

# Sudden unexpected death in epilepsy: Impact, mechanisms, and prevention

## ■ ABSTRACT

Patients with refractory epilepsy face an elevated risk of sudden death, with rates as high as 1% per year. This phenomenon, known as sudden unexpected death in epilepsy (SUDEP), is believed to be a seizure-related occurrence, but the exact underlying mechanisms are uncertain. Both pulmonary and cardiac pathophysiologies have been proposed. The cardiac mechanism of greatest interest is the precipitation of arrhythmias by seizure discharges via the autonomic nervous system. SUDEP prevention has centered on effective seizure control, and epilepsy surgery has reduced SUDEP incidence in a number of studies. Additional prophylaxis methods are needed, however, for the large number of patients with treatment-refractory epilepsy. Future research should aim to clarify whether the association between seizures and autonomic dysfunction and cardiac arrhythmias extends to a demonstrable cardiac mechanism for SUDEP.

**T**he intimate interplay between heart and brain is well illustrated in epilepsy and may underlie the mechanism of one of its most devastating consequences: sudden unexpected death in epilepsy (SUDEP). This article will briefly describe the potential mechanisms of SUDEP, elaborate on the evidence for a likely cardiac pathophysiology, and review considerations in SUDEP prevention. We begin with a couple of brief case presentations and an epidemiologic overview to illustrate the concept and significance of SUDEP.

## ■ CASE PRESENTATIONS

### A patient with near-SUDEP

*The following is an actual message received by one of the authors:*

*Dr. Najm: A quick note regarding a 27-year-old male patient of yours with cerebral palsy and seizure disorder. Yesterday, while being transported from floor to floor, he had a cardiac arrest and was successfully resuscitated. Immediately after the code he developed seizures, which were treated with phenytoin and lorazepam. He is now in the neurointensive care unit. Thank you.*

This case represents a scenario of near-SUDEP in which death was prevented by the fortuitous presence of immediate medical assistance at the time of cardiac arrest. Had this patient been home at the time of this incident, he almost certainly would have simply been found dead in his bed, like many SUDEP victims.

### A typical case with multiple risk factors

*A 32-year-old man underwent left temporal lobectomy at the Cleveland Clinic for treatment of medically refractory focal epilepsy. His seizure frequency improved after surgery, but he continued to have rare convulsions. Nevertheless, he discontinued all his anticonvulsant medications on his own. One year later, he was found dead on his bathroom floor. No obvious cause of death was identified.*

This case illustrates several characteristics of the patient typically at risk for SUDEP: young, male, with intractable poorly controlled epilepsy, and not taking antiepileptic medications.

## ■ EPIDEMIOLOGY AND RISK FACTORS

Epilepsy affects 1% of the US population. Among those affected by epilepsy, SUDEP is a common cause of mortality. Estimates of SUDEP incidence range from 0.7 to 1.3 cases per 1,000 patient-years in large cohorts of patients with epilepsy<sup>1,2</sup> and from 3.5 to 9.3 cases per 1,000 patient-years in anticonvulsant drug registries, medical device registries, and epilepsy surgery programs.<sup>3-5</sup> SUDEP accounts for up to 17% of all deaths in patients with epilepsy<sup>6,7</sup> and exceeds the expected rate of sudden death in the general population by nearly 24 times.<sup>6,8</sup>

Several potential risk factors for SUDEP have been investigated, but results from different studies are

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conflicting. Consistently identified risk factors include young age, early onset of seizures, refractoriness of epilepsy, the presence of generalized tonic-clonic seizures, male sex, and being in bed at the time of death. Weaker risk factors include being in the prone position at the time of death, having one or more subtherapeutic blood levels of anticonvulsant medication, having a structural brain lesion, and being asleep.<sup>9</sup> The current consensus is that SUDEP is primarily a “seizure-related” occurrence, but the exact mechanisms underlying SUDEP are unknown.

## ■ PROPOSED MECHANISMS

### Pulmonary pathophysiology

Central apnea and acute neurogenic pulmonary edema are the two major proposed pathways linking seizures to SUDEP. Evidence exists for each pathway.

**Central apnea.** In a prospective study of patients in an epilepsy monitoring unit, central apnea lasting at least 10 seconds was observed postictally in 40% of the recorded seizures.<sup>10</sup> Otherwise healthy young epilepsy patients have been reported to develop central apnea immediately following complex partial seizures.<sup>11</sup> Neurotransmitters mediating the brain’s own seizure-terminating mechanism could also be inhibiting the brainstem and causing postictal apnea.

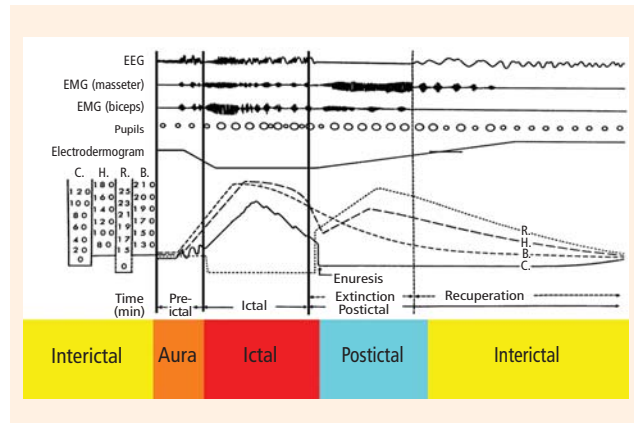
**Acute neurogenic pulmonary edema** has been well described in relation to severe head injury and subarachnoid hemorrhage. Pulmonary edema is frequently found in SUDEP patients at autopsy.<sup>12</sup> Intense generalized vasoconstriction induced by massive seizure-related sympathetic outburst can lead to increased pulmonary vascular resistance, and thereby may mediate acute pulmonary edema.

These two mechanisms—central apnea and acute neurogenic pulmonary edema—are not mutually exclusive. In the only animal model of SUDEP, one third of animals died from hypoventilation and had associated pulmonary edema at autopsy.<sup>13</sup> Limited opportunities for realistic and practical interventions to reverse SUDEP risks related to pulmonary causes have hindered further development of these concepts.

### Cardiac pathophysiology

The most significant and widely discussed cardiac mechanism of SUDEP is cardiac arrhythmia precipitated by seizure discharges acting via the autonomic nervous system.<sup>14-19</sup>

**Centers of autonomic control are also key epileptic foci.** A tight interconnected network exists throughout the neuraxis to control various elements of the car-

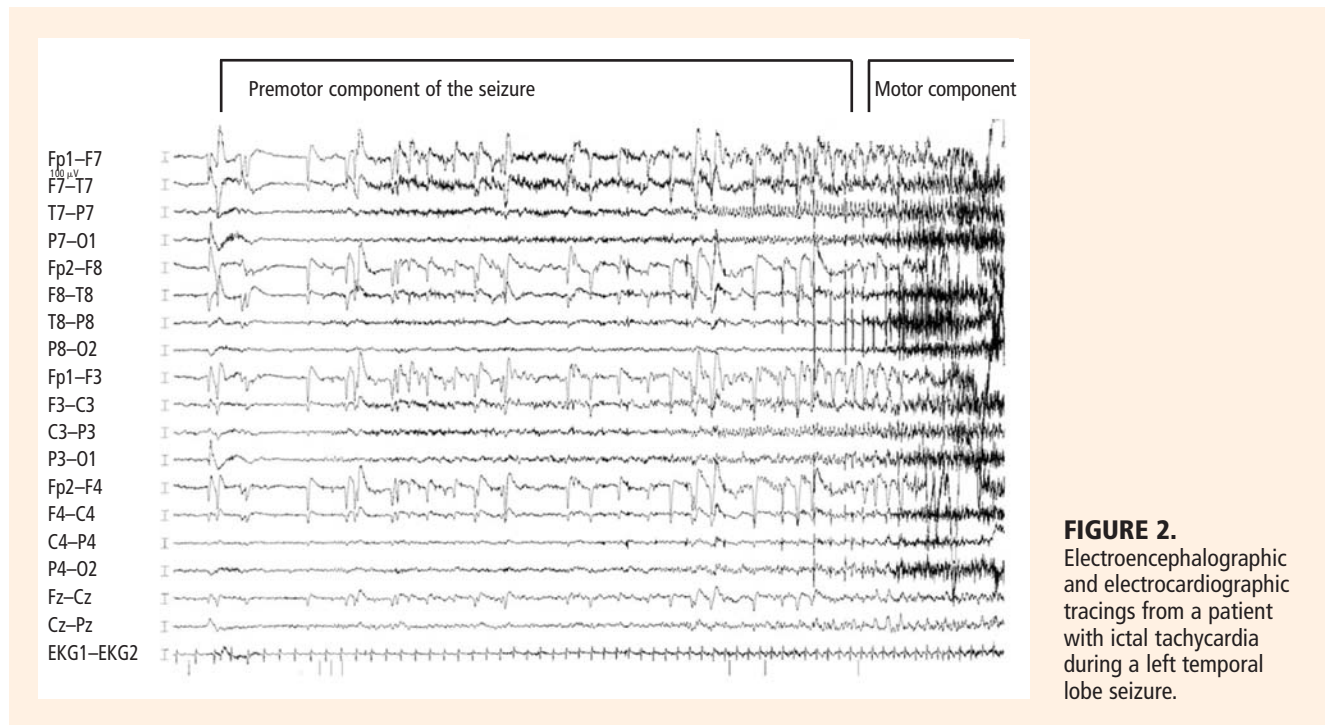


**FIGURE 1.** Autonomic changes during a motor seizure. Clear increases in the heart rate (H) and blood pressure (B) correspond to a suppression in the respiratory rate (R) during the ictal phase. Autonomic changes continue well after the ictal event is finished. C = cystogram.

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diovascular autonomic system. A solid understanding of this network provides useful insights for consideration of a cardiac pathophysiology of SUDEP. Key components of the central cortical control of autonomic functions include the insula, the anterior cingulate gyrus, and the ventromedial prefrontal cortex. The insula represents the primary viscerosensory cortex, while the cingulate gyrus and prefrontal cortices form the premotor autonomic region. At the subcortical level, the hypothalamus provides the interface with the endocrine stimuli and triggers corresponding autonomic responses to maintain homeostasis. The amygdala, an integral component of the limbic system linking the cortical and subcortical centers already mentioned, mediates the autonomic response to emotions. In addition to playing a key role in autonomic control, the insula, amygdala, cingulate gyrus, and prefrontal cortex also represent the most common foci of partial epilepsy, which leaves no mystery behind the frequent observation of autonomic changes in relation to epileptic seizures.<sup>19</sup> **Figure 1** provides an overall illustration of those changes.

**Experimental evidence.** Heart rate changes, including bradycardia, tachycardia, and even asystole, have been repeatedly provoked by electrical brain stimulation of the limbic system and insular cortex.<sup>19</sup> Some studies have suggested a lateralized influence of the insulae on cardiovascular autonomic control. In one study, intraoperative stimulation of the left posterior insula elicited a cardioinhibitory response and hypotension, whereas stimulation of the right anterior



**FIGURE 2.** Electroencephalographic and electrocardiographic tracings from a patient with ictal tachycardia during a left temporal lobe seizure.

insula elicited tachycardia and hypertension.<sup>20</sup> Such results have not always been reproducible.<sup>21–23</sup> Other studies have suggested a localization-related influence of the limbic system on cardiovascular responses. Stimulation of the amygdala has not led to the ictal tachycardia that is commonly seen in epileptic seizures, suggesting that cortical involvement is needed for the development of tachycardia.<sup>24</sup>

**Clinical evidence.** Clinically, a similarly wide spectrum of cardiac arrhythmias has been reported during seizures.<sup>10,14,25–28</sup> Illustrative examples are shown in **Figures 2 and 3**. Ictal cardiac arrhythmias occurred in 42% of hospitalized epilepsy patients in one study, with the most common being an irregular series of abrupt rate changes toward the end of the electroencephalographic (EEG) seizure discharge.<sup>14</sup> In another study, analysis of R-R intervals during the first 10-second period of EEG discharge showed a significant early heart rate increase in 49% of seizures; the corresponding figure for an early heart rate reduction was 25.5%.<sup>26</sup> Ictal asystole, atrial fibrillation, repolarization abnormalities, and bundle branch blocks have also been reported.<sup>10,16,17,27,29</sup> The hypothesis that such arrhythmias are more prominent in SUDEP patients than in the general epileptic population could provide a direct extension of these observations to a specific subgroup of epilepsy patients. Evaluation of clinical and EEG characteristics of SUDEP patients would then represent an indirect

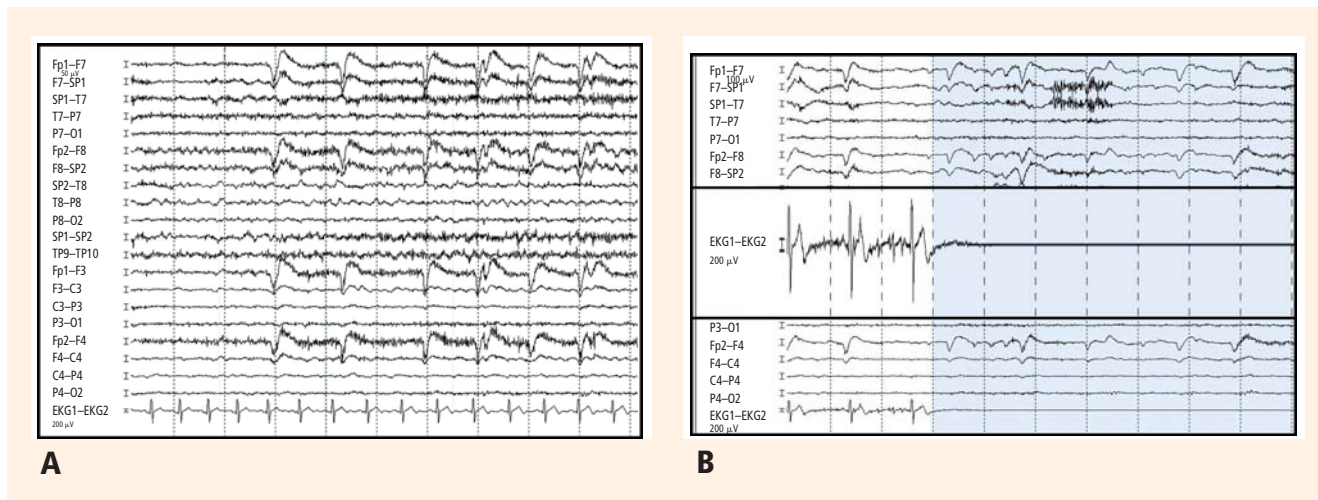
investigation of the experimentally observed heart rate changes with various cortical stimulation experiments.

**ECG abnormalities and seizure characteristics.** The occurrence of ictal electrocardiographic (ECG) abnormalities has been correlated to certain clinical seizure characteristics. In one study, mean seizure duration was longer in patients with ECG abnormalities than in those without such changes.<sup>16</sup> In other studies, generalized tonic-clonic seizures have been associated with increased occurrence and severity of ictal ECG abnormalities relative to complex partial seizures.<sup>16,17</sup> Those same clinical seizure characteristics were correlated with a higher risk of SUDEP.<sup>30</sup> This suggests an interrelation between seizure semiology, ECG abnormalities, and SUDEP.

## ■ SUDEP PREVENTION

### Epilepsy control is first line of defense

A careful consideration of the incidence of SUDEP in various patient populations suggests that controlling patients' epilepsy might just be the best method of preventing SUDEP. While estimated SUDEP incidence ranges from 0.7 to 1.3 cases per 1,000 patient-years in population-based studies of patients with epilepsy,<sup>1,2</sup> this rate escalates by nearly tenfold (3.5 to 9.3 cases per 1,000 patient-years) in cohorts with severe epilepsy, such as those derived from anticonvulsant drug registries, medical device registries, and



**FIGURE 3.** Electroencephalographic and electrocardiographic tracings from a patient with ictal bradycardia (A) and then asystole (B) during a right temporal lobe seizure.

referral centers.<sup>3-5</sup> Therefore, medical control of seizures might reduce the incidence of SUDEP.

### Epilepsy surgery cuts SUDEP risk for many patients

Studies involving epilepsy surgery programs also suggest that successful epilepsy surgery reduces the impending risks of SUDEP. In cohorts in which the estimated risk of SUDEP is almost 1% per year without surgery, SUDEP incidence was significantly lower following epilepsy surgery. In a study of 305 patients who underwent temporal lobe epilepsy surgery in the United Kingdom, the incidence of SUDEP following surgery was 2.2 cases per 1,000 person-years, and only one-third of SUDEP cases were among seizure-free patients.<sup>31</sup> A similar incidence of 2.4 cases per 1,000 person-years was seen following epilepsy surgery in 596 Swedish patients; none of the 6 SUDEP patients in that study was seizure free.<sup>32</sup> In a US study, no SUDEP cases occurred among 256 seizure-free patients with a follow-up of about 5 years after epilepsy surgery.<sup>33</sup>

In our own experience at the Cleveland Clinic, we have reported on outcomes among 70 patients who underwent frontal lobectomy<sup>34</sup> and among 371 patients who underwent temporal lobectomy.<sup>35</sup> In the frontal lobectomy study,<sup>34</sup> 2 of the 39 patients who had persistent seizures following surgery died of SUDEP during follow-up, whereas none of the 31 patients who remained seizure free were dead up to 10 years after surgery. In the temporal lobectomy report,<sup>35</sup> 2 of the 141 patients with ongoing postoperative seizures died of SUDEP, as compared with none of the 230 patients who were seizure free after a mean follow-up of 5.5 years.

### Additional means of prophylaxis needed

Unfortunately, as many as 30% to 40% of patients with epilepsy continue to suffer intractable epilepsy despite all the available treatment modalities, including epilepsy surgery. For these patients, controlling seizures to reduce the risk of SUDEP is neither a possible nor a realistic means of avoiding this devastating condition, and alternative methods of prophylaxis must be sought.

### CONCLUSIONS AND FUTURE RESEARCH

Patients with refractory epilepsy currently face a life-long risk of sudden death as high as 1% per year.<sup>3</sup> Elucidating the mechanisms of SUDEP might lead to preventive measures, which could have significant implications in reducing mortality in this patient population. Abundant evidence exists that autonomic dysfunction and cardiac arrhythmias are associated with seizures. The missing links in establishing a cardiac mechanism for SUDEP now include the following: (1) evidence of cardiac arrhythmias generally observed in seizures as a risk factor for SUDEP, (2) determination of clear electrophysiologic characteristics—from EEG and ECG standpoints—of patients at risk for SUDEP, and (3) clarification of the role of cardiac mechanisms in SUDEP and the role that cerebral influences on autonomic function might play. Early identification of patients at risk of SUDEP would offer a unique opportunity for early intervention to prevent this devastating condition.

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