

# Sudden Unexpected Death in Epilepsy. Risk Factors, Possible Mechanisms and Prevention: A Reappraisal

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**Abstract-** People with epilepsy are more likely to die prematurely than those without epilepsy. The most common epilepsy-related category of death is sudden unexpected death in epilepsy (SUDEP), accounting for up to one fifth of epilepsy deaths in some series. SUDEP is more common in populations of people with intractable epilepsy, the annual incidence being as high as one in 200 patient years in these settings. The majority of people dying with SUDEP have a history of generalised tonic clonic seizures, and high seizure frequency and polytherapy also seem to be risk factors. The goal of treatment should therefore be seizure freedom, using the lowest effective number and dosage of AEDs. Evidence for many other risk factors is conflicting. The most commonly suggested mechanisms for SUDEP are cardiac abnormalities and apnoea, but the cause of SUDEP is still unknown. Clarification of risk factors and establishment of the mechanisms of SUDEP are important so that as many people as possible can be saved from SUDEP.

**Key Words:** Epilepsy, Epilepsy-related sudden death, SUDEP

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## INTRODUCTION

People with epilepsy are known to be at risk of premature death compared with those without epilepsy- the standardised mortality ratio (SMR) is between two and three<sup>(1)</sup>. In those dying shortly after diagnosis the cause of death is most frequently the underlying cause of the epilepsy<sup>(2-4)</sup>. SMRs are increased in people with epilepsy for conditions apparently unrelated to the epilepsy, such as neoplasia (excluding CNS tumours)<sup>(3)</sup> and heart dis-

ease<sup>(5)</sup>; reasons for this are unclear. People with epilepsy are more likely to have accidents, and may die from them<sup>(6)</sup>. They are more likely to drown<sup>(5,7)</sup>, and may also be at increased risk from suicide<sup>(8)</sup>. They may die in status epilepticus, although many people presenting in status do not have pre-existing epilepsy<sup>(9)</sup>. However, the most common epilepsy-related category of death in people with chronic uncontrolled seizures is SUDEP- Sudden Unexpected Death in Epilepsy-which accounts for almost 20% of epilepsy deaths in some series<sup>(3,10,11)</sup>. It

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has been estimated that the risk of sudden death for a young adult with epilepsy is almost 24 times as high as for an adult without epilepsy<sup>(12)</sup>.

SUDEP can be defined as '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 toxicological or anatomical cause for death'<sup>(13)</sup>. The other commonly used definition includes death occurring suddenly and unexpectedly, during normal activities and benign circumstances, excluding death from trauma or intractable status epilepticus, in an individual diagnosed with epilepsy; no obvious medical cause of death should be found<sup>(14)</sup>. In 1868 Bacon noted the occurrence of 'sudden death in a fit'<sup>(13)</sup> and over 30 years later Spratling found that some deaths in people with epilepsy were the direct result of a seizure, with no other explanation found<sup>(15)</sup>. Despite this, in the 1960's it was suggested that 'there is no reason why ...someone with epilepsy... should not live as long as he would if he did not have epilepsy'<sup>(16)</sup>. Awareness has again increased over recent years, yet in many countries the medical profession has been reluctant to consider SUDEP<sup>(17)</sup>. Indeed, there is little comparative data on the incidence of SUDEP in different countries.

By definition, the cause of SUDEP is unknown. Nevertheless establishing risk factors can be useful; individual patients can be advised on minimising avoidable risks, and evaluation of risk factors can point to areas of future research to try to establish potential causes and mechanisms of SUDEP. Epidemiological studies to evaluate risk factors are, however, fraught with problems.

Most studies of SUDEP have been in selected populations. In the majority (about 70%) of people with newly incident epilepsy the seizures remit, with or without the use of Anti Epileptic Drugs (AEDs); SUDEP is rare in these populations<sup>(18)</sup>. Whilst studying this group might provide valuable insights, searching for risk factors would require meticulous follow up of large cohorts. Groups studied have therefore usually had a more severe form of epilepsy than most, with tertiary care clinics<sup>(19)</sup>, people ever hospitalised<sup>(20)</sup>, residential groups<sup>(21)</sup> or surgi-

cal candidates<sup>(22)</sup> being followed. Some studies use AED prescriptions to identify people with epilepsy<sup>(23,24)</sup>. Whilst this method will correctly identify many people with epilepsy, it will exclude people taking no AEDs and will include people taking AEDs for alternative diagnoses (such as neuropathic pain, trigeminal neuralgia, bipolar affective disorders, migraine prophylaxis). Many studies have used death certificates for case ascertainment, but this method is hampered by the lack of consistency in certification of deaths in many parts of the world. In a long-running study of people with epilepsy in the US, epilepsy was on the certificate of less than 10% of 187 patients who died during the study period<sup>(25)</sup>. Similarly, in an Australian study of deaths in children, of 20 deaths attributable to epilepsy, in only 11 (55%) was epilepsy entered on the death certificate<sup>(26)</sup>. A recent UK study of death certificates found that epilepsy was on the death certificate of only 16/243 people with epilepsy who died<sup>(27)</sup>. In the latter study, in many cases the absence of epilepsy on the certificate was probably correct, as it was unlikely that the epilepsy had contributed to the death. Case-control studies can provide more information of risk factors, but these seem to vary according to whether the controls are those with epilepsy who died of conditions other than SUDEP, or people living with epilepsy<sup>(28)</sup>.

Overall, in all studies the risk of sudden death in epilepsy is found to be elevated. It is usually estimated as between 1:500 patient/years and 1:1000 in community based populations with epilepsy, and as up to 1:100 in surgical series. Death rates from various studies are listed in the table.

## RISK FACTORS FOR SUDEP

Of the many risk factors suggested for SUDEP, few have been proved conclusively. Evidence is frequently conflicting; the size of the cohort studied, the control group used, the methodology of the study and the definition of SUDEP may all affect the risk factors identified<sup>(16,28)</sup>. More consistent risk factors include young adulthood, early age of onset of seizures, presence of generalised tonic clonic seizures, higher frequency of

**Table.** SUDEP rate in selected populations of people with epilepsy

Study	Study population	SUDEP rate
Nashef 1995 <sup>(19)</sup>	Tertiary referral centre, UK	1:200
Racoosin 2001 <sup>(36)</sup>	Add on trials for new AEDs	1:263
Nashef 1995 <sup>(21)</sup>	Children with epilepsy and learning difficulty in residential school, UK	1:295
Klenerman 1993 <sup>(69)</sup>	Severe epilepsy in long term residential care, UK	1:261
Timmings 1998 <sup>(33)</sup>	Patients at Cardiff, UK, Epilepsy unit	1:500
Derby 1996 <sup>(24)</sup>	UK General Practice Research Database. Refractory epilepsy (>2 AEDs concurrently)	1:667
Langan et al 1998 <sup>(30)</sup>	Retrospective and prospective study of post mortem registers. Ireland	1:680
Walczak 2001 <sup>(11)</sup>	Prospectively recruited from three epilepsy centres, USA	1:826
Ficker 1998 <sup>(12)</sup>	All persons with epilepsy diagnosed in Rochester Minnesota	1:2857

seizures, polytherapy and poor adherence to AED regimen. Others suggested have been male gender, symptomatic epilepsies versus idiopathic, Afro-American background, frequent changes of dose or type of AED, alcohol abuse, presence of comorbid learning disability and presence of nocturnal seizures.

#### Age at death

The definitions of SUDEP require no anatomical or toxicological cause for death found at post-mortem examination<sup>(13,14)</sup>. Many elderly people have evidence of cerebrovascular or cardiovascular disease and it may be difficult to exclude this as a cause of death; as a result the elderly are less likely to fulfil this negative requirement of the definition, and so be classified as SUDEP. Additionally, death rates are usually quoted as age-specific standardised mortality ratios, which relate to the rate of death in the general population, and this is much higher in the elderly. Thus the rate of SUDEP in the elderly may be falsely low.

Different studies have found different decades of peak incidence of SUDEP: third and fourth decades<sup>(29)</sup>, second and fifth decades<sup>(15)</sup>. Mean ages of death range from 26 to 37 years<sup>(14,17,19,30-33)</sup>. However, SUDEP may occur in children<sup>(21,34)</sup>.

#### Age of onset of seizures

A retrospective study investigating deaths in a tertiary referral centre population with chronic refractory epilepsy found the age of onset to be slightly, but significantly, lower in the SUDEP group than in the group who

died of causes other than SUDEP (mean age 8.2 years vs 12.7 years)<sup>(35)</sup>. A case-control study in Sweden found that, in men, onset of epilepsy in childhood or early adolescence compared with onset after 45 years increased the relative risk of SUDEP almost 18 times. This association was not significant in women<sup>(20)</sup>. Other studies have found long duration of epilepsy in people dying with SUDEP<sup>(14,17,19,32-34)</sup>. Young age of onset of seizures is often correlated with long duration of epilepsy. A study of mortality in AED development programmes did not, however, find that the SUDEP rate increased with the duration of the epilepsy<sup>(36)</sup>.

#### Presence of tonic-clonic seizures

SUDEP is usually unwitnessed, but when witnessed, often follows a generalised tonic clonic seizure (GTCS). Evidence for a seizure prior to death is frequently, but not always, found at post-mortem examination. In the study comparing patients with epilepsy who died with SUDEP with those dying from other causes there were signs of seizures occurring immediately before death in 67% of SUDEP patients compared with 35% in the non-SUDEP group<sup>(35)</sup>. Of 15 witnessed cases of SUDEP in another study, 12 occurred in association with a generalised tonic-clonic seizure<sup>(37)</sup>. A study comparing people with epilepsy who died compared with those who survived, found that more of those who died had a history of GTCS than those who were alive, and that the frequency of GTCS was significantly greater in those who died. Conversely the same study found no difference in these variables between those who died of SUDEP com-

pared with those who died from other causes<sup>(38)</sup>. However, this study presumed SUDEP to be the cause of death in any whose death was attributed to epilepsy (and who had no other known cause of death). Studies in both children<sup>(21,39)</sup> and adults<sup>(12,15,30,32,33,35,40)</sup> have found that most, if not all, cases of SUDEP in whom the seizure type was known, had a history of GTCS. Some of these seizures may have partial onset<sup>(41)</sup>. A prospective cohort study of patients at three American epilepsy centres found that increasing numbers of GTCS in the year before the last hospital visit was a risk factor for women<sup>(11)</sup>.

### Seizure frequency

Many studies of death in epilepsy have been undertaken in different populations, and together they confirm SUDEP as a real phenomenon. Higher rates of SUDEP are reported from studies of individuals with intractable epilepsy, however, and it is suggested that seizure severity and frequency are risk factors<sup>(42)</sup>. However, some authors have suggested that seizures are often infrequent or rare in people dying with SUDEP<sup>(15,32,40)</sup>, suggesting that seizure frequency is not a significant risk factor. Comparing these older studies with the more recently published Swedish nested case-control study<sup>(20)</sup> showed remarkably similar findings, but different conclusions were drawn. The studies showed that seizures occurred at least monthly in 32%<sup>(40)</sup>, 43%<sup>(32)</sup> and 42%<sup>(20)</sup>. The Swedish study compared subjects who died from SUDEP with 3 living controls per subject, matched for age, sex and assessment period. They found the seizure frequency to be the factor most strongly associated with an increase risk of SUDEP, showing the importance of using living subjects from the same population group with epilepsy as controls in this type of study. A case-control study conducted in the UK found that 11-20 or 21-50 tonic-clonic seizures in the previous 3 months was a risk factor compared with those with five seizures or fewer, although more than 50 seizures did not appear as a significant risk factor, perhaps due to small numbers<sup>(31)</sup>.

A large community based study of people with newly-diagnosed epileptic seizures, followed up for 14 years, found that neither recurrent seizures nor cumulative seizure recurrence were found to be significant time-

related factors in overall cohort mortality<sup>(2)</sup>. This study has only reported one case of SUDEP<sup>(18)</sup>, confirming the rarity of SUDEP in this type of population.

## Anti-epileptic Drug Therapy

### (1) Polytherapy

Several studies suggest increased risk of SUDEP with increasing number of AEDs used. One study used simultaneous AEDs as a surrogate for persistent seizures<sup>(23)</sup> whilst others found the increased risk associated with polytherapy was still significant after adjusting for seizure frequency<sup>(11,20)</sup>. However, neither the tertiary referral centre study comparing those dying with SUDEP with those dying from other causes<sup>(35)</sup>, nor an Australian prospective coroners' study also comparing SUDEP deaths with those dying from other causes<sup>(43)</sup> found any increased risk with polytherapy.

### (2) Specific AEDs

It has been suggested that the use of certain AEDs may predispose to SUDEP. SUDEP occurred before modern AEDs were developed<sup>(33)</sup>, but its frequency has not decreased with advances in therapy<sup>(15)</sup>. Some authors suggest that carbamazepine may be associated<sup>(31,33)</sup>, but this is disputed by others<sup>(11,44)</sup>. Carbamazepine has been shown to affect the conduction system of the heart, and to affect the autonomic nervous system<sup>(45)</sup>.

Studies have been undertaken on new AEDs after a high incidence of SUDEP was noted in clinical trials<sup>(14,36)</sup>. These studies showed that SUDEP does not appear to be related to the use of specific AEDs, but that the higher rate in clinical trials of new drugs is due to the high-risk patients who are entered into such trials<sup>(36,46)</sup>.

### (3) Non-adherence to drug regimen, and subtherapeutic, or suprathreshold AED levels

Studies have found subtherapeutic levels of AEDs in many patients dying from SUDEP<sup>(15,32,34,35,47)</sup>, sometimes associated with a history of poor adherence to drug regime<sup>(34)</sup>, whilst others have found no difference in those dying from SUDEP and those from other causes<sup>(44)</sup> or from living controls<sup>(11)</sup>. Toxic levels in some patients have also been documented<sup>(15,47)</sup>. The Swedish case con-

trol study found the relative risk of SUDEP was elevated in those whose carbamazepine levels were above the therapeutic range at last drug monitoring, with an even higher risk if high carbamazepine levels were present in those on polytherapy or with frequent dose changes. This increased risk was not found in patients on phenytoin<sup>(48)</sup>.

#### **(4) Change in AEDs**

Anecdotal evidence suggests that SUDEP is also more likely to occur at times of AED change<sup>(49,50)</sup> and mechanisms for this have been suggested<sup>(51)</sup>. The Swedish study found that frequent changes of AED dosage was a risk factor<sup>(20)</sup>, and also that patients who had had therapeutic drug monitoring performed during a two year observation period were less likely to die from SUDEP than those who had not<sup>(48)</sup>. The UK case-control study found that lifetime use of four or more AEDs increased the odds of SUDEP compared with lifetime use of one or two, but also that having never taken AEDs also increased the risk<sup>(31)</sup>.

#### **Gender**

Many studies have found more males than females in those dying with SUDEP, eg male:female 1.7:1<sup>(39)</sup>, 1.8:1<sup>(33)</sup>, 2:1<sup>(30)</sup>, 2.3:1<sup>(29)</sup>, 2.5:1<sup>(17)</sup>, 3.3:1<sup>(32)</sup>. However, other studies found no difference in the SUDEP rate in males and females<sup>(35,36,38)</sup>. The Swedish case control study found different risk factors in males and females, but found the annual incidence rate of SUDEP was 1.4/1000 in both men and women, despite the male/female ratio in the deaths being almost 3:2<sup>(20)</sup>. The study population, who had been admitted to hospital with a diagnosis of epilepsy, included more men than women; people admitted to hospital may have additional diagnoses, and this may affect the sex distribution. A few studies, including the American study at three epilepsy centres<sup>(11)</sup>, have found the incidence of SUDEP to be higher in women than men. A study of the incidence of SUDEP in young people with epilepsy and learning difficulty investigated 14 deaths due to SUDEP of whom 71% were girls. However, the school had a preponderance of females due to a previous admissions policy, and the rate of SUDEP

per cases per pupil year was similar for males (1:287) and females (1:298)<sup>(21)</sup>.

#### **Race**

Two early studies suggested that SUDEP is more common amongst Afro-American populations<sup>(15,32)</sup> but this could be due to selection bias. It does not appear to have been studied recently.

#### **Alcohol**

Alcohol abuse has been suggested as a risk factor for SUDEP<sup>(32,52)</sup>. This may in some cases be due to selection bias, as those with problems with alcohol have different hospital admission rates. The Swedish case-control study found no association with alcohol abuse<sup>(20)</sup>.

#### **Epilepsy syndromes**

Some authors have found SUDEP to be more common amongst those with remote symptomatic epilepsy and neurological deficits presumed present from birth<sup>(39,42)</sup>. However, a retrospective study of patients with chronic refractory epilepsy at a tertiary referral centre found more patients with primary generalised seizures in the SUDEP group than in the group of patients with epilepsy who died from other causes<sup>(35)</sup>. Similarly the Swedish case control study found an increased risk of SUDEP among men with idiopathic generalised epilepsy compared with localisation-related symptomatic epilepsy<sup>(20)</sup>.

#### **Presence of nocturnal seizures**

Many people dying with SUDEP are found in or near the bed<sup>(35)</sup>. It has been suggested that nocturnal seizures may, therefore, be a risk factor for SUDEP. However, this has not been clearly established. People are less likely to be with others during the night, and so seizures are more likely to be unwitnessed. Studies in children at a school for children with epilepsy<sup>(21)</sup>, and a recent case control study<sup>(31)</sup> both suggest that supervision may be an important preventative factor; this needs to be studied further.

#### **Presence of learning disability**

The American cohort study found that, compared

with those with IQ of at least 80, those with an IQ of less than 70 were five times as likely to die from SUDEP<sup>(11)</sup>. A cohort study in Canada found that SUDEP incidence was higher in those with a history of hospitalisation for learning disability<sup>(23)</sup>. However, other studies have found no such association<sup>(43)</sup>.

## SUGGESTED MECHANISMS

By definition, the cause of death in SUDEP is currently unknown. The rate of SUDEP is probably lower in children than adults, with two possible explanations; children with epilepsy are more likely to be observed, even when asleep, than adults with epilepsy<sup>(39)</sup>, strengthening the argument in favour of supervision, and epilepsy starting in childhood frequently has different aetiology from that starting in adult life<sup>(39)</sup>, and the aetiology may influence the cause of SUDEP in this age group.

The definitions of SUDEP require that post-mortem examination does not reveal a toxicological or anatomical cause of death<sup>(13,14)</sup>. However, some changes thought insufficient to cause death are frequently found at post-mortem in people dying of SUDEP, and these may throw light on the cause of death. Pulmonary oedema is frequently found, although not considered sufficiently severe to cause death. Increased liver weight and, in males, heart weight have also been recorded<sup>(32,53)</sup>, and cerebral oedema, often despite decreased brain weight. Neuropathological studies have failed to show consistent changes sufficient to cause death in people dying from SUDEP although anoxic nerve cell changes have been seen in a small number of brains<sup>(53)</sup>.

Three main hypotheses exist for the cause of SUDEP. These are unstable cardiac rhythms, apnoea (central or obstructive) and cessation of brain activity.

### Cardiac abnormalities

#### (1) Heart rate variability

Heart rate variability is a function of the balance between sympathetic and parasympathetic activity on the heart. Analysis of the frequency domain, where the low frequency (LF) band is due largely to sympathetic influence (with some influence from the parasympathetic ner-

vous system), and the high frequency (HF) band is due to the parasympathetic influence<sup>(51,54)</sup>, can be used to assess autonomic cardiac control<sup>(55)</sup>. Studies in sleep have shown reduced HRV and higher LF/HF ratio in children with epilepsy, and it is thought that alterations of autonomic control of cardiac activity may play an important role in SUDEP<sup>(56)</sup>. In a group of 43 army recruits with untreated generalised tonic-clonic seizures the LF/HF ratio, recorded within 36 hours of a GT seizure, was significantly increased ( $p=0.006$ ) compared with a group of age and sex matched controls<sup>(54)</sup>. Further, 12 patients with medically intractable partial and secondarily generalised seizures who were withdrawn abruptly from carbamazepine were monitored. The mean LF/HF ratio increased significantly suggesting enhanced sympathetic activity in sleep<sup>(51)</sup>. The authors suggest that this change may be relevant to the pathophysiology of SUDEP, and that it is probable that similar autonomic effects may accompany sudden withdrawal of other AEDs.

#### (2) Cardiac arrhythmias

In a study of ictal cardiorespiratory variables conducted in 17 patients at a UK telemetry unit, an increase in heart rate was found in 91% of 41 seizures monitored, and transient bradycardia in five seizures (four patients), the latter always in association with a change in respiratory pattern<sup>(57)</sup>. The tachycardias were thought to be a sympathetically mediated consequence of seizure discharge. Bradycardia may occur in the presence of apnoea, and the authors suggest that this may contribute to the bradyarrhythmias recorded, with apnoea playing the central part. Cardiorespiratory reflexes diminish with age, so this fits with SUDEP being more common in young adults.

Electrocardiographic (ECG) changes in patients with intractable partial seizures have been studied. Thirty-five complex partial and 16 secondarily generalised seizures in 43 subjects were analysed. Seventy percent of subjects had either ECG abnormalities (16%) or tachycardias (30%) or both (23%) during the ictal and/or post-ictal period, including six patients who had potentially serious ECG abnormalities<sup>(58)</sup>. The ECG findings were consistent with excess autonomic discharge, and could

have been due to increased circulating plasma catecholamines or to direct autonomic stimulation of the heart. ECG abnormalities were more likely to be seen in longer seizures (mean 204 seconds vs 71 seconds for seizures with no ECG abnormalities) and ictal ECT abnormalities were also more likely to occur with GTCS. Additional evidence for the chances of death being caused by arrhythmias may be inferred from the fact that certain anti arrhythmic drugs, such as flecainide, have also been associated with sudden death; these drugs act by blocking sodium channels, as do some AEDs<sup>(55)</sup>. Furthermore, alcohol excess has sometimes been suggested as a risk factor for SUDEP, and this may predispose to autonomic instability as well as precipitate seizures<sup>(29)</sup>.

One study sought to find the frequency of cardiac asystole in patients with medically intractable epilepsy<sup>(59)</sup>. The authors retrospectively analysed the records of patients who had undergone long-term video-EEG/ECG monitoring. Of 1244 patients, 5 patients had periods of asystole (4 to 60 seconds duration) in 11 of 19 seizures. All the seizures were focal in origin and the 5 patients had temporal lobe or frontal lobe epilepsy of either left or bilateral lateralisation. Most seizures were simple partial (13 seizures, asystole in six, one patient), four were complex partial (asystole in three, two patients) and only two (asystole in both, two patients) were secondarily generalised. Two patients had previous cardiac disease and two had simultaneous central ictal apnoea during the asystole.

Another study compared EEG and ECG data obtained during life from 21 people who later died from SUDEP (6 definite and 15 possible) with data obtained from 43 comparison patients who, at the time of data collection, had not suffered SUDEP<sup>(60)</sup>. Most (81%) SUDEP patients had symptomatic or cryptogenic partial epilepsy, 14% had IGE and one had symptomatic generalised epilepsy. Nine patients had both complex partial seizures (CPS) and Generalised Tonic Clonic seizures (GTC), seven had CPS only, three had GTC only and three had GTC and absences. The comparison patients had CPS and GTC (42%), CPS only (51%) or GTC only (7%). SUDEP patients were more likely to have seizures

during sleep than the comparison group. Fifteen of the 16 (94%) SUDEP patients who had had ictal ECGs had tachycardia during or shortly after seizures, compared with 84% of the comparison group; the maximal heart rate was significantly higher in SUDEP patients than comparison patients. The seizure-associated heart rate increases in SUDEP patients were more marked when seizures arose from sleep; 14/16 SUDEP patients in whom the state of wakefulness was known died in their sleep. The authors hypothesise that SUDEP occurring during sleep could be mechanistically similar to sudden cardiac deaths. The latter occur most frequently in the mornings, and are thought to be related to sudden surges in catecholamines associated with awakening.

Loop recorders implanted in 20 patients with refractory partial seizures captured ECGs in 377 seizures in 19 patients over a two year period<sup>(61)</sup>. All patients experienced sinus tachycardia during at least some seizures. Heart rates did not differ significantly with different types of seizures. Ictal bradycardia of less than 40 beats per minute occurred in only eight seizures in seven patients. Four patients had severe bradycardia, or periods of sinus arrest lasting more than three seconds, requiring the insertion of a permanent pacemaker. Most patients had seizures without cardiac events similar to the seizures with cardiac events. The authors postulate that asystole might underlie SUDEP in some patients.

### **(3) Other cardiac pathology**

Post mortem examinations in males dying with SUDEP have sometimes found higher heart weights than expected<sup>(32)</sup>. However, another study compared the hearts of ten patients who died from SUDEP with ten controls who did not have epilepsy and who died from a cause which was not primarily cardiac and found no significant differences in either morphological abnormalities of the cardiac conduction system or the degree of coronary artery stenosis<sup>(62)</sup>.

It has been pointed out that fatal arrhythmias cannot cause the pulmonary oedema frequently seen at autopsy, as this takes time to develop<sup>(6)</sup>. This may suggest that some unwitnessed deaths are not as sudden as previously thought. This view is also suggested by some neu-

ropathological studies of SUDEP<sup>(53)</sup>, in which anoxic nerve cell changes were seen in a small proportion of brains; these features are at odds with a sudden death, and are not usually recognisable histologically until 4-6 hours after the insult<sup>(53)</sup>. These studies suggest that SUDEP may not always be as sudden as the definitions implies, and may sometimes take place over a matter of hours.

### Apnoea

Studies in sheep with induced seizures have shown that pulmonary, but not systemic, pressure increases in proportion with seizure duration; this drives fluid into the lung parenchyma. In a study comparing animals who died within 5 minutes of the start of the seizure with those that did not die, the main difference was a fall in pO<sub>2</sub> and a parallel increase in pCO<sub>2</sub> in those that died. There was no difference between the groups of animals in ECG, seizure activity or plasma catecholamine levels, but those that died had increased extravascular lung water compared with the long-lived animals. The authors conclude that the cause of sudden death in this model is centrally induced apnoea<sup>(63)</sup>. Post-mortem studies in humans have found pulmonary oedema in people who died from SUDEP.

In the study looking at ictal cardiorespiratory changes in adults (see above), apnoea of at least ten seconds duration occurred in almost 60% (10/17) of patients, and in over 40% (20/47) of seizures. It was noted in all of three secondarily generalised tonic clonic seizures, a minority (1/8) of tonic seizures and almost half (16/35) of complex partial seizures. Apnoea was central in all cases, but was followed by obstructive apnoea in 3/10 patients<sup>(57)</sup>.

A case report of a young woman undergoing video-EEG supports the theory of the primary event being apnoea. Immediately after the end of the fourth recorded GTCS she developed persistent apnoea. Her ECG remained steady initially, but then slowed progressively until the heart stopped under a minute later. Evaluation after resuscitation showed no evidence of airway obstruction, or of pulmonary oedema<sup>(64)</sup>.

### Cessation of brain activity

A single case report of an intracranially monitored SUDEP suggests that this occurred as a result of cessation of brain activity after a secondarily generalised seizure. The EEG showed a seizure starting, in sleep, in the right mesial temporal region and this spread to the other hemisphere, continuing in a generalised fashion for several minutes. The pattern on the original side then flattened, followed by spindling spike discharges for a few seconds, followed by complete cessation of activity on that side. 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, but there was no recording of respiratory activity. There was no obvious sign of breathing difficulty. Post-mortem examination showed mild congestion of the lungs. It is suggested that, in this instance, the cessation of the seizure could have also resulted in cessation of all life functions, with a failure to restart any activity. It is also suggested that this was not secondary to anoxia, as both hemispheres were not simultaneously affected<sup>(65)</sup>.

One author suggests that seizure-induced release of GABA and other neuro-inhibitory peptides may cause excessive brainstem inhibition, contributing to death. This normal physiological seizure-terminating mechanism could, in excess, cause blunting of the central hypoxic and hypercarbic respiratory drive, resulting in post-ictal respiratory arrest and death due to hypoxia and secondary cardiac arrhythmia. This failed re-establishment of respiration in the post-ictal phase could explain the fact that SUDEP sometimes seems to occur after a seizure<sup>(33)</sup>.

It may be that there is more than one cause of SUDEP. One study describes four witnessed deaths. Two people were recovering shortly after a seizure when they became cyanotic and died<sup>(34)</sup>. A further one died in a convulsion and a fourth died suddenly without apparently having had a convulsion. The authors suggest that the former two had delayed respiratory arrest followed by secondary cardiac arrest and the latter two a lethal cardiac arrhythmia, one in association with a generalised seizure and the other possibly in association with a partial seizure. In this study of 44 deaths, 86% had pul-



monary congestion or oedema at post-mortem examination, but the post-mortem findings were not linked with the clinical histories. The investigators in another study interviewed witnesses of 15 cases of SUDEP<sup>(37)</sup>. Death occurred in association with a generalised tonic-clonic seizure in 12 cases, and in a further case the subject indicated that he was going to have a seizure, before collapsing. Another collapsed 5 minutes after recovery from a seizure. The witnesses of 12 deaths felt that the person dying had difficulty breathing, and obstruction to respiration may have contributed to death in two cases. Thus, both cardiac arrhythmias and apnoea are potential causes of death in these witnessed cases.

### IMPLICATIONS FOR RESEARCH AND CLINICAL CARE

Some suggested risk factors for SUDEP such as age, duration of epilepsy and gender are never subject to manipulation. As seizure frequency and polytherapy are strong candidates as risk factors, however, the goal of treatment should be seizure freedom, using the lowest effective number and dosage of AEDs. In both the Swedish<sup>(20)</sup> and UK<sup>(31)</sup> case control studies, the risk was increased in people in whom it was not possible to establish some aspects of the history. The UK National Sentinel Clinical Audit of epilepsy-related deaths found that 54% of adults had received inadequate care or had major errors in their care, and that 39% of adult deaths were probably or potentially avoidable<sup>(66)</sup>. Seizure frequency at the last secondary care consultation was documented in only 75% cases, and in over a quarter of those it was vague or unclear. Therapeutic management was considered to be inadequate for one fifth of subjects. Whilst not all the deaths in the audit were SUDEP, quality of care issues remain the same.

An Australian case-controlled study found that the risk of SUDEP was increased in males with localisation-related epilepsy<sup>(67)</sup>. The authors suggest that, as neither of these factors is open to manipulation, there is no requirement to discuss this with patients; indeed, they suggest that the patient's right 'not to know' may override the right to know. This study showed that there was no dete-

rioration of seizure status at the time of death, but did not appear to have looked at seizure frequency itself. Other studies have found that seizure frequency<sup>(20)</sup>, and the presence of GTCS<sup>(30)</sup>, are important risk factors, which we can aim to treat. Some studies have found that the relatives of people dying from SUDEP wished they had known of the risk of sudden death<sup>(41,68)</sup>. Whilst knowledge of the risks of epilepsy may not prevent death, some evidence suggests that observation, positioning and, where necessary, stimulation after a seizure may protect against death<sup>(21)</sup>; the UK case-control study found that the presence of supervision at night decreased the risk<sup>(31)</sup>. People with epilepsy who know of the risks might also be more adherent to drug regimes and avoidance of trigger factors, thus reducing the frequency of seizures.

Clarification of risk factors and establishment of the mechanisms of SUDEP are important for establish preventative measures for SUDEP. The many studies of SUDEP to date have provided conflicting evidence for risk factors; it is difficult to eliminate causes of bias and confounders. At the present time, striving for full seizure control is the best we can manage.

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