respiratory drive and impaired movement and righting reflexes²⁸. Despite early reports of an increased incidence of structural lesions in patients with SUDEP^{7,16,43}, this has not been confirmed by more recent, controlled studies^{21,27,28}. While there is evidence that psychotropic medication can influence the risk of sudden death in general, there is no convincing evidence of this being particularly relevant in SUDEP.

Pathophysiology of SUDEP

Pathophysiological mechanisms of SUDEP are likely to be heterogeneous and may be multifactorial. Theories propounded have focused on autonomic disturbance – particularly cardiac arrhythmias and central and obstructive apnoea and neurogenic pulmonary oedema. Additionally, the possibility of structural or functional cardiac pathology predisposing patients with epilepsy to cardiac events has been proposed.

Cerebrogenic autonomic control

The components of the central autonomic network involved in the functional relationships between cortical, subcortical and somatic regions have been elucidated from experimental and human stimulation and lesional studies. For example, it has been demonstrated that

limbic structures, especially the amygdala and pyriform cortex, modulate hypothalamic function, and stimulation of these foci can elicit both sympathetic and parasympathetic visceromotor autonomic responses⁴⁴.

Other than visual inspection of a standard 12-lead ECG, more sophisticated methods to interrogate the cardiac autonomic system have been developed, for example, measures of heart rate variability (HRV). In its simplest form this is measured in a time domain analysis as the standard deviation of R-R wave intervals^{45,46}. Frequency domain analysis permits the calculation of high-frequency (HF) and low-frequency (LF) components which assess the relative contribution of parasympathetic and sympathetic autonomic activity⁴⁷.

Cardiac mechanisms

Structural cardiac pathology. The exclusion of cardiac pathology as a contributing factor in SUDEP is challenging due to the presence of, for example, subtle abnormalities that only a detailed microscopic examination of cardiac tissue can elucidate, such as conducting system fibrosis or cardiomyopathy⁴⁸, tissue decomposition precluding the acquisition of suitable material for evaluation, lack of an appropriate control group for comparison, and the possibility of a functional rather than a structural disorder, such as ion channelopathies or pre-excitation syndromes, with normal macroscopic and microscopic examinations being implicated⁴⁹.

Increased cardiac weight has been observed in male SUDEP cases compared to control subjects⁷ although more recent studies, using more convincing methodology, have failed to replicate this earlier finding and cardiac weight is not considered to differ between SUDEP and non-SUDEP cases⁵⁰⁻⁵². Minor, non-specific pathological changes presumed to be non-fatal, such as atherosclerosis, conducting system fibrosis and diffuse myocardial fibrosis have been identified in SUDEP cases^{27,51,53}. It has been postulated that neurogenic coronary vasospasm may be implicated, and that if recurrent, this may eventually progress to perivascular and interstitial fibrosis⁵⁴. This may, in turn, predispose the heart to arrhythmogenesis, particularly in the setting of considerable autonomic imbalance during seizures^{55,56}. The occurrence and significance of these pathological changes in SUDEP is not universally agreed however^{50,57} and the full characterisation of the relationship between myocardial pathology and acute and recurrent seizures remains unclear at the present time.

Inter-ictal. At the simplest level, inter-ictal cardiac function can be evaluated by visually assessing a standard 12-lead ECG, primarily for evidence of conduction abnormalities, although these are frequently normal⁵⁸⁻⁶⁰ or show only minor, non-significant changes⁶¹. However, a recent preliminary study of 128 patients with severe refractory epilepsy and learning disability revealed inter-ictal ECG abnormalities in approximately 60% of patients, including first-degree atrio-ventricular block and poor R-wave progression⁶².

Early experimental studies demonstrated that inter-ictal epileptiform activity was associated with sympathetic and parasympathetic autonomic dysfunction, in a time-locked synchronised pattern^{63,64}. In the first clinical reports, analysis of inter-ictal heart rate variability in 19 patients with refractory temporal lobe epilepsy revealed frequent, high-amplitude fluctuations in heart rate which were most pronounced in poor surgical candidates⁶⁵. More recently, reduced sympathetic tone, demonstrated by decreased low-frequency power, has been seen in both focal and, albeit less markedly, primary generalised epilepsy^{45,60,65,66}. Overall, there is some evidence for inter-ictal cardiac autonomic dysfunction in patients with both focal and generalised epilepsy, possibly modulated by antiepileptic medication, in particular carbamazepine. There are conflicting reports in the literature however, suggesting that the relationship between inter-ictal epileptiform activity, antiepileptic medication and autonomic function has not yet been fully characterised.

Ictal. Arrhythmias, conduction block and repolarisation ECG abnormalities, such as atrial fibrillation, marked sinus arrhythmia, supraventricular tachycardia, atrial and ventricular premature depolarisation, bundle-branch block, high-grade atrioventricular conduction block, ST segment depression and T wave inversion have been reported in up to 56% of seizures. Abnormalities appear to be more common in nocturnal, prolonged and generalised seizures than in focal seizures or those occurring during wakefulness^{44,67-70}.

Sinus rate change is the most common cardiac accompaniment to ictal discharge. Sinus tachycardia has been reported in 50–100% of seizures, and is dependent on the definition used and population studied^{58-60,70-76}. Although the heart rate in ictal tachycardia is typically 100–120 beats per minute⁵⁸, there are reports of rates exceeding 170 beats per minute, even during simple partial seizures^{59,71}. Ictal tachycardia is most commonly seen in the early ictal phase, soon after seizure onset^{71,73,75,76}, or rarely before clear evidence of electroclinical onset⁷⁰. This contrasts with ictal bradycardia which is seen during the late ictal phase or in the immediate post-ictal period^{77,78}. There is some evidence for right-sided lateralisation and temporal lobe localisation in patients with ictal tachycardia^{72,73,76}, corroborating the reports of early experimental and clinical stimulation studies^{79,80,81}, although it is important to note that most temporal lobe seizures are associated with ictal tachycardia, irrespective of lateralisation. In contrast, in patients with unilateral temporal lobe epilepsy being evaluated with extensive intracranial EEG electrodes, irrespective of lateralisation of ictal onset, heart rate was seen to increase incrementally as new cortical regions anywhere in the brain were recruited⁸².

Although ictal tachycardia is almost universally observed, ictal bradycardia has received more attention due to the potential progression to cardiac asystole and intuitive but unproven association with SUDEP.

The first report of ictal asystole was by Russell in 1906, who noted the disappearance of a young male patient's pulse during a seizure⁸³. The published literature since that time is, unsurprisingly, mostly case reports or small series studies, which significantly limit the number and confidence of any conclusions extracted from the data. Ictal bradycardia is observed in <5% of recorded seizures^{59,73,75,84}, but may occur in a higher percentage of patients, because a consistent cardiac response to each apparently electroclinically identical seizure is not seen⁵⁹.

A recent literature review revealed that of 65 cases of ictal bradycardia with sufficient EEG and ECG data, seizure onset was localised to the temporal lobe in 55%, the frontal lobe in 20%, the frontotemporal region in 23%, and the occipital lobe in 2%. Information regarding seizure-onset lateralisation was available in 56 cases. Seizure onset was lateralised to the left hemisphere in 63%, the right in 34%, and bilaterally in 4%. Interestingly, of 22 cases with EEG data available at the onset of the bradycardia, 12 showed bilateral hemispheric ictal activity, while six showed left-sided, and four showed right-sided activity⁷⁸. No control group data is available however. Nevertheless, it appears that there is a trend towards the left temporal lobe being implicated in ictal bradycardia, however this is not sufficiently specific to be valuable localising semiological information^{78,84}.

Ictal asystole, lasting between 4 and 60 seconds, is reported, albeit rarely, in patients with refractory epilepsy^{40,59,70,85-87}. In addition, experimental data suggests that ictal bradyarrhythmias can lead to complete heart block⁶⁴. Short periods of EEG/ECG monitoring may underestimate the prevalence of ictal asystole. For example, evaluation of a database of 6825 patients undergoing inpatient video-EEG monitoring found ictal asystole in only 0.27% of all patients with epilepsy. In contrast, a study reported on 19 patients with refractory focal epilepsy who were implanted with an ECG loop recorder for up to 18 months. Over 220,000

patient hours of ECG recording were monitored, during which time 3377 seizures (1897 complex partial or secondarily generalised tonic-clonic seizures and 1480 simple partial seizures) were reported by patients. Cardiac rhythm was captured on the implantable loop recorders in 377 seizures. Ictal bradycardia was seen in 0.24% of all seizures over the study period, and 2.1% of the recorded seizures. Seven of the 19 patients experienced ictal bradycardia. Four of these had severe bradycardia or periods of asystole which led to the insertion of a permanent pacemaker. Notably, only a small proportion of seizures for every patient were associated with significant cardiac events despite identical seizure characteristics⁵⁹.

Extrapolation of ictal bradyarrhythmias to a mechanistic explanation for SUDEP remains elusive. This is, at least partly, due to a lack of clinical evidence of common factors shared by patients with ictal bradyarrhythmias and SUDEP and the difficulty in ascertaining the importance of ictal bradyarrhythmias in SUDEP in relation to other proposed mechanisms, including other intrinsic cardiac abnormalities or apnoea and hypoxia which may aggravate arrhythmias.

Respiratory mechanisms

It is likely that primary respiratory dysfunction is involved in an important proportion of SUDEP^{40,88-94}. Alterations in respiration such as coughing, sighing, hyperventilation, irregular breathing, apnoea, increased bronchial secretions, laryngospasm, respiratory arrest, and neurogenic pulmonary oedema have all been described with seizures^{40,92,94-96}. Some form of respiratory compromise is commonly reported in witnessed cases of SUDEP⁹⁷. Electrical stimulation of multiple brain areas, particularly in limbic and temporal regions, has been demonstrated to influence respiratory activity^{98,99}, supporting the potential for seizures arising from or involving these brain regions to alter respiratory function. Central apnoea can occur secondary to the ictal discharge, acting at either the cortical or medullary level or possibly as a result of secondary endogenous opioid release influencing the brainstem respiratory nuclei directly. During post-ictal impairment of consciousness, hypercapnia and hypoxia may be less potent respiratory stimuli.

In a study of 17 patients with epilepsy who underwent polysomnography with cardiorespiratory monitoring in a supervised environment, ictal apnoea of greater than 10 seconds in duration was demonstrated in 20 out of 47 seizures. Oxyhaemoglobin saturation decreased to less than 85% in 10 seizures. Central apnoea, which may evolve during a focal or generalised seizure, was seen more frequently than obstructive apnoea, however the study was in a controlled environment and assistance may have minimised the likelihood of obstructive apnoea being observed⁴⁰. Larger series have since expanded the descriptions of hypoxaemia accompanying seizures¹⁰⁰⁻¹⁰². Oxygen desaturations <90% are common, occurring in approximately one-third of generalised and non-convulsive seizures¹⁰⁰. Significant desaturations have also been noted in limited electrographic seizures without clear clinical accompaniments¹⁰³. In a small number of cases (<5%), these desaturations may be profound, with measured oxygen saturation (SaO₂) <70%¹⁰⁰. Interestingly, transient bradycardia or sinus arrest has been seen in association with ictal apnoea suggesting that the reported seizure-related arrhythmias may be consecutive to ictal apnoea⁴⁰. Additional reports of ictal apnoea are typically case studies recorded incidentally during video-EEG telemetry⁹⁰⁻⁹². In a study of 135 SUDEP cases, 15 of which were witnessed, observers described respiratory difficulties, such as apnoea and obvious respiratory obstruction, in 12 patients, although the conclusions that may be drawn are significantly limited by the quality of the retrieved information and lack of additional relevant cardiorespiratory parameters⁹³. Witnesses have reported a delay between the seizure and time of death which is more consistent with primary respiratory inhibition followed by respiratory arrest and the development of hypoxia and pulmonary oedema, than 'primary' ictal cardiac asystole²⁰. Peri-ictal hypoxaemia has been associated with male gender, younger age in children,

symptomatic generalised epilepsy, temporal onset seizures, seizure lateralisation (right in adults; left in children), seizure duration, contralateral electrographic seizure spread, AED polytherapy and MRI-negative epilepsy¹⁰⁰⁻¹⁰². In a patient experiencing a seizure with oxygen desaturation, the probability of recurrence with subsequent seizures is 0.43¹⁰⁰.

Neurogenic pulmonary oedema, which may in itself be insufficient to be fatal, has been implicated in theories regarding respiratory dysfunction and SUDEP following a number of postmortem reports and case studies^{7,20,89,96}. In a sheep model of ictal sudden death, animals that died had a greater increase in pulmonary vascular pressure and hypoventilation. When airway obstruction was excluded by tracheostomy, central apnoea and hypoventilation were observed in all, causing or contributing to death in two, whereas a third animal developed heart failure with significant pathologic cardiac ischaemic changes^{88,104}. The apparent protective effect of supervision favours an important primary role for respiratory factors²², as these can be influenced by relatively unskilled intervention, such as airway protection, repositioning, or stimulation. It is unknown what proportion of SUDEP cases may be prevented by such intervention.

Suppression of cerebral activity

The possibility of progressive suppression and eventually cessation of cerebral activity as a cause of SUDEP, despite normal cardiac function, was introduced with the publication of a case report of an intracranially monitored patient who died of SUDEP in which a seizure started in one hemisphere and then spread to the other after several minutes. The EEG pattern on the original side then changed to burst-suppression with spindling spike discharges, followed by complete cessation of activity. The other hemisphere continued to show spike discharges until ceasing suddenly a few seconds later. A pulse artefact on the EEG continued for a further two minutes; there was no recording of respiratory activity. It was postulated that the loss of EEG activity was not preceded by anoxia as both hemispheres were not simultaneously affected¹⁰⁵. Post-ictal generalised EEG suppression (PGES) occurs in up to 65% or more of adult patients with convulsive seizures¹⁰⁶ and has been reported in monitored SUDEP or near SUDEP cases¹⁰⁷. It has been shown that >50 seconds of PGES significantly increases the adjusted odds ratios for SUDEP and for each one-second increase in the duration of PGES, the odds of SUDEP increases by a factor of 1.7%¹⁰⁶. However, a small retrospective study of 17 SUDEP cases and matched controls found no significant differences in either presence or duration of PGES between the two groups¹⁰⁸ and a clear link between PGES and SUDEP continues to be elusive. A recent study evaluated sympathetic and parasympathetic changes in seizure patients by measuring electrodermal activity and heart rate variability¹⁰⁹. An increase in electrodermal activity response amplitude and a decrease in parasympathetic-modulated high-frequency power of heart rate variability were directly correlated to prolonged PGES. It is possible that PGES may serve as a marker of post-ictal autonomic dysregulation. The precise nature of the pathophysiological association is unclear. Excessive post-ictal brainstem inhibition due to seizure-induced release of GABA and other neuro-inhibitory peptides may contribute to death in some patients. This may be compounded by antiepileptic medication³⁶. This endogenous seizure-terminating mechanism could result in blunting of the central hypoxic and hypercarbic respiratory drive, resulting in post-ictal respiratory arrest, subsequent exacerbation of hypoxia, further cardiac destabilisation and death due to hypoxia and secondary cardiac arrhythmia. This is consistent with the observation that SUDEP occurs after a seizure, and could be a consequence of failed re-establishment of respiration in the post-ictal phase. It has been shown that patients with PGES are significantly more likely to be motionless in the post-ictal period and to have simple resuscitative interventions performed (suction, oxygen administration, placed in recovery position, vital signs checked)¹¹⁰. PGES in such individuals may indicate deeper post-ictal coma, more delayed arousal and, at least hypothetically, a predisposition to SUDEP. One study compared secondarily generalised convulsive seizures with and without PGES, and found that oxygen desaturation duration and extent, as well as peak end-tidal CO₂ elevation,

were more marked in patients with PGES but there was no evidence of a relationship with central apnoea¹¹¹. Early nursing interventions that reduced peri-ictal hypoxaemia were also associated with shortening of PGES duration¹¹². It remains controversial whether the occurrence of PGES is associated with increased risk of SUDEP^{106,108}.

SUDEP and epilepsy surgery

There is compelling evidence that patients with poorly controlled, predominantly generalised tonic-clonic seizures are at greatest risk of SUDEP, and a seizure is frequently seen as the terminal event. Intuitively therefore, good seizure control should translate into a reduced risk of SUDEP. The mortality rates of 393 patients who underwent epilepsy surgery were evaluated. The standardised mortality ratio (SMR) for patients with recurrent seizures post-operatively was 4.69, with a SUDEP incidence of 7.5/1000 patient-years, whereas in patients who became seizure free, there was no difference in mortality rate compared with an age- and sex-matched population¹¹³. This compares with similar studies which, for example, found a SMR of 1.8 in those with a good post-operative outcome versus 7.4 in those who failed surgery¹¹⁴. Conversely, in a large, population-based epilepsy surgery cohort, there was no association between mortality rates and seizure outcomes, although there was a clear difference between patients who underwent surgery (SUDEP incidence 2.4/1000 patient-years) and those who failed pre-surgical assessment (SUDEP incidence 6.3/1000 patient-years)¹². There has been recent interest in the tenet that there is a common factor predisposing to surgical failure and an increased risk of SUDEP so that patients who respond poorly to surgery also carry an increased risk of SUDEP and that, overall, surgery does not alter the risk of SUDEP¹¹⁵. Proposed common factors include temporal lobe epilepsy which extends beyond the temporal lobe into the insula, frontal orbital or frontal operculum region which may favour ictal arrhythmias, central apnoea and secondary generalisation. This, in turn, would increase the risk of SUDEP and the wide epileptogenic field would translate into a poor post-operative seizure outcome¹¹⁵. Mortality studies performed in patients with vagal nerve stimulators have shown that excess mortality associated with refractory epilepsy reduced as a function of duration of use. The rate of SUDEP was 5.5/1000 patient-years in the first 24 months and 1.7/1000 patient-years thereafter, possibly reflecting gradual increase in efficacy over time. Stabilisation of measures of heart rate variability post-VNS implantation¹¹⁶⁻¹¹⁸ have paralleled the improved mortality rates, although these findings are not universal^{119,120}.

Implications for management

Despite a wealth of studies reporting on proposed risk factors or mechanisms of SUDEP this has not yet been translated into targeted therapeutic interventions and a reduced incidence of SUDEP. In spite of this being a fundamental goal in the management of patients with epilepsy, there has been a paucity of studies specifically addressing preventive or therapeutic strategies.

Given the disturbance in cardiac autonomic control in patients with epilepsy, there has been speculation as to whether cardiotropic medication, such as beta-antagonists, may have a protective effect, although no studies have been performed in this regard⁶⁹. Experimental studies in rats with audiogenic seizures and ictal apnoea have shown that selective serotonin reuptake inhibitors have a protective effect¹²¹, although relevant confirmatory clinical studies are lacking. Of interest however, is the recent finding of neuropathological evidence of involvement of the medullary serotonergic network in sudden infant death syndrome (SIDS) cases with a significantly lower density of serotonin receptor binding sites, particularly in male SIDS cases compared to controls¹²². Whether pharmacological modulation of the brainstem serotonergic network or cardiac autonomic function results in a protective effect remains to be seen.

The implications of the observed ictal asystole in a small cohort of patients to a larger, more representative, group of epilepsy patients is unknown. If this finding is confirmed, the potential role of pacemaker insertion in preventing a proportion of SUDEP cases needs to be assessed.

Supervision of patients with epilepsy has emerged as the only clinically important protective factor, independent of seizure control. The basis for this remains unclear but may relate to body positioning and alleviation of obstructive apnoea or possibly brainstem arousal mechanism^{11,18,22,93}.

Existing techniques for monitoring apnoea in other clinical contexts suffer from limitations which make them unsuitable for SUDEP prevention. These include the size and weight of monitors, duration of real-time monitoring, difficulty of use in unsupervised conditions and, most importantly, very poor sensitivity and specificity, mostly due to signal artefacts. Oximetry, for example, suffers from artefacts and false alarms, and the delay between beginning of apnoea and detection of oxygen saturation drop causes warnings to come late.

The first clinical study of a novel wearable apnoea detection device (WADD) has been undertaken, which proved that the device works even in the presence of artefacts in healthy subjects and individuals with sleep apnoea. WADD was evaluated in 20 healthy subjects and 10 individuals who had been referred for evaluation of possible sleep apnoea. WADD had 99.2% sensitivity, and 99.6% specificity for detection of voluntary 15–30 second apnoea whereas the automatic software of the state-of-the-art FDA approved ambulatory SOMNO system (SOMNOmedics GmbH) had 37.8% sensitivity and 90.5% specificity. For spontaneous apnoea during natural sleep and considering the expert clinician scorer as the gold-standard WADD had 91% sensitivity and 99.5% specificity. In contrast the SOMNO system had 12.1% sensitivity and 99.4% specificity.

The device that has been created for epilepsy patients is smaller than the prototype used in the above study, weighing 7.5 g instead of 17 g. The device is attached to the neck with a hydrocolloid plaster of less than 5 cm diameter and can remain in place at least overnight; it can provide over 90% sensitivity and specificity for detection of potentially dangerous apnoeas¹²³.

The ideal system for monitoring a patient's movements should have a high sensitivity and specificity, be easy to operate and be unobtrusive. Several attempts have been made to develop devices in order to alert patients and carers to an ongoing seizure, but unfortunately these attempts have universally had a very low sensitivity and specificity^{124,125}. Current approaches for SUDEP prevention are primarily based on detecting rhythmic movement caused by tonic-clonic seizures, with devices that are either worn by the person or installed in the bed. The ideal device should be validated with simultaneous ictal EEG recordings. The stationary bed seizure monitors function by either detecting noises originating from the rhythmic banging on the bed during the clonic phase of a generalised tonic-clonic seizure (GTCS) or from the bed springs¹²⁴, or changes in mattress pressure during abnormal movements¹²⁵. Several products are commercially available, but none of them have been tested in a clinical setting, and sensitivity and specificity are disappointingly low. The wearable devices are based on accelerometry signals, either alone¹²⁶ or in combination with other modalities¹²⁷. A commercially available wireless wrist accelerometer sensor tested in a clinical setting detected GTCS with a high sensitivity (90%) and a low rate of false alarms (0.2/day)¹²⁸. The next step would be to test it in a more naturalistic environment. Surface electromyography (EMG) during convulsive seizures is another way to detect ongoing epileptic seizures. The tonic phase of GTCS is characterised by a marked increase in

amplitude-derived parameters and tonic seizures have a marked increase in frequency. The devices are worn on the biceps and multicenter studies are currently ongoing.

In the UK the NICE Guidelines state that tailored information and discussion between the individual, family and/or carers and healthcare professional should take account of the small but definite risk of SUDEP¹²⁹. Several studies have suggested that the relatives of people who died from SUDEP wished they had known of the risk of sudden death^{18,130}. While it is not certain that knowledge of the risks of epilepsy would necessarily prevent death, some evidence suggests that observation, positioning and, where necessary, stimulation after a seizure may protect against death. It is also likely that patients who know of the risks of epilepsy might be more adherent to AED regimens and the avoidance of trigger factors, thus reducing the frequency of seizures. In contrast, a cohort-controlled study of SUDEP from Australia concluded that as there were no clear risk factors that were modifiable by practical intervention, disclosure to the patient of the possibility of SUDEP was inappropriate¹³¹.

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