Sudden unexpected death in epilepsy: risk factors and potential pathomechanisms

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Abstract | Sudden unexpected death in epilepsy (SUDEP) is the most common cause of death directly related to epilepsy, and most frequently occurs in people with chronic epilepsy. The main risk factors for SUDEP are associated with poorly controlled seizures, suggesting that most cases of SUDEP are seizure-related events. Dysregulation in cardiac and respiratory physiology, dysfunction in systemic and cerebral circulation physiology, and seizure-induced hormonal and metabolic changes might all contribute to SUDEP. Cardiac factors include bradyarrhythmias and asystole, as well as tachyarrhythmias and alterations to cardiac repolarization. Altered electrolytes and blood pH, as well as the release of catecholamines, modulate cardiac excitability and might facilitate arrhythmias. Respiratory symptoms are not uncommon during seizures and comprise central apnea or bradypnea, and, less frequently, obstruction of the airways and neurogenic pulmonary edema. Alterations to autonomic function, such as a reduction in heart rate variability or disturbed baroreflex sensitivity, can impair the body's capacity to cope with challenging situations of elevated stress, such as seizures. Here, we summarize data on the incidence of and risk factors for SUDEP, and consider the pathophysiological aspects of chronic epilepsy that might lead to sudden death. We suggest that SUDEP is caused by the fatal coexistence of several predisposing and triggering factors.

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Introduction

The notion that an epileptic seizure could, by itself, trigger death has long been disputed. Nevertheless, the risk of sudden death as the result of a seizure was recognized by Bacon in 1868,[1] and even earlier descriptions of such fatalities can be found (Box 1). The entity of sudden unexpected death in epilepsy (SUDEP) is now acknowledged, but clear risk profiles and effective preventive measures for such deaths are still lacking. Growing interest in SUDEP in both the clinical and basic sciences, however, has provided insight into the possible underlying pathophysiological mechanisms of the condition. In this Review, we summarize potential factors that predispose individuals to SUDEP, and discuss the possible mechanisms through which seizures might induce death.

Features

Clinical criteria

SUDEP is defined as a sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in a patient with epilepsy, with or without evidence of a seizure and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicological or anatomical cause of death.[2] Cases fulfilling all these criteria are termed 'definite SUDEP'; however, if a postmortem examination is lacking, the cause of death is classified as 'probable SUDEP'.[3] The term 'possible SUDEP' refers to cases in which SUDEP cannot be

ruled out, but where insufficient evidence relating to the circumstances of death exists and no postmortem report is available. Differential diagnoses of SUDEP include other epilepsy-related deaths (for example, accidents as a consequence of seizures, and status epilepticus), deaths related to the disease underlying the epilepsy (for example, cerebrovascular disease), and unrelated deaths (for example, pneumonia).

Key points

- Sudden unexpected death in epilepsy (SUDEP) is the most frequent cause of death directly related to epilepsy, and most often occurs in individuals with chronic epilepsy
- The most important risk factors for SUDEP are related to poorly controlled seizures, suggesting that SUDEP is a seizure-related event
- Cardiac arrhythmia, respiratory dysfunction, dysregulation of systemic or cerebral circulation, and seizure-induced hormonal and metabolic changes have all been suggested as potential pathomechanisms in SUDEP
- SUDEP is most probably triggered by the peri-ictal concurrence of a number of predisposing and precipitating factors

Box 1 | A historical account of sudden unexpected death in epilepsy

An account of sudden unexpected death in epilepsy was given by George Washington, the first US president.[154] His stepdaughter had refractory epilepsy and suddenly died shortly after an epileptic seizure, aged 17 years. Washington wrote: "She rose from dinner about four o'clock in better health and spirits than she appeared to have been in for some time; soon after which she was seized with one of her usual fits, and expired in it, in less than 2 minutes, without uttering a word, a groan, or scarce a sigh. This sudden and unexpected blow, I scarce need add has almost reduced my poor wife to the lowest ebb of misery."[154]

Incidence

Epidemiological data on the incidence of SUDEP are greatly influenced by the methodology employed and the type of epilepsy population being assessed. Results are often affected by disparities in SUDEP criteria. The standardized mortality ratio for sudden death in young people with epilepsy (aged 20–40 years) in the general population has been estimated to be 24 (95% CI 8–55).[4] SUDEP, however, is a relatively rare event in people with epilepsy, with incidence rates ranging from 0.1 to 2 per 1,000 person-years.[5] In selected epilepsy populations, the incidence rates are considerably higher. Notably, the incidence rate can reach 6–9 per 1,000 person-years in candidates for epilepsy surgery.[5]

Circumstances of death

The circumstances of death in cases of SUDEP are remarkably similar, with death seeming most likely to occur during or shortly after a seizure.[6,7] Most of the deaths are unwitnessed and often occur at home—in bed or by the bed—during the night.[7–11] Circumstantial evidence of a recent seizure is frequently present, such as the presence of a bitten tongue, urinary incontinence, and/or a disrupted environment.[8] The large majority of witnessed deaths are reported to occur after a generalized tonic–clonic seizure.[6,7] In such deaths, breathing difficulties are frequently observed.[6,7]

Postmortem findings

To fulfill the clinical definition of SUDEP, obvious causes of death have to be absent at postmortem examination. Congestion of various organs, in particular the lungs and the brain, and minor aspiration are, however, frequently encountered,[12,13] and cardiac lesions have been described.[14] Evidence of acute neuronal injury in the hippocampus has been reported in some people with SUDEP, which supports the notion that death follows a recent seizure.[13]

Risk factors

Risk factors for SUDEP have been assessed in a number of retrospective case–control studies. When interpreting the results from these investigations, consideration should be given to the control groups that were employed. Some of the studies used non-SUDEP deaths as controls, which provided insight into the circumstances surrounding death. Other studies enrolled living people with epilepsy into the control group, enabling information regarding which individuals with epilepsy were at risk of SUDEP to be gathered.[5] The results from the latter studies are of particular relevance to clinical practice, and are summarized in Table 1.

Consistent patterns in the clinical profile of SUDEP have emerged, despite variation in the methodologies used and the risk factors assessed in different studies. The risk factors most consistently associated with SUDEP include poor seizure control, antiepileptic drug (AED) polytherapy, and a long duration of epilepsy. In nearly all studies, the occurrence of frequent seizures (particularly generalized tonic–clonic seizures) was found to predispose patients to SUDEP.[7,9,11,15,16] Furthermore, a long duration of epilepsy was found to increase the risk of SUDEP in three out of six studies.[7,9,16]

Despite the various definitions used for polytherapy, the use of multiple AEDs was associated with an increase in the risk of SUDEP in six out of eight case–control studies. Polytherapy might be an independent risk factor for SUDEP or a surrogate marker for poor seizure control. To examine these possibilities, the risk of SUDEP attached to polytherapy was analyzed after adjusting for seizure frequency. The analysis indicated that the use of three AEDs was associated with a higher risk of SUDEP than was monotherapy.[9] Results from another study, however, found that the risk of SUDEP was increased in people who did not use AEDs to control their seizures, compared with individuals who used one or two AEDs (odds ratio 22, 95% CI 4–106).[11]

The risk of SUDEP according to the type of AED taken has been investigated in three studies.[7,11,17] Results from two of these studies pointed towards a slight increase in the risk of SUDEP in patients using carbamazepine.[11,17] Another study, investigating the relationship between

Table 1 | Results from SUDEP case–control studies using living people with epilepsy as controls

Study	Study design	Number of cases/ controls	Preventative factors (strong and weak factors)*	Factors with no statistical effect	Provocative factors (high risk and low risk factors)‡
Langan *et al.* (2005)[11]	Retrospective case–control study; multiple sources; age and geographical location matched	154/616	Supervision at night with special precautions§ (strong) Supervision at night in the same room; asthma (weak)	Duration of epilepsy; seizure type; psychotropic medication; learning disabilities; alcohol or drug abuse; family history of SD; recent AED withdrawal	History of GTCSs; >10 vs <6 GTCSs in the last 3 months; use of no AEDs vs 1–2 AED (high) Use of CBZ; use of >4 AEDs vs 1–2 AEDs (low)
Hitiris *et al.* (2007)[7]	Retrospective case–control study carried out at an epilepsy center; age, gender and epilepsy type matched	62/124	Long duration of epilepsy (weak)	History of GTCSs; seizure in the past 3 or 6 months	Polytherapy‖; early age at epilepsy onset (≤15 years of age); a seizure within the last year (low)
Nilsson *et al.* (1999);[9] Nilsson *et al.* (2001)[18]	Population-based prospective cohort study; patients were on specific AEDs; age and gender matched	57/171	Cerebrovascular disease (weak)	Other underlying disorders; epilepsy type; febrile seizures; variation in AED levels; high or low phenytoin levels	>1 AED and >2 seizures per year (high) >2 seizures per year; early age at epilepsy onset (≤15 vs >45 years of age); use of >1 AED; 3–5 vs no changes of AED dosage per year; use of anxiolytics; no TDM vs 1–3 TDM in the last 2 years; high CBZ levels (>40 μM) (low)
Beran *et al.* (2004)[10]	Conducted at an epilepsy clinic; age, gender and epilepsy type matched	21/21	None found	Handedness; alcohol use; deterioration of epilepsy‖	Use of >1 AED (low)
Walczak *et al.* (2001)[16]	Prospective cohort study carried out at an epilepsy clinic; not matched	20/80	None found	Epileptogenic structural lesion; psychotropic drugs; subtherapeutic AED levels	>50 seizures per month; duration of epilepsy (>30 vs <15 years) (high) >1 GTCS within the past year; IQ <70; use of >2 AEDs; female sex (low)
Williams *et al.* (2006)[155]	Prospective case–control study; patients were on specific AEDs; not matched	16/69	None found	None found	Increased variability in hair AED concentration (low)
Timmings (1993)[17]	Retrospective case–control study conducted at an epilepsy unit; not matched	14/1,806	None found	Age; duration of epilepsy; number of AEDs taken; seizure frequency	Male sex; idiopathic GTCS¶; CBZ use¶ (low)
Jick *et al.* (1992)[156]	Retrospective case–control study; used an AED prescription database; not matched	11/20	None found	Age at epilepsy onset; seizure type; seizure frequency; number of AEDs taken	Mental retardation (low)
McKee & Bodfish (2000)[15]	Conducted in residential care for mental retardation; not matched	11/unknown	None found	Age; sex	Increase in seizure frequency in the last year; polytherapy; non-ambulatory status (low)

*Strong factor characterized by OR or RR 0.1–0.99; weak factor characterized by OR or RR <0.1. ‡High risk factor characterized by OR or RR >10; low risk factor characterized by OR or RR 1.1–10. §Regular checks throughout the night or a listening device. ‖Not defined. ¶Exact OR not given. Abbreviations: AED, antiepileptic drug; CBZ, carbamazepine; GTCS, generalized tonic–clonic seizure; IQ, intelligence quotient; OR, odds ratio; RR, relative risk; SD, sudden death; TDM, therapeutic drug monitoring.

AEDs and sudden death, reported that high levels of carbamazepine (>40 μM) were more frequently found among people who died of SUDEP than in living controls.[18] The results relating to carbamazepine, however, should be interpreted with caution, as a high level of the drug could be a surrogate marker for poor seizure control. Overall, the evidence for a deleterious effect of an individual AED seems tenuous. Moreover, no strong reason exists to avoid any particular AED to prevent SUDEP.[19]

Night supervision (including special precautions, such as the use of listening devices) was associated with a substantial decrease in the risk of SUDEP in one large case–control study.[11] This finding is in keeping with the fact that most cases of SUDEP are unwitnessed.[7–11] Furthermore, the observation that all 14 cases of SUDEP that were related to a pediatric residential school, where children were carefully supervised at night, occurred during the vacation period, also seems to underscore

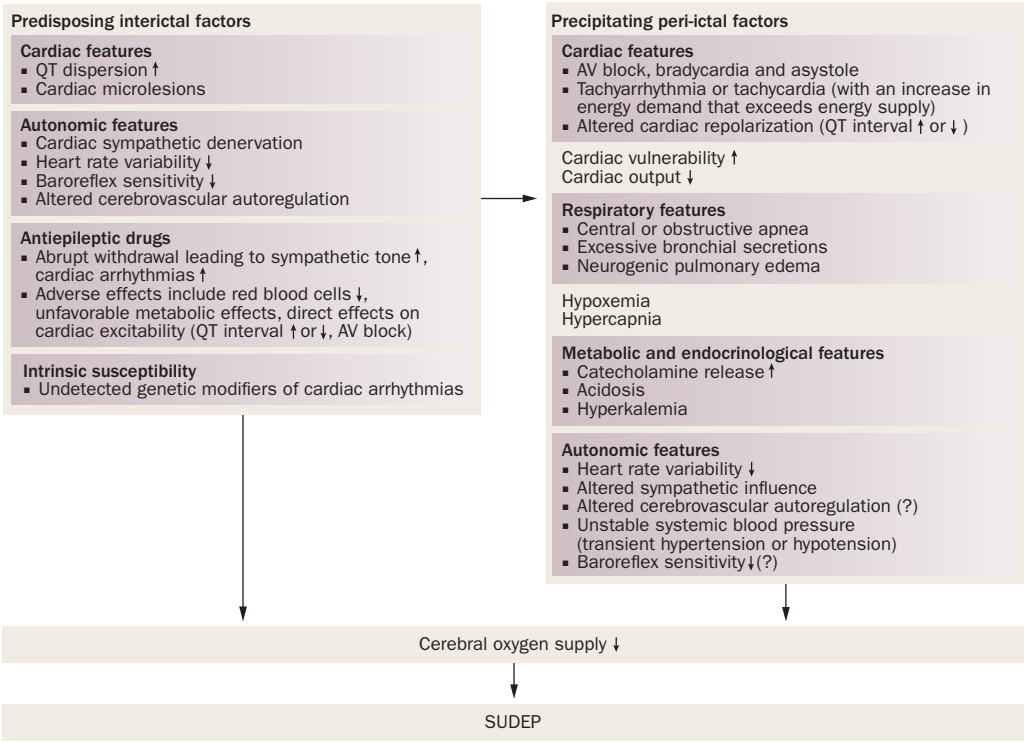

Figure 1 | Factors that might affect SUDEP. The severity of these factors and their coincidence in seizures might lead to a fatal decrease in the cerebral oxygen supply, and, hence, sudden unexpected death. The question marks highlight factors for which only limited evidence exists for involvement in chronic epilepsy. Abbreviations: AV, atrioventricular; SUDEP, sudden unexpected death in epilepsy.

the importance of surveillance in the peri-ictal period.[20] Night supervision might prevent SUDEP by enabling correct positioning, stimulation of the patient, or clearing of the airway.

Other potential protective factors for SUDEP include a history of asthma and/or cerebrovascular disease;[9,11] however, these findings have not yet been reproduced. A family history of sudden death is not associated with an increase in risk of SUDEP.[11] In case–control studies that used non-SUDEP deaths among people with epilepsy as controls, youth was reported to be a risk factor for SUDEP.[5] Case–control studies that used living people with epilepsy as controls, however, found no association between age and the risk of sudden death related to seizures.[15,16] Conflicting results exist for the effect of gender on the risk of SUDEP. Data from one report indicated that being male appeared to increase the risk of SUDEP;[17] however, other studies have either failed to confirm an effect of sex,[15] or suggested a female preponderance in relation to SUDEP.[16] In summary, the risk factors identified by controlled studies were mainly related to chronic uncontrolled epilepsy. Seizure control seems, therefore, to be of paramount importance in the prevention of SUDEP.

Pathophysiology

For most people with epilepsy, seizures are fully controlled with AEDs. Some individuals, however, continue to have recurrent seizures and take AEDs chronically, both of which might have detrimental effects. Recurrent seizures and/or chronic use of AEDs can lead to interictal, and, eventually, irreversible modifications of body functions, which might shape the body's acute response to seizures. Seizures cause challenging physical and mental stress that can trigger potentially life-threatening peri-ictal cardiorespiratory and metabolic conditions.[21] As the supply of oxygen is crucial for the functional and structural integrity of various organs, for the remainder of the Review we focus on the interictal and peri-ictal mechanisms that are likely to impair cerebral blood supply, and, hence, facilitate sudden death in chronic epilepsy (Figure 1). We will discuss the possible roles of dysregulation of cardiac and respiratory physiology, changes in the hormonal and metabolic systems, and dysfunction of systemic and cerebral circulation in SUDEP.

Dysregulation of cardiac physiology

Sudden death in the general population most often results from cardiac arrhythmias (either bradyarrhythmias or tachyarrhythmias). Cardiac arrhythmias are caused by derangements in cellular cardiac electrophysiology, namely, malfunctioning of the cardiac ion channels that control cardiac excitability and excitation–contraction coupling. Structural cardiac abnormalities facilitate the occurrence of such arrhythmias.[22] Cardiac interstitial fibrosis, for example, allows tachyarrhythmias, caused

by re-entrant excitation, to be maintained, while fibrosis of the specialized cardiac conduction system can precipitate heart block. Studies on monogenic inherited cardiac arrhythmia syndromes, however, have demonstrated that ion channel dysfunction can cause cardiac arrhythmias and sudden death in the absence of such structural abnormalities.[23]

In cardiac electrophysiology, ion channels can be subdivided into those that cause cardiac depolarization (sodium and calcium channels) and those that cause repolarization (potassium channels). Disrupted depolarization (reflected by prolongation of the PR and QRS intervals on electrocardiograms [ECGs]) can facilitate tachyarrhythmias caused by re-entrant excitation, and bradyarrhythmias resulting from heart block. By contrast, disrupted repolarization (reflected by prolongation of the QT interval on ECGs) can lead to triggered activity and culminate in torsade de pointes ventricular tachycardia, while very rapid repolarization (shortening of the QT interval) can facilitate re-entrant excitation. Emerging studies are focusing on the factors that modify cardiac ion channel function, and, hence, might contribute to the occurrence of cardiac arrhythmias and sudden death.[24] Such factors include the autonomic nervous system, drug use, and hormonal and metabolic factors. Ion channels that are functionally expressed in both the heart and the brain are also of particular research interest.[25] Indeed, ion channel dysfunction, resulting from mutations in genes encoding ion channel subunits, has been proposed to underlie both epilepsy and an increase in the risk of lethal cardiac arrhythmias.[26]

Regulation of heart rate variability

Heart rate variability (HRV) reflects the beat-to-beat alterations in the heart rate and is mainly modulated by parasympathetic and sympathetic activity.[27] In people with chronic temporal lobe epilepsy (TLE) compared with healthy controls, HRV is substantially reduced, particularly during night time.[28,29] This finding could be relevant to SUDEP, which occurs most frequently at night.[11,30] In healthy populations or in people with heart diseases, a decrease in HRV has been shown to increase the rates of cardiac mortality and sudden cardiac death.[27] A reduction in HRV reflects an imbalance between sympathetic and parasympathetic cardiac control. The data relating to changes in sympathetic and parasympathetic tone in epilepsy are somewhat inconclusive, although the results are suggestive of a decrease in parasympathetic tone and/or an increase in sympathetic tone.[31–35] Interestingly, defects in HRV and cerebrovascular autoregulation—the capacity of blood vessels in the brain to keep cerebral blood flow constant within a given range of blood pressure and to react to changes in carbon dioxide levels—were found to improve after epilepsy surgery, suggesting that both autonomic parameters are related to seizure control.[32,36] Indeed, patients with a poor surgical outcome were found to have a more pronounced HRV impairment than those individuals with a good outcome.[37]

Cardiac sympathetic regulation can be quantified by measuring cardiac ^{123}I-metaiodobenzylguanidine (MIBG) uptake. MIBG is taken up by myocardial sympathetic nerve terminals, enabling the regional and global distribution of cardiac sympathetic innervation to be quantified. MIBG uptake was reduced in people with chronic TLE, compared with healthy controls, suggesting that postganglionic sympathetic innervation was impaired in the former group, possibly as a result of neuronal cell loss.[38] Cardiac sympathetic denervation, as measured by MIBG uptake, was also more pronounced in people with TLE who experienced ictal asystolic episodes than in TLE patients without ictal asystole.[39] Furthermore, sympathetic cardiac denervation continued after epilepsy surgery, but the progress was most pronounced in those patients with persisting seizures.[40] Overall, the evidence from studies using MIBG suggests that seizures might trigger sympathetic denervation.

A reduction in cardiac sympathetic innervation could lead to an increase in the heart's sensitivity to adrenergic stimulation, perhaps via an increase in the density or sensitivity of β-adrenergic receptors. Such changes would increase the pro-arrhythmogenic action of the catecholamines.[41] Denervation hypersensitivity might also explain the apparent increase in the influence of sympathetic tone on heart rate regulation, which could potentially lead to detrimental increases in heart rate during seizures,[42] and cause abnormal heart rate recovery after seizures. Epilepsy, therefore, seems to be associated with decreases in HRV and cardiac sympathetic innervation. Reductions in both of these autonomic parameters are related to poor seizure control and, therefore, might serve as markers for SUDEP.

Changes in cardiac structure and function

Subtle perivascular and interstitial fibrotic lesions in the heart have been found in people with epilepsy and in cases of SUDEP.[14,43,44] These lesions could serve as potential sites for the generation and maintenance of fatal arrhythmias. As mentioned above, the sympathetic influence on the heart rate can be considerably increased during seizures (especially generalized tonic–clonic seizures). High levels of sympathetic activity can cause transient dilatation of ventricular walls, which can lead to left ventricular dysfunction (known as stress-induced or Takotsubo cardiomyopathy).[45] Takotsubo cardiomyopathy was reported to occur with generalized tonic–clonic seizures, and could further compromise cardiac output, leading to an insufficient peri-ictal supply of oxygen.[46]

The electrical properties of the heart might also be altered during the course of epilepsy, although existing data are inconclusive. Ambulatory ECG monitoring showed that the occurrence of interictal cardiac arrhythmias (such as an increase in the number of premature ventricular or atrial beats, or the occurrence of bigeminy or trigeminy) in people with epilepsy (5.3%) was similar to that found in the general population or in matched control patients.[47] 12-lead resting ECG recordings

displayed higher heart rates (in line with an increase in sympathetic influence or a decrease in parasympathetic tone) and slightly longer QT intervals in people with epilepsy than in matched controls.[48] ECG abnormalities, such as bundle branch block, T-wave alterations, and first-degree atrioventricular (AV)-block, were found in up to ~35% of people with pharmacoresistant epilepsy and no evidence of underlying cardiac disease.[49] Other studies, however, did not observe any interictal ECG abnormality.[50]

QT dispersion (QTd)—the difference between the longest and the shortest QT intervals within a 12-lead ECG—is considered by some to reflect the spatial distribution of cardiac repolarization. A large QTd indicates a more-heterogeneous ventricular repolarization throughout the ventricular wall and neighboring areas than a short QTd. An increase in QTd is a potential cause of ventricular arrhythmias, by facilitating the development of ventricular microcircuits that lead to re-entrant tachycardia.[51] Evidence now exists for an increase in QTd in adults and children with pharmacoresistant epilepsy.[52,53] The reason why the QTd is increased in these cases is not known.

Tachycardia and cardiac injury

Sudden fatal cardiac arrhythmias are commonly thought to be involved in the pathophysiology of SUDEP. Indeed, some ECG features that predict an increase in the risk of cardiac mortality or sudden cardiac death in a healthy population, or in those with other medical conditions, occur during or shortly after seizures in a considerable proportion of people with chronic epilepsy.[51,52] The predominant cardiac feature during seizures, however, is an increase in heart rate, which has been reported to occur in 73–99% of seizures and 92–100% of people with epilepsy (including SUDEP patients).[42,49,52,54–57] Ictal heart rates above 150 bpm were reported in 12–48% of seizures and 13–16% of patients.[42,52,54,57] One study indicated that ictal heart rates were higher in SUDEP patients than in controls.[58] Such elevated heart rates might favor the onset of cardiac injury.[59] In ECG recordings, cardiac infarctions can be mirrored by alteration of the ST segment. Indeed, peri-ictal ST-segment depression or elevation occurred in up to 7.2% of seizures and in up to 41% of patients[49,56–59] Peri-ictal ST-segment alterations might, therefore, indicate transient cardiac injury during pronounced tachycardia. A transient cardiac injury could, in turn, facilitate potentially lethal cardiac arrhythmias and might cause the cardiac microlesions that occur in people with epilepsy and SUDEP patients. Results from one study indicate that serum markers for cardiac injury might be elevated after a seizure, even in children in whom cardiac structural changes (for example, coronary artery disease) are absent.[60] By contrast, cardiac troponin T blood levels (a marker for cardiac injury) were not elevated following seizures (without any apparent peri-ictal pathological ECG abnormality) in adult patients with epilepsy.[61]

Bradycardia and bradyarrhythmia

Ictal bradycardia and bradyarrhythmia are probably caused by an increase in parasympathetic activity or a disruption of sympathetic activity resulting from propagating ictal activity in the respective autonomic cortical or subcortical networks.[62,63] Ictal bradycardia (or asystole) can also develop secondary to apnea,[64] as a decrease in heart rate is part of a physiological cardiovascular response to apnea.[65] Ictal bradycardia is less frequent than tachycardia, and was detected in 0–6.4% of seizures and in 0–13.6% of patients with epilepsy during prolonged video-EEG telemetry.[42,49,56,57,66] When assessed with ambulatory long-term ECG recordings, ictal bradycardia occurred in only 2.1% of the total number of seizures, but was experienced by 37% of patients.[67] Ictal asystole lasting up to 60 s was reported in 0.27–0.4% of patients during prolonged video-EEG telemetry,[68,69] and in 16% of people with epilepsy monitored with ambulatory long-term ECG recordings.[67] Asystole or bradycardia of short duration (a few seconds) might be a benign condition;[70] however, longer episodes (for example, tens of seconds to minutes) of bradycardia or asystole that occur in conjunction with severe hypoxemia could lead to a fatal decrease in cerebral oxygen supply and sudden death. This premise is in line with data on seizure-related deaths in experimental animal models. In various acute seizure models, most animals died with evidence of prior ictal episodes of bradycardia or asystole.[71–73]

Other types of cardiac arrhythmias

In humans and animals, electrical stimulation of or seizure-like activity in various cerebral regions, including limbic and insular structures, affect cardiac excitability and produce premature atrial or ventricular beats, as well as alterations in cardiac repolarization.[74–76] Indeed, peri-ictal cardiac arrhythmias in humans and animals commonly include pronounced sinus arrhythmia, premature ventricular or atrial beats, AV-nodal escape beats, and bundle branch blocks.[42,49,54,57,77] Paroxysmal supraventricular tachycardia, atrial fibrillation, and transient AV blocks of varying severities have also been reported.[42,56,58] Analysis of the available peri-ictal ECG data revealed that these cardiac arrhythmias occurred in up to 31% of seizures and up to 72% of patients;[42,49,52,54,56–58] however, a clear association between the occurrence of cardiac arrhythmias and seizure types has not been established (R. Surges, unpublished data).[49,52,57]

Alterations to cardiac repolarization are associated with an increase in the risk of developing fatal arrhythmias, as shortening or prolongation of the QT interval beyond the normal limits increases the risk of ventricular tachyarrhythmia.[78] Genetically caused (long QT syndrome) or acquired prolongation of the QT interval favor the onset of the potentially lethal torsade de pointes arrhythmia. Seizure-related QT lengthening above pathological upper limits was observed in adults (including SUDEP patients) and children with epilepsy.[52,79] In an earlier study, QT prolongation by

an average of 35 ms in 6 out of 11 SUDEP patients was associated with interictal cortical discharges.[80] Potential mechanisms of ictal QT prolongation include cerebral dysregulation (notably, with involvement of the insular cortex),[76] hypercapnia and hypoxia,[81,82] and release of catecholamines,[83,84] as well as nonuniform sympathetic or parasympathetic cardiac activity (resulting in nonuniform cardiac repolarization).[71]

In contrast to long QT syndromes, genetically caused short QT syndromes have only been described in the past few years.[85] Mutations in cardiac voltage-gated potassium and calcium channels shorten the QT interval and lead to a reduction in the ventricular refractory period, which is a potential cause of life-threatening reentrant ventricular tachyarrhythmias. Moreover, transient, abnormal QT shortening was found to frequently occur with generalized tonic–clonic seizures (R. Surges, unpublished data). Notably, the combination of a short QT interval and an increase in QTd, as described in people with epilepsy (R. Surges, unpublished data),[52] facilitated ventricular tachyarrhythmia in an animal model of short QT syndrome.[86] Shortening of the QT interval can be induced by raised catecholamine levels, hyperkalemia and acidosis,[85,87,88] all conditions that occur during or shortly after generalized tonic–clonic seizures.[72,83,89] The clinical importance of abnormal ictal QT shortening is currently unclear, but such a reduction in the QT interval might be involved in the pathophysiology of SUDEP in the context of generalized tonic–clonic seizures. The hypothesis that perictal ventricular tachyarrhythmias, which might be facilitated by alterations in cardiac repolarization, are involved in SUDEP is partially supported by an experimental study in which two out of nine animals died of ventricular fibrillation following seizure-like activity.[71] Importantly, ventricular tachycardia and fibrillation were also reported after a secondary generalized tonic–clonic seizure in a patient with epilepsy who had no underlying cardiac disease.[90]

Role of antiepileptic drugs

Unequivocal clinical data relating to the potential role of AEDs in SUDEP are lacking.[19] AEDs might prevent SUDEP by improving seizure control. Conversely, AEDs might potentially trigger SUDEP following their sudden withdrawal, or by exerting direct effects on cardiac control. Poor adherence of epilepsy patients to their AED regimens results in insufficient seizure control. Furthermore, abrupt AED withdrawal can considerably increase sympathetic tone during sleep and the occurrence of cardiac arrhythmia.[91,92] Poor adherence to treatment, therefore, is a plausible reason for seizure aggravation and might lead to SUDEP.[93] Cases of SUDEP, however, do not necessarily involve those patients with poor adherence to AED regimens. In a postmortem study, SUDEP patients displayed similar levels of AEDs to individuals with epilepsy who had died of causes other than epilepsy.[94]

AEDs have various adverse effects that might contribute to SUDEP. Carbamazepine and other AEDs can slow cardiac conduction, probably by inhibition of voltage-gated cardiac sodium channels.[95,96] Carbamazepine-induced AV conduction block is, however, uncommon in elderly patients who do not have notable pre-existing AV conduction defects.[97] Lamotrigine has been shown to inhibit cardiac rapid delayed rectifier potassium channels *in vitro*.[98] Such inhibition might be expected to lengthen cardiac repolarization and the QT interval, which, in turn, could increase the risk of fatal ventricular tachyarrhythmia.[99] A case series of four consecutive SUDEP patients on lamotrigine therapy suggested a role for lamotrigine—by prolongation of the QT interval—in causing SUDEP.[100] Controlled clinical studies, however, showed no QT prolongation at routinely used doses of lamotrigine.[97,101]

AED-induced QT shortening might also occur with the use of carbamazepine, rufinamide or primidone.[97,102,103] The clinical importance of drug-induced QT shortening is not known, but is the subject of increasing research. QT shortening, like QT prolongation, could increase the risk of fatal tachyarrhythmia.[78,88]

AEDs might predispose patients to SUDEP by other noncardiac-mediated pathways. For example, AEDs can reduce the number of red blood cells.[104,105] The resulting deficit in the blood oxygen supply would contribute to the challenging cardiorespiratory and metabolic conditions during seizures. Evidence from patients using carbamazepine to control their seizures suggests that AEDs might also unfavorably alter plasma fatty acid profiles.[106] Disruption to such profiles might affect neuronal and cardiac excitability, as fatty acids contribute to the properties of cell membranes. The clinical relevance of AEDs to the occurrence of SUDEP however, is still unclear and requires further investigation.

Intrinsic susceptibility to sudden death

Apart from epilepsy-related and seizure-related factors, SUDEP patients might display other, unknown conditions that facilitate sudden death. Such conditions are probably not associated with prominent morphological modifications and, therefore, are not uncovered during postmortem analysis. Suggested candidates for undetected comorbidities include mutations in ion channels that lead to lethal cardiac arrhythmias. The postmortem detection of a mutation in *SCN5A*, the gene that encodes the main pore-forming subunit of the cardiac voltage-gated sodium channel, was described in a patient with idiopathic epilepsy who died suddenly.[107] One might be tempted to speculate that in a proportion of presumed cases of SUDEP, the patients actually died of cardiac arrhythmias caused by unknown genetic mutations. By contrast, patients with paroxysmal cardiac arrhythmias might be misdiagnosed as having epilepsy.[108] The coexistence of epilepsy and paroxysmal cardiac arrhythmia could also be caused by the expression of mutant forms of the same ion channel isoforms in both the heart and

the brain, as demonstrated in expression and biophysical studies.[26] This hypothesis is supported by the finding that patients with cardiac long QT syndrome type 2 more often displayed seizure phenotypes than patients with cardiac long QT syndrome type 1 or type 3.[109] Long QT syndrome type 2 is caused by mutations in voltage-gated potassium channels, which are expressed in the heart and the hippocampus (the latter being a frequent site of seizure generation in TLE).

Dysregulation of respiratory physiology

Interictal respiratory function does not seem to be altered in people with epilepsy.[36,110,111] By contrast, respiratory symptoms commonly occur during seizures, and range from coughing, belching and hyperventilation to respiratory arrest. Hyperventilation and tachypnea are observed during seizures that originate in the temporal or frontal lobe,[112,113] although these respiratory symptoms probably do not have a pivotal role in the mechanisms underlying SUDEP. Peri-ictal respiratory difficulties and laborious breathing were frequently reported in witnessed SUDEP events.[6] Such difficulties are most probably attributable to ictal dysfunction of the cortical and subcortical areas involved in the regulation of breathing, as electrical stimulation of the temporal pole, hippocampus and insula have been shown to reduce or abolish respiratory movements.[114,115] Indeed, postictal central or obstructive apnea was reported in two patients who nearly experienced SUDEP.[116,117]

Central hypopnea or apnea are the most common causes of seizure-related respiratory difficulties, and occur more frequently than obstructive or mixed apnea.[64,118,119] Hypopnea or apnea lead to pulmonary hypoventilation, and, subsequently, a compromised exchange of oxygen and carbon dioxide. Indeed, oxygen saturation levels were found to be <90% during 20–30% of all seizures and in 13–66% of adults with epilepsy,[64,118–120] and severe desaturation (<70%) was reported in ~4% of all seizures. Overall, the mean oxygen desaturation levels ranged from 71–83% and lasted 69–76 s in patients with epilepsy during seizures.[64,118–120] Importantly, hypoxemia was accompanied by increases in carbon dioxide partial pressure above 50 mmHg (hypercapnia) in some seizures.[118]

Aside from mechanical dysfunction, respiration can be further impaired by compromised alveolar gas exchange, which results from excess bronchial secretions or pulmonary edema. Neurogenic pulmonary edema (NPE) was reported to be a pathological hallmark in postmortem studies of SUDEP patients.[12,30,121,122] NPE can be triggered by various insults to the CNS, all of which cause a systemic and massive, centrally-mediated adrenergic stimulation. Stimulation of pulmonary blood vessels and capillaries induce pulmonary vasoconstriction and an increase in both pulmonary hydrostatic pressure and capillary permeability, the latter being aggravated by an additional inflammatory component.[123] Depending on the triggering CNS insult, NPE develops over minutes (for example, after a major head trauma) to a few hours (for example, after a minor or moderate head trauma). NPE is associated with a relatively high mortality rate if left untreated; however, the condition usually resolves within 1–3 days following therapeutic intervention.[123] Postictal NPE is rare, but can occur after generalized tonic–clonic seizures or status epilepticus.[124] Two findings, however, suggest that NPE alone does not have a predominant role in SUDEP. First, in most witnessed cases of SUDEP, the patients died shortly after a seizure (that is, within minutes rather than hours),[6,12] whereas clinically manifest NPE would probably take longer to develop after a single generalized tonic–clonic seizure. Second, in a sheep model of sudden death in epilepsy, NPE in combination with central hypoventilation, but not NPE alone, was associated with seizure-related deaths.[125] Severe NPE with rapid onset, however, would cause respiratory insufficiency and might lead to SUDEP.

In summary, respiratory dysfunction is not uncommon in seizures and can result in severe hypoxemia and hypercapnia. Respiratory dysfunction has a detrimental effect on tissue oxygenation, which could be fatal in the context of an increase in energy demand. Fulminant postictal NPE, although rare, might also cause SUDEP. Cardiorespiratory interactions could further compromise peri-ictal cardiac function and thereby facilitate SUDEP. Apnea can lead, via a physiological cardiorespiratory reflex, to a drastic decrease in heart rate,[64,65] whereas hypoxemia and hypercapnia can both prolong cardiac repolarization, which might increase the risk of ventricular tachyarrhythmias.[81,82]

Hormonal and metabolic changes

Various hormones, such as prolactin, vasopressin, adrenocorticotropic hormone, cortisol, oxytocin and adrenaline, are released during generalized tonic–clonic seizures.[83,126,127] Furthermore, seizure-related changes in electrolytes and blood pH have been reported in humans and animal models.[72,89,125,128] For example, plasma potassium levels increased twofold 4 minutes after the induction of generalized seizures in a sheep model of status epilepticus, and were accompanied by a substantial decrease in pH.[125] Both hyperkalemia and acidosis affect cardiac excitability, influencing heart rate, ectopic activity and cardiac repolarization.[84,88,129] These hormonal and metabolic changes might all contribute further to the onset of bradyarrhythmias or tachyarrhythmias and thereby facilitate seizure-related sudden death.

Disturbed systemic and cerebral circulation

Interictal resting systemic blood pressure is within normal limits in most individuals with epilepsy.[130,131] Studies addressing the effects of stimuli such as standing, isometric contraction, and the Valsalva maneuver, on blood pressure regulation in people with epilepsy produced mixed results, with such individuals displaying either normal or slightly abnormal responses.[130–132]

Interictal baroreflex sensitivity was reduced in people with TLE compared with healthy controls,[34] and this decrease is likely to impair the body's capacity to maintain the blood pressure within a given range. A sudden drop in systemic blood pressure, therefore, might be counteracted with an insufficient increase in vasoconstriction or heart rate, thereby reducing cerebral blood supply. Blood vessels in the brain can usually maintain a constant cerebral blood flow within a given range of blood pressure, and can react to changes in carbon dioxide levels. In people with epilepsy, however, interictal cerebrovascular autoregulation seems to be impaired, probably as the result of an increase in sympathetic tone.[31,36,133] Impaired cerebrovascular autoregulation could increase an individual's susceptibility to hypoperfusion under challenging cardiorespiratory conditions.

In humans and animals, electrical stimulation of the cortical networks involved in autonomic function (for example, the insular cortex and the temporal lobe) has been reported to cause decreases and increases in blood pressure, suggesting an asymmetric representation.[114,134] For example, activation of the left hemisphere predominantly led to hypotension.[134] During seizures, arterial blood pressure commonly increases; however, blood pressure can also decrease or exhibit no change.[128,135] In some animal models of acute seizures, dying animals displayed seizure-related hypotension or a substantially decreased blood pressure compared with the surviving animals.[72,73,125] Furthermore, baroreflex function was impaired during seizures in an animal model.[73] Thus, peri-ictal hypotension and a compromised baroreflex function, as reported in people with chronic TLE,[34] might contribute to SUDEP. In the case of peri-ictal hypotension, impaired baroreflex sensitivity would decrease the compensatory upregulation of blood pressure and thereby exacerbate the insufficient cerebral blood flow.

Cerebral blood flow is tightly coupled to metabolic and functional changes in brain activity. In partial epilepsy, for example, seizures are associated with an increase in cerebral blood flow, followed by postictal hypoperfusion in the region of seizure activity.[136] Cerebral blood flow is also substantially influenced by mechanisms of cerebrovascular autoregulation. Data on seizure-related changes in cerebrovascular autoregulation are sparse. In one peri-ictal study, cerebrovascular autoregulation seemed to be normal when tested 14 minutes after a generalized tonic–clonic seizure.[128] By contrast, postictal cerebrovascular autoregulation was considerably impaired in an animal model of acute seizures.[137] Seizure-related hypoxemia can persist for up to 5–10 minutes postictally.[118] If impaired cerebrovascular autoregulation and hypoxemia coincide with a decrease in cardiac output (for example, caused by ictal bradyarrhythmia or arterial hypotension), a fatal breakdown of cerebral blood flow could result, leading to cerebral dysfunction, structural damage, and, ultimately, sudden death. This mechanism might partly explain the 'cerebral shutdown' hypothesis. This hypothesis is based on the observation that in three people with epilepsy who underwent an EEG recording during SUDEP, ictal EEG activity suddenly ceased, being replaced by a 'flat' EEG.[138–140] This finding suggests that electrical cerebral shutdown might be the primary event in the process that leads to sudden death. The flat EEG, however, might only represent the loss of cortical activity, and brainstem function could still be intact. Unfortunately, unequivocal data on synchronous and continuous ECG and systemic blood pressure were lacking in these reports, so an exact reconstruction of the events is impossible. A sudden cessation of electrical activity on the EEG is, however, a common feature of cerebral hypoperfusion in syncope and might explain the abrupt EEG changes in SUDEP.[141] Accordingly, in an animal model of acute seizures, a sudden decrease in cerebral perfusion (induced by carotid artery occlusion) led to an abrupt halt in seizure activity and a flat EEG.[142] Ictal hypotension and bradyarrhythmia can occur in people with epilepsy and might cause cerebral hypoperfusion, and, thereby, cerebral shutdown, if cerebrovascular and autonomic reflex mechanisms are impaired.

Summary, conclusions and perspectives

In this article, we reviewed the various risk factors for SUDEP and the pathophysiological aspects of seizures and chronic epilepsy that could potentially cause sudden death (Figure 1). The high peri-ictal occurrence of precipitating factors contrasts with the rather lower incidence of SUDEP. This difference suggests that the presence of single factors, or the simultaneous presence of several factors with only weak or moderate severity, is not sufficient to cause seizure-related death. For example, ictal asystole for several seconds, in the absence of other factors, is likely to be a benign condition,[70] whereas ictal asystole occurring together with severe central apnea, during generalized convulsions, might lead to a fatal decrease in cerebral oxygen supply and sudden death. Thus, SUDEP is most probably caused by the peri-ictal coincidence of several precipitating factors. This 'fatal coincidence' hypothesis is also supported by experimental findings in animal models.[72,125]

SUDEP is usually not witnessed or monitored, and remains somewhat of a 'black box' phenomenon. Predicting and preventing SUDEP are, therefore, challenging tasks. Patients with medically refractory epilepsy, particularly with frequent generalized tonic–clonic seizures, are likely to have a higher risk of SUDEP than people with well-controlled epilepsy, and might benefit from nocturnal seizure-alerting systems or supervision.[11,143] Attempts to identify clear-cut electrocardiographic predictors for SUDEP in medically refractory epilepsy have so far failed (R. Surges, unpublished data).[52,58] Reasonable evidence suggests that an increase in sympathetic influence in chronic epilepsy and during seizures might have a crucial role in SUDEP.[32,58,83] Future studies that attempt to counteract sympathetically mediated pro-arrhythmogenic effects in people with epilepsy who are at higher risk of SUDEP should, therefore, be considered. For example,

regular intake of β-blocking agents could theoretically reduce the risk of SUDEP in people who have medically refractory epilepsy and experience a large number of generalized tonic–clonic seizures. The administration of β-blocking agents is further supported by the findings that such agents have antiepileptic and antiarrhythmic properties in both people with epilepsy and an animal model of acute seizures.[144–146] The use of β-blocking agents, however, must be rigorously tested, as the drugs could have deleterious effects in patients who experience ictal bradycardias or asystoles.

Another approach that might have a place in the prevention of SUDEP involves the implantation of a combined cardiac pacemaker–defibrillator device in people with epilepsy who have frequent generalized tonic–clonic seizures.[147] Furthermore, the administration of the selective serotonin re-uptake inhibitor (SSRI) fluoxetine in a genetic mouse model of audiogenic seizures was found to reduce seizure-related respiratory arrest.[148] Indeed, fluoxetine has been suggested to have antiepileptic properties;[149] however, the drug at high doses might induce generalized tonic–clonic convulsions and interact with other AEDs.[150,151]

Aside from these medical interventions, people with chronic epilepsy who are at a high risk of sudden death, as well as their relatives could benefit from being informed about SUDEP.[152] Individuals with epilepsy who adhere poorly to their AED treatment regimen might improve their adherence following education. Moreover, emergency measures, such as resuscitation techniques, should be taught to close relatives of at-risk individuals. To complement the development of preventative measures for SUDEP, studies should be conducted to further explore the commonalities between the genetic basis of epilepsy and the intrinsic risk of fatal cardiac arrhythmias. Such investigations might require the implementation of specialized genetics clinics.[153]

Sudden death might be a rare phenomenon in epilepsy, but, SUDEP is a relatively frequent cause of mortality among people with refractory epilepsy. A number of issues need to be addressed to achieve progress in the field of SUDEP research and to develop effective prevention. As for other rare medical conditions and 'orphan' diseases, sufficient research funding for SUDEP is a considerable issue, and financial support from the pharmaceutical industry and governmental agencies is needed. Patients who are at risk of SUDEP need to be clearly identified and must be assessed for the negative effects of seizures, epilepsy-related cardiorespiratory dysfunction, and pharmacological interactions. Such assessments will require the collaboration of specialists in several areas before additional pharmacological intervention (for example, administration of cardioprotective therapy or SSRIs) can be deployed. The initiation of controlled pharmacological trials that enlist people with chronic epilepsy who are at a high risk of sudden death could be a way forward. National and international SUDEP registers could facilitate research on genetic susceptibility factors, and the development of appropriate animal models for SUDEP would aid the testing of preventative strategies.

Review criteria

The Review was based on a search of the PubMed database using the terms "epilepsy" and "sudden death", with no time limits on publication date. Only articles of particular relevance to the pathophysiology of sudden unexpected death in epilepsy, according to our judgment, were retrieved and reviewed. Where indicated, data from some of our own unpublished work were also included.

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