

## Sudden Unexpected Death in Epilepsy – An Overview of Current Understanding and Future Perspectives

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### Abstract

Sudden unexpected death in epilepsy (SUDEP) is likely to be the most common cause of disease-related mortality in people with epilepsy. The most commonly encountered scenario is that a previously healthy person is found dead in bed by family. Patients with frequent generalised tonic-clonic seizures are at highest risk but SUDEP can occur in patients who have never had convulsions. The mechanisms of SUDEP are poorly understood but seem to be related to seizure-related cardiac, respiratory or cerebral dysfunction. Seizure control is the only clear strategy to prevent SUDEP but that is not possible in the 30 % of patients with treatment-resistant epilepsy. Understanding the pathophysiology of SUDEP may lead to prevention strategies for patients who continue to have seizures despite maximal therapy.

### Keywords

Epilepsy, sudden unexpected death in epilepsy, serotonin, adenosine, channelopathy

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People with epilepsy have a two- to threefold increased mortality<sup>1</sup> and are 24 times more likely to die of sudden death compared with the general population.<sup>2</sup> Although injuries associated with seizures, suicides, adverse effects of medications and the underlying aetiology of the epilepsy contribute to this increased mortality, sudden unexpected death in epilepsy (SUDEP) is the leading cause of death in patients with refractory epilepsy. SUDEP is defined as a sudden and unexpected non-traumatic or non-drowning-related death in a patient with epilepsy that may or may not be due to a recent seizure.<sup>3</sup> On autopsy, there is no evidence of anatomical (e.g. myocardial infarction) or toxicological (e.g. drug overdose) cause of death. If no autopsy was performed, the death is called 'probable' SUDEP if there is no known alternative explanation for death (e.g. pre-existing heart disease) and 'possible' if there is a competing explanation for death.

Most often, the death is unwitnessed and the patient is found in bed the following morning.<sup>4</sup> However, evidence suggests that the deaths are likely to be seizure-related. In a series of 15 witnessed SUDEP cases, all but one death occurred during or after a convulsive seizure; the remaining death occurred after a typical aura.<sup>5</sup> Pathological evidence also supports the role of terminal seizures; immunohistological examination of hippocampi of SUDEP cases has revealed elevated neuronal heat-shock protein 70 expression, a marker of acute

neuronal injury that is often elevated after seizures, compared with non-SUDEP cases.<sup>6</sup>

SUDEP is a categorical term and may have multiple aetiologies (see below). The incidence of SUDEP in the general epilepsy population has been reported to be 0.09–1.2/1,000 person-years. This incidence is higher, 1.1–5.9/1,000 person-years, in patients with medically refractory epilepsy and even higher, 6.3–9.3/1,000 person-years, in patients who have failed resective epilepsy surgery<sup>7,8</sup> (see *Figure 1*). In several case-control studies, the greatest risk factor for SUDEP was frequent seizures, especially generalised tonic-clonic seizures.<sup>4,9–11</sup> Other commonly identified risk factors were early age of epilepsy onset/long duration of epilepsy, young adult age (20–40 years old), male sex, variable anti-epileptic drug (AED) levels and AED polytherapy.<sup>7,8</sup> Some AEDs have been associated with elevated risk of SUDEP such as carbamazepine<sup>12</sup> and lamotrigine,<sup>9,13</sup> but this has not been found consistently. Some retrospective studies have identified factors associated with reduced risk of SUDEP such as having a roommate or other form of nocturnal supervision.<sup>4,14</sup> Factors that may modify SUDEP risk identified in case-control studies are summarised in *Table 1*.

The mechanisms underlying SUDEP are unclear and it is likely to be the common endpoint for a variety of causes. Hypotheses, often

**Table 1: Factors Associated with Sudden Unexpected Death in Epilepsy Risk Reported in Case-control Studies****Factors Associated with Increased Sudden Unexpected Death in Epilepsy Risk**

<i>Ongoing seizures:</i>	<i>Antiepileptic drug therapy:</i>
Frequent seizures	• Lack of AED use
GTCS (>3 per year)	• Subtherapeutic levels
Long epilepsy duration	• Polytherapy (>3 AEDs)
Young adults	• >2 AED changes/year
Early epilepsy onset	• Rapid AED withdrawal
<i>Neurological status:</i>	• Carbamazepine use
• Intelligence quotient <70	• Lamotrigine use
• Non-ambulatory	
• History of major neurological insult	

**Factors Associated with Decreased Sudden Unexpected Death in Epilepsy Risk**

Seizure remission  
 Successful epilepsy surgery  
 Nocturnal supervision  
 Recent addition of AED

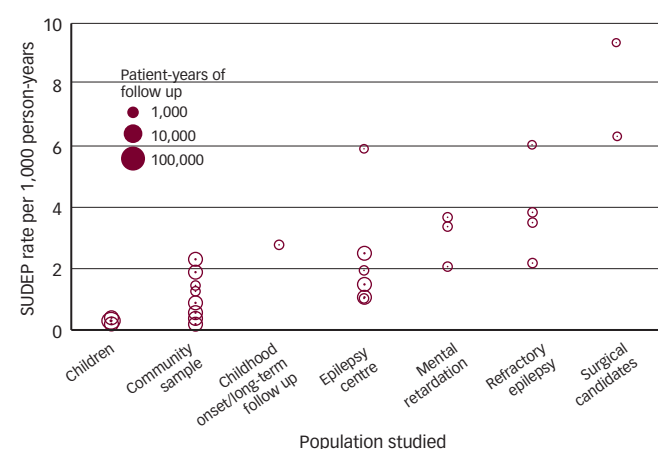
Factors found consistently in multiple studies are shown in bold (reviewed in Tomson et al., 2008, Devinsky, 2011).<sup>7,8</sup> AED = anti-epileptic drug; GTCS = generalised tonic-clonic seizure.

generated from observed SUDEP and near-SUDEP in epilepsy monitoring units, include seizure-related respiratory failure, cardiac arrhythmia, 'cerebral electrical shutdown', or combinations of these. The frequency of respiratory and cardiac changes during seizures that do not lead to death in patients with epilepsy suggest that SUDEP may result from failure of mechanisms that allow patients to recover from seizure-induced cardiopulmonary derangements. The proposed mechanisms are reviewed below; however, it is likely that in many cases, SUDEP is multi-factorial in nature with an interaction between seizures, genetics, AEDs, respiratory drive, arousability, oxygenation, and other aspects of cardiopulmonary function (see *Figure 2*).

**Primary Respiratory Mechanisms**

Ictal hypoventilation has been reported in several animal models of seizures. A study of bicuculline-induced status epilepticus in tracheostomised sheep found central hypoventilation and hypercarbia in all eight animals examined and was directly related to the death of one of the three animals that died.<sup>15</sup> Hypoventilation has also been demonstrated to be the cause of seizure-related death in certain mouse strains susceptible to audiogenic seizures.<sup>16</sup> Respiratory arrest can be prevented in these mice, which have altered expression of 5-hydroxytryptamine (5-HT) receptors in brainstem respiratory centres<sup>17</sup> by pretreatment with fluoxetine, a selective serotonin re-uptake inhibitor (SSRI).<sup>18</sup> In three cases of witnessed SUDEP or near-SUDEP in epilepsy monitoring units, seizure-associated apnoea preceded cardiac arrest.<sup>19</sup> In another patient, death was felt to be the consequence of obstructive apnoea due to laryngospasm.<sup>20</sup>

In patients undergoing video-electroencephalographic (EEG) monitoring, several studies have found that the majority of secondarily generalised tonic-clonic seizures and about one-third of partial seizures without secondary generalisations are associated with hypoxaemia.<sup>21-22</sup> In one study, in a subset of patients that underwent airflow and chest monitoring, central apnoea was seen in 44 % of seizures, obstructive apnoea in 2 % and mixed apnoea in 7 %. End-tidal CO<sub>2</sub> (ETCO<sub>2</sub>) monitoring in another subset revealed a rise in ETCO<sub>2</sub> with every seizure associated with a significant oxygen desaturation.<sup>23,24</sup> However, ETCO<sub>2</sub> changes were prolonged and persisted through the post-ictal period despite normal respiratory effort, suggesting

**Figure 1: Reported Incidence of Sudden Unexpected Death in Epilepsy**

Sudden unexpected death in epilepsy (SUDEP) per 1,000 person-years across 30 studies of various populations. Marker size is proportional to number of person-years of follow-up in each study. Source: data from Tomson et al., 2008,<sup>7</sup> Devinsky, 2011<sup>8</sup> and Sillanpaa and Shinnar, 2010.<sup>65</sup>

ventilation-perfusion mismatch may also be involved in seizure-related respiratory dysfunction.<sup>24</sup> A follow-up study demonstrated that in 10 patients undergoing intracranial EEG recording, apnoeas only occurred with contralateral seizure spread,<sup>25</sup> suggesting that bihemispheric dysfunction or involvement of subcortical pathways leads to respiratory dysfunction. Although significant respiratory dysfunction was rarely observed, even mild-moderate degrees of post-ictal hypoxaemia can lead to potentially pro-arrhythmic changes in cardiac repolarisation.<sup>26</sup>

**Primary Cardiac Mechanisms**

Seizures have numerous effects on cardiac function that could potentially lead to fatal arrhythmias. Most seizures are associated with significant tachycardia, potentially placing significant demands on the myocardium. In one series, 40 % of patients had ictal or post-ictal ST segment changes of >1 mm following complex partial seizures or generalised tonic-clonic seizures suggestive of myocardial ischaemia,<sup>27</sup> although one small study found no elevations of post-ictal troponins.<sup>28</sup> Some cases of seizure-related cardiac dysfunction have been associated with Takotsubo syndrome, a poorly understood cardiomyopathy that manifests as heart failure and haemodynamic instability following excessive catecholamine release,<sup>29</sup> the purported mechanism behind being 'scared to death'. In a retrospective examination of EEG/electrocardiographic (EKG) data of 21 patients who died of SUDEP or suspected SUDEP, patients in the SUDEP group had a higher maximal heart rate, particularly when seizures occurred from sleep, compared with matched controls.<sup>30</sup> Ictal bradycardia is rarer, occurring in less than 2 % of patients and perhaps related to seizure spread to the left insular cortex. Ictal asystole lasting up to 60 seconds have been shown to occur in less than 0.4 % of patients undergoing video-EEG monitoring.<sup>31</sup> However, prolonged recordings with implantable loop recorders have shown that 16 % of patients with refractory epilepsy without a history of heart disease had significant bradycardias and asystoles with some (2.6 %) of their seizures.<sup>32</sup> Seizures have also been shown to affect cardiac repolarisation. A recent study demonstrated that in a series of patients undergoing video-EEG monitoring, most seizures were associated with a lengthening of the corrected QT interval (QTc).<sup>33</sup> This increase was minimal in most cases but in 12 % of seizures there was a >60 ms increase in QTc that is thought

to be modestly pro-arrhythmic, especially if coupled to underlying long QT syndrome.<sup>34</sup> The greatest increase was seen with generalised tonic-clonic seizures and right temporal complex partial seizures. In support of a cardiac cause of SUDEP, several autopsy series of patients with SUDEP revealed evidence of pathological interstitial and perivascular cardiac fibrosis. Two patients with SUDEP or near-SUDEP during video-EEG monitoring had documented seizure-related ventricular tachycardia.<sup>35,36</sup>

### Primary 'Electrocerebral Shutdown'

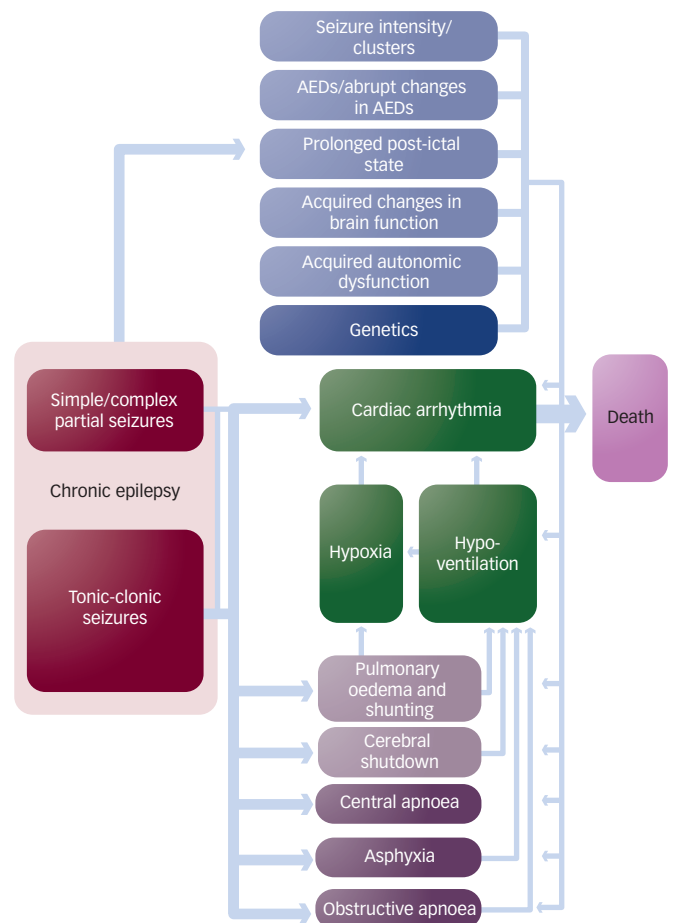
The concept of 'electrocerebral shutdown', whereby mechanisms of seizure suppression lead to instability of brainstem autonomic function or loss of protective reflexes, is proposed by some to explain observed cases of SUDEP and near-SUDEP. In three of thirteen cases of observed SUDEP and near-SUDEP recorded with EEG monitoring, there was evidence of a severe post-ictal suppression of EEG activity with central apnoea that preceded changes in EKG.<sup>7,37</sup> Little is understood about the mechanisms that may underlie this phenomenon and it is also not clear if hypoxaemia contributes to this phenomenon because none of the reported patients had pulse oximetry recorded. A recent retrospective case-control study identified a prolonged duration of post-ictal EEG suppression, an electrophysiological marker of severe global cerebral dysfunction after a seizure, as a potential risk factor for SUDEP.<sup>37</sup> However, this was not confirmed in another series of SUDEP cases.<sup>38</sup> Some authors speculate that this prolonged post-ictal coma leads to failure of protective arousal mechanisms and makes the patient susceptible to potentially lethal airway obstruction or hypercapnia from re-breathing exhaled CO<sub>2</sub>, which can further suppress cerebral recovery.<sup>39</sup> This is the scenario in which repositioning or stimulation of the patient by an observer may (theoretically) prevent SUDEP.

Post-ictal electrocerebral shutdown may be due to the endogenous mechanisms that terminate seizures. One neurotransmitter implicated in seizure termination and potentially SUDEP is adenosine, which is released by astrocytes post-ictally and has potent anticonvulsant properties.<sup>40,41</sup> In addition, stimulation of brainstem adenosine receptors can lead to cardiopulmonary dysfunction in animal models.<sup>42</sup> Mice with impaired clearance of adenosine because of pharmacological blockade of adenosine kinase and adenosine deaminase died after seizures provoked by kainic acid injection. Survival in this putative model of SUDEP could be prolonged by pretreatment of caffeine, an adenosine receptor antagonist.<sup>43</sup> Further research is needed to examine the role of adenosine in post-ictal arousal and cardiopulmonary function.

### Autonomic Dysfunction

Autonomic system dysfunction may be common in people with epilepsy, potential predisposing them to seizure-related cardiac or pulmonary dysfunction. Heart rate variability (HRV), a correlate of autonomic nervous system balance, is reduced in patients with refractory epilepsy. Spectral analysis in some studies reveals a relative increase in sympathetic tone and decrease in parasympathetic tone and impaired baroreceptor function in people with epilepsy.<sup>44</sup> HRV may be particularly reduced at night when many deaths occur. Reduced HRV is associated with increased mortality in patients with heart disease but its role in SUDEP risk is not known. In a recent study, one measure of vagal influence on HRV, the root mean square differences of successive RR intervals, was inversely correlated with a composite score of SUDEP risk factors (frequency of seizures, frequency of generalised tonic-clonic seizures, duration of epilepsy, polytherapy).<sup>45</sup> Changes in HRV may be due in part to AEDs. Carbamazepine has been

**Figure 2: Diagram of Possible Mechanisms of Sudden Unexpected Death in Epilepsy**



*Chronic epilepsy (light red) leads to acquired structural and functional changes in brain function (light blue). Seizures (dark red), typically generalised tonic-clonic seizures, are followed by acute changes in respiratory, cardiac and brain function (purple, green). In the right setting and under the influence of modifying acquired (light blue) or genetic factors (dark blue; e.g. cardiac channelopathies, 5-hydroxytryptamine receptor polymorphisms), seizure-associated cardiopulmonary derangements and failure of protective reflexes may lead to death (pink). AED = anti-epileptic drug. Source: adapted and modified from Devinsky, 2011.<sup>8</sup>*

shown to reduce HRV in healthy volunteers but not to the degree seen in people with epilepsy.<sup>46</sup> The role of the epileptic focus in autonomic changes is not clear. Although some studies have demonstrated normalisation of HRV following anterior temporal lobectomy,<sup>47</sup> other studies have not.<sup>48</sup> The role of autonomic dysfunction in the cascade of events leading to death is not clear; excess sympathetic activity may predispose to fatal arrhythmias or cardiomyopathy.

### Genetics

Some cardiac channelopathies associated with long QT syndrome may also be associated with a predisposition for epilepsy, making some patients susceptible to both seizures and to sudden cardiac death. In one series of patients with long QT syndrome, *KCNH2* mutations (LQT2) were associated with a personal or family history of epilepsy.<sup>49</sup> Recently, one patient with witnessed seizure-associated torsades de pointes and type 2 long QT syndrome (LQT2) was reported;<sup>50</sup> another patient with SUDEP at age 25 years and idiopathic generalised epilepsy was found to have long QT syndrome due to *SCNA5* mutation (LQT3).<sup>51</sup> Two mutant mice, one with a knock-out of the *KCNQ1* potassium channel gene (LQT1)<sup>52</sup> and another with a knockout of the *KCNA1* shaker-type potassium channel (*K<sub>v</sub>1.1*) gene<sup>53</sup> were found to have epilepsy and cardiac arrhythmias with a high rate of

seizure-related cardiac death. Interestingly,  $K_v1.1$  is not significantly expressed in cardiac myocytes and does not contribute to cardiac action potentials. However, it is highly expressed in the vagus nerve, and mice lacking the channel have hyperactive vagal activity.<sup>52</sup> High rates of SUDEP are seen in Dravet syndrome, a severe infantile epilepsy syndrome due to a mutation in the *SCNA1* sodium channel gene.<sup>54</sup>

Little is known about genetic mutations associated with seizure-related apnoea. Some hypotheses have been generated from understanding sudden infant death syndrome (SIDS), which, like SUDEP, is a heterogeneous condition; however, in some cases, it is thought to be due to a failure of central respiratory mechanisms. Brainstem serotonin neurons have recently been shown to be crucial for mediating arousal in response to hypercapnia.<sup>55</sup> In pathological series, infants with SIDS were found to have decreased serotonergic binding in brain stem autonomic and respiratory centres. Polymorphisms in the gene encoding the serotonin transporter 5-HTT, or its promoter, have been associated with cases of SIDS.<sup>56</sup> Serotonergic function may also be important for maintenance of upper airway tone during sleep; 5HT-2A receptors are the predominant receptor subtype in hypoglossal motor neurons, and polymorphisms in the gene encoding this receptor have been associated with obstructive sleep apnoea in adults.<sup>57</sup> The findings that SSRIs reduce seizure-related hypoxaemia in humans and death in mouse models of seizures suggest that similar serotonergic mechanisms may also be involved in SUDEP. In one retrospective series, seizures in patients who were taking SSRIs were less likely to be associated with hypoxaemia ( $SaO_2 < 85\%$ ) than in patients that were not on SSRIs,<sup>58</sup> but this was only true for seizures that did not secondarily generalise.

## Sudden Unexpected Death in Epilepsy Prevention

There are no definitive treatments to prevent SUDEP; however, based on identified risk factors in epidemiological studies, experts recommend several interventions to mitigate the risk. Given the clear association of SUDEP with uncontrolled epilepsy, good seizure control is the logical strategy for prevention. This is supported by a recent meta-analysis of 112 randomised, placebo-controlled clinical trials of add-on AED therapy for refractory partial epilepsy.<sup>59</sup> The authors found that the rates of SUDEP were about seven times lower in patients who received adjunctive AEDs at therapeutic doses than those who received placebo. Therefore, ensuring that patients are on a sufficient dose of AED appropriate for their epilepsy syndrome is likely to be a key strategy to mitigate the risk of SUDEP. In addition, an evaluation for epilepsy surgery should be offered to appropriate patients (those who have failed two

or more AED trials, or who have had seizures for more than a year). However, alternative strategies are needed for the ~50 % of patients with refractory epilepsy that are not candidates for epilepsy surgery. Nocturnal supervision, especially from someone who is able to provide assistance, such as repositioning or basic first aid after a seizure, may be a strategy to limit SUDEP. However, this is often not practical or desired. Several devices are being developed to detect seizures, mostly convulsive, and alert caregivers, including watch-based<sup>60</sup> and under mattress<sup>61</sup> motion detectors. However, whether these devices or even rapid post-ictal intervention can prevent SUDEP remains unknown.

In addition, patients with refractory epilepsy should undergo cardiac evaluation. Pre-existing structural heart abnormalities, QTC abnormalities or arrhythmias may predispose these patients to sudden death. Some groups of experts advocate a screening EKG for all epilepsy patients.<sup>62</sup> Patients with a history of ictal asystole, even if self-limited, should be considered for pacemaker implantation, particularly if asystole is symptomatic; this often presents as a collapse (hypotonic, eyes closed) during otherwise typical complex partial seizures. Nocturnal oxygen via a nasal cannula may be a strategy to limit ictal hypoxaemia and possibly reduce the risk of SUDEP. Indeed, in a study of mice with high rates of fatal audiogenic seizures, an oxygen-rich environment (2 minutes of 100 %  $O_2$ ) completely prevented seizure-related deaths.<sup>16</sup> Although the interventions described above make sense, there is no prospective evidence of their effectiveness.

## Conclusions

Although SUDEP has been recognised as an important cause of death in people with epilepsy for over a century,<sup>63</sup> it is only recently that we have begun to unravel its causes. The mechanisms linking seizures and the final common pathway of cardiopulmonary collapse are varied but each may present targets for intervention. The consensus is that most if not all patients should be made aware of SUDEP (see Brodie and Holmes for a review),<sup>64</sup> primarily to maximise compliance and avoidance of seizure triggers such as sleep deprivation and alcohol use. Whether there are other ways of decreasing SUDEP risk, such as nocturnal supervision, remains unproven. Further research is needed to understand the pathophysiology of SUDEP to decrease epilepsy-related mortality. Given that SUDEP is rare, further research is likely to be carried out using a collaborative multicentre approach. In addition, any studies of potential interventions are likely to require identification of surrogate endpoints to test their efficacy in a cost-effective and timely manner. ■

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