

Review Article

The Role of Autonomic Factors in Sudden Unexpected Death in Epilepsy

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Abstract

Sudden unexpected death in epilepsy (SUDEP) is the most important direct epilepsy-related cause of death. Despite its growing recognition amongst clinicians caring for patients with epilepsy, the exact pathophysiologic mechanisms behind SUDEP have not yet been fully elucidated. However, autonomic effects of seizures are thought to most likely to contribute to sudden unexpected death. Such autonomic effects may affect the heart. These include peri-ictal tachycardia, bradycardia, asystole, repolarization abnormalities, and/or reduced heart rate variability. Respiration may also be affected by seizures, with resulting hypoventilation, apnea, and hypoxemia. More recently, postictal generalized EEG suppression (PGES) has been hypothesized to be an electrophysiologic marker of increased SUDEP risk. If the cortical neuronal inhibition suggested by PGES affects deeper subcortical and brainstem structures, it may interfere with respiratory drive and result in apnea, putting patients at risk for sudden death. Given that SUDEP occurs less frequently than any peri-ictal autonomic disturbance in isolation, it is possible that death only occurs when several precipitating factors come together in a "perfect storm." Increasing our understanding of SUDEP will require further exploration of ictal and interictal autonomic dysfunction in patients with seizures. It is only through such research that we may one day understand SUDEP enough to fully prevent it.

INTRODUCTION

Sudden unexpected death in epilepsy (SUDEP) is the most important direct epilepsy-related cause of death. It is defined as a sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in a person with epilepsy. It may or may not occur in the setting of an epileptic seizure and excludes deaths resulting from status epilepticus [1]. A diagnosis of "definite SUDEP" can be made if the aforementioned criteria are met and an autopsy is performed, revealing no toxicological or anatomical cause of death. "Probable SUDEP" can be diagnosed if the aforementioned criteria are met but an autopsy is not performed. "Possible SUDEP" is defined as a situation in which the aforementioned criteria are met but competing causes of death are present. An "unclassified" SUDEP is defined as a situation in which no autopsy is performed, insufficient evidence relating to the cause of death exists, but SUDEP cannot be excluded [1].

The estimated incidence of SUDEP is 1.8 per 1,000 patient-years [2]. However, higher incidences (3-9/1,000 patient-years) have been reported in patients with medically intractable epilepsy [3]. SUDEP is fortunately rarer in the pediatric population. However, it is still estimated to have an incidence between 1-2 per 10,000 patient years in this population [4]. In all persons

with childhood-onset lifelong epilepsy, the lifetime risk of SUDEP is approximately 7%. However, in the subpopulation of those with lifelong refractory epilepsy, the lifetime risk approaches 35% [5]. In the United States, nearly 2000 SUDEP deaths are thought to occur each year. This equates to a years of potential life lost (YPLL) of 73000/year. This exceeds the YPLLs attributed to many other neurologic diseases, including amyotrophic lateral sclerosis, multiple sclerosis, Alzheimer disease, and Parkinson disease [5].

The most consistently identified risk factor for SUDEP is poorly controlled seizures, particularly generalized tonic-clonic seizures (GTCs) [6-10]. Less-robust risk factors for SUDEP identified in previous studies include antiepileptic drug (AED) polytherapy, usage of specific AEDs (such as carbamazepine and lamotrigine), developmental delay/intellectual disability, nocturnal seizures, young age at seizure onset, longer duration of epilepsy, and normal neuroimaging [6-10]. Such recognized historical risk factors have led to the development of risk factor inventories for sudden unexpected death such as the SUDEP-7 inventory [11]. Conversely, supervision at night has been suggested to be protective against sudden unexpected death [6].

While the exact pathophysiology of SUDEP has not been fully elucidated, ictally-mediated autonomic dysfunction is

most likely responsible. Such dysfunction may involve cardiac disturbances, including peri-ictal tachycardia, bradycardia, asystole, repolarization (QTc) anomalies, and/or reduced heart rate variability (HRV). Peri-ictal hypoxemia and respiratory suppression may also be involved. More recently, postictal generalized electroencephalography (EEG) suppression (PGES) has been hypothesized by some to be an important mechanism contributing to sudden unexpected death. By exploring autonomic phenomena which occur during the peri-ictal period, it may be possible to learn more about the dysfunction that ultimately contributes to SUDEP. With such knowledge, it may one day be possible to implement preventative strategies beyond improved seizure control to reduce the risk of this dreaded phenomenon.

Peri-ictal tachycardia

The most commonly observed seizure-related autonomic disturbance is peri-ictal tachycardia. Tachycardia has been documented during and/or after a majority of seizures. For example, in a cohort of 76 adult and pediatric epilepsy monitoring unit (EMU) patients and 218 seizures, ictal tachycardia was recorded in 57% of seizures and at least one seizure in 76% of patients [12]. Peri-ictal tachycardia was significantly associated with a number of potential SUDEP risk factors, including seizure generalization, higher number of failed AEDs, and normal neuroimaging. Patients with ictal tachycardia were also more likely to have ictal hypoxemia [12]. The association of ictal tachycardia with normal neuroimaging is particularly intriguing. A previous study found abnormal MRIs to be associated with a reduced risk of SUDEP [13]. It was previously hypothesized that such a survival benefit was secondary to lesional patients being more likely to proceed to resective epilepsy surgery (and subsequently achieve seizure freedom). However, the significant association of peri-ictal tachycardia with normal neuroimaging suggests there may be inherent differences between lesional and non-lesional epilepsy with regards to autonomic disturbances. One possibility involves ion channelopathies which predispose patients to both seizures and cardiac rhythm disturbances [6-10]. If true, such dysfunction could theoretically be amenable to treatment, reducing the risk of subsequent sudden unexpected death.

Based on stimulation studies involving the insular cortex, Oppenheimer et al. hypothesized peri-ictal tachycardia was more likely to result from right hemispheric seizures [14]. However, when investigated in patients during recorded seizures, peri-ictal tachycardia has more consistently been documented with mesial temporal lobe onset and seizure generalization [12].

One potential link between SUDEP and peri-ictal tachycardia was the finding of higher maximal ictal heart rates in patients who later died of SUDEP versus controls with refractory focal onset seizures [15]. In addition, more significant postmortem fibrotic changes in the deep and subendocardial myocardium have been documented in SUDEP cases versus controls [16]. These changes could be the result of myocardial ischemia from repetitive seizures. The sympathetic over-activity responsible for peri-ictal tachycardia may also cause transient dilatation of ventricular walls and left ventricular dysfunction. If such stress induced

cardiomyopathy was severe enough to diminish cardiac output, oxygen supply during periods of stress (particularly a GTC) might be compromised enough to result in sudden unexpected death.

Peri-ictal bradycardia and asystole

Peri-ictal bradycardia is defined as a seizure-related reduction in heart rate to less than the second percentile for age. This autonomic phenomenon is rare, being documented in only 2-3.7% of seizures [12,17]. Peri-ictal bradycardia has been associated with seizure clustering (greater than 3 recorded seizures during any 24 hour period of monitoring) and frequent seizures (a history of greater than or equal to 50 seizures per month). In one study of pediatric epilepsy patients, only focal onset seizures of extratemporal onset were characterized by peri-ictal bradycardia. However, this finding did not reach statistical significance [17]. The cortical stimulation studies by Oppenheimer et al. suggested that bradycardia resulted from left hemispheric epileptiform activity [14]. However, this has not been consistently supported by subsequent research. Rather, such peri-ictal autonomic phenomena have been more frequently observed when epileptiform activity is present bilaterally on scalp EEG [18].

Peri-ictal asystole is defined as the absence of a heartbeat for greater than or equal to 4 seconds during or immediately after an epileptic seizure. This autonomic phenomenon is rare, occurring in less than 0.5% of seizures recorded in EMUs [19]. Larger percentages of asystole in patients with seizures has only been reported in one study. This study, which involved 19 patients with medically intractable focal onset seizures implanted with loop recorders, documented significant bradycardia/asystole necessitating pacemaker implantation in 4 patients (21%). This included 3 patients (16%) with potentially fatal asystole documented with their implantable loop recorders [20].

Peri-ictal asystole can be difficult to detect based solely on history without corresponding video EEG and electrocardiogram (ECG) recordings. Clinical cues suggesting ictal asystole include loss of consciousness, loss of muscle tone, and (if upright) falls [19]. It may also be possible to witness other seizure semiologies (e.g. auras, behavioral arrest, and/or oral/manual automatisms) prior to the above cues.

Some have argued that AEDs alone (versus AEDs and pacemaker implantation) are adequate to treat ictal asystole. However, the need for pacemaker implantation is supported by research into the effect of cardiac pacing on seizure-related injury rates. In a survey of 7 patients with documented ictal asystole who underwent cardiac pacing from 1990-2004, the mean falls rate decreased from 3.28 falls/month to 0.005 falls/month [21]. Trends favoring reductions in seizure-related fractures and motor vehicle accidents were also observed. Three patients were even able to successfully decrease their AED dosages following pacemaker placement [21]. A possible explanation for this benefit would be the direct influence of cardiac pacing on cardiac vagal afferents and their connections to the brain. If true, this would be similar to the anticonvulsant effects that are thought to underlie vagus nerve stimulation [22].

The contribution of peri-ictal asystole to at least some cases of SUDEP has been suggested by ECGs showing bradycardia

progressing to asystole in association with monitored SUDEP and near-SUDEP cases [23]. If peri-ictal bradycardia/asystole was the cause for SUDEP, the risk could theoretically be reduced with pacemaker implantation. However, further evidence is needed before clinicians can definitively conclude cardiac pacing is protective against SUDEP. Contrary evidence exists, with two studies documenting cerebral hypoperfusion as a promoter of early seizure termination [24,25]. When comparing seizure duration in patients with syncopal ictal asystole, non-syncopal ictal bradycardia, and non-bradycardic seizures, it has been discovered that seizures with ictal asystole were significantly shorter in duration [25]. Such earlier termination may arise through a number of factors promoted by hypoperfusion, including neuronal glucose depletion, impaired mitochondrial metabolism, and reduced adenosine triphosphate (ATP) production. These can reduce neuronal excitability via impairment of the sodium/potassium ATPase, opening of potassium channels, decreased glutamate receptor activation, and accumulation of endogenous inhibitory mediators such as adenosine and endocannabinoids [26]. Acidosis may also play a role via impairment of N-methyl-D-aspartate (NMDA) receptor function, activation of acid-sensitive TASK-type potassium channels, uncoupling of connexins, and diminishing gap junction conductance [26]. Given such findings, it is more likely that ictal bradycardia and asystole are part of a vicious cycle of events that culminate in sudden death rather than the solitary cause.

Peri-ictal cardiac repolarization (QTc) abnormalities

It has long been known that lengthening of the QT interval may result in torsades de pointes, while shortening of the QT interval can facilitate a re-entrant ventricular tachycardia [27]. However, the role of such cardiac repolarization abnormalities contributing to SUDEP is less robustly recognized. Previous studies have identified that peri-ictal lengthening of QTc can occur. In a study of adult and pediatric epilepsy patients undergoing video EEG monitoring, it was shown that the mean maximum ictal QTc was significantly longer than the mean maximum pre-ictal QTc utilizing three of the most common QTc correction formulas (Bazett, Fridericia, and Hodges) [12]. Ictal-associated clinically significant QTc prolongation occurred in 4.8% of recorded seizures; all occurred in adults and were non-generalized temporal lobe seizures. Profound ictal-associated QTc prolongation (> 500 ms) was observed in 2.9% of seizures. This was also only observed in adult patients with temporal lobe seizures [12]. Reanalysis of data from that study revealed no correlation between peri-ictal QTc changes and hypoxemia. This contrasts with another published study which suggested QTc lengthening and shortening were significantly more likely to accompany seizures with hypoxemia [28].

Enhanced QTc shortening and persistent tachycardia have previously been reported after secondarily GTCs [29]. However, the occurrence of peri-ictal QTc shortening is likely less than QTc prolongation. Ictal markedly short QT intervals (QTc < 340 ms) were observed in only 3.8% seizures in one study [12]. That same study documented no seizures with profoundly attenuated QT intervals (QTc < 300 ms). When examining patient demographics, no SUDEP risk factors were found to be significantly associated with QT interval changes [12].

The link between SUDEP and QTc changes has been strengthened by studies invoking shared genetic mutations. Cardiac depolarization/repolarization anomalies have been documented in previous SUDEP victims. One had a *SCN5A*-encoded cardiac Nav1.5 sodium channel mutation [30]. Another had a *RYR2*-encoded cardiac ryanodine receptor/calcium release channel mutation [31]. It can be tempting to link QTc lengthening with temporal lobe seizures, particularly given that genes associated with long QT syndromes (e.g. *KCNH2*) are expressed in hippocampal astrocytes [32]. However, caution is needed before definitively invoking a link. This is particularly true given that only one case of ventricular fibrillation progressing to asystole and death following a monitored focal onset seizure has been published [33].

SUDEP and heart rate variability (HRV)

Decreased HRV is known to be associated with increased risk of sudden cardiac death. Such decreased HRV has also been documented in people with epilepsy. This includes patients with chronic temporal lobe epilepsy and Dravet syndrome, two populations at greater risk of SUDEP [34,35]. Such reduced HRV is likely secondary to seizure-related reductions in cardiac sympathetic innervation. This is suggested by studies showing reduced cardiac ¹²³Imetaiodobenzylguanidine (MIBG) uptake in people with chronic temporal lobe epilepsy versus healthy controls [36]. Such changes may increase cardiac sensitivity to adrenergic stimulation, thereby increasing the risk of catecholamine-induced arrhythmias and resulting death.

Peri-ictal hypoxemia

Peri-ictal hypoxemia is the second most commonly observed autonomic change accompanying epileptic seizures. It is recorded in association with 25% of seizures, including at least one seizure in 35% of patients monitored in EMUs [12]. This is similar for pediatric and adult patients. Almost 27% of pediatric seizures and at least one recorded seizure in nearly 49% of children have been characterized by oxygen saturations falling to less than 90% [17]. Ictal hypoxemia is correlated with prolonged seizure duration and normal neuroimaging [12]. In pediatric patients, such oxygen desaturations have been associated with seizure generalization, prolonged seizure duration, and tapering of AEDs [17].

Prior to 2012, most studies detailing peri-ictal hypoxemia were based on digital pulse oximetry recordings. Although such technology is standard for recording oxygenation in many EMUs, it can only be considered an indirect measure of cerebral tissue oxygenation. It measures oxygenation from peripheral tissues and may be falsely lowered from peripheral vasoconstriction which does not concurrently affect cerebral structures. However, with the advent of non-invasive cerebral tissue oximeters, it is now possible to more directly measure cerebral tissue hypoxemia. Two studies have documented that such monitoring is feasible in patients undergoing epilepsy monitoring, including patients with GTCs [37,38]. Although the sample size was low, one of the studies suggested both primary and secondarily GTCs were associated with significantly lower ictal and post-ictal regional cerebral oxygen saturation (rSO₂) values versus minimum recorded pre-ictal values. A significant difference between such values was not documented for focal onset seizures without generalization

[37]. There were trends for higher SUDEP-7 Inventory scores in patients with one or more recorded seizures with a %rSO₂ reduction of > 20%. Such scores were not significantly different in patients with one or more seizures characterized by other markers of autonomic dysfunction including PGES or peri-ictal digital pulse oximetry desaturations [37].

It is believed that peri-ictal hypoxemia is most likely a consequence of seizure-related hypoventilation. Up to 50% of seizures may be marked by central apnea, with 9% marked by mixed or obstructive apnea [39]. Such mechanisms for peri-ictal hypoxemia are supported by concurrent rises in end-tidal CO₂ during monitored seizures [39]. Peri-ictal hypoventilation and apnea may be secondary to disruption of brainstem respiratory centers by repetitive seizure discharges. However, other potential causes, including seizure-induced right-to-left shunts and neurogenic pulmonary edema, cannot be completely excluded [40].

A connection between peri-ictal hypoxemia and SUDEP has been suggested by both postmortem and electrophysiologic studies. Moderate to severe pulmonary edema has been documented in a majority of SUDEP cases at autopsy [41]. In addition, up to 80% of witnessed SUDEP cases have been characterized by reports of respiratory difficulties immediately preceding death [42]. Much of the current research into seizure-related respiratory compromise resulting in SUDEP has focused on parallels with sudden infant death syndrome (SIDS). This is particularly with regards to dysfunction of the rostral medulla and its centers controlling respiration and gasping [40]. Such centers are modulated by serotonin and norepinephrine, leading some to hypothesize pharmacologic manipulation of these receptors may reduce the risk of SUDEP. Such pharmacologic manipulation has already been proven to reduce the chances of sudden unexpected death in two mouse models (*Lmx1b^{f/f/p}* and *DBA/2*) [43,44]. However, confirmatory evidence in humans is currently lacking. Only a single small retrospective study in humans has shown a reduced occurrence of ictal hypoxemia in those concurrently taking selective serotonin reuptake inhibitors (SSRIs). This reduction was only seen in focal onset seizures without secondary generalization [45]. Further investigation is needed before clinicians can confidently prescribe medications such as SSRIs to epilepsy patients to reduce the risk of hypoxemia-related sudden death.

Post-ictal generalized EEG suppression (PGES)

PGES is defined as the absence of scalp EEG activity viewed at < 10 microvolts amplitude. In a retrospective study of 10 patients who later died of SUDEP versus 30 controls, PGES was discovered to be significantly longer in the SUDEP group [46]. The odds of dying from SUDEP were increased when PGES duration was greater than 50 seconds. Such odds quadrupled when the duration was greater than 80 seconds [46]. Such EEG suppression has also been correlated with autonomic changes including sympathetic activation and parasympathetic suppression [47]. Early peri-ictal nursing interventions which may be protective against SUDEP, including administration of supplemental oxygen, oropharyngeal suction, and repositioning, have been shown to reduce the duration of PGES [48]. However, not everyone involved in SUDEP research is convinced of its association with PGES. There has

been at least one study which failed to confirm a link between PGES in monitored patients who subsequently died suddenly and unexpectedly [49].

PGES is not unique to adult epilepsy patients. It has been observed following 16.1% seizures in 32.4% children undergoing video EEG monitoring [50]. In children, only primary and secondarily GTCs were marked by PGES. PGES in this population was also significantly associated with other potential autonomic risk factors for SUDEP including peri-ictal tachycardia and hypoxemia. Children with PGES had significantly higher SUDEP-7 Inventory scores than children without PGES. Conversely, SUDEP-7 scores were not significantly different between children with or without peri-ictal tachycardia, bradycardia, or hypoxemia [50]. Although indirect, such findings suggest PGES may be a stronger electrophysiologic marker of SUDEP risk than either peri-ictal heart rhythm disturbances or oxygen desaturations.

PGES is hypothesized to contribute to sudden unexpected death via inhibition of brainstem respiratory centers. The cortical neuronal inhibition suggested by PGES may extend to deeper subcortical and brainstem structures, interfering with respiratory drive and resulting in apnea [46]. In adults, lower mean oxygen saturation nadirs, longer desaturations, and lower end tidal CO₂ measurements have been documented in seizures marked by PGES [51]. It is possible that PGES is part of a vicious cycle of events, including reduced activity of pulmonary stretch receptors, increased carotid chemoreceptor sensitivity, and asystole, that ultimately culminates in sudden death [52]. Another possibility is that PGES may reflect the severity of seizure-related intrinsic pulmonary dysfunction. This is supported by a lack of significant differences in apnea durations in seizures with and without PGES [51].

CONCLUSION

Although the exact mechanisms behind SUDEP have not yet been elucidated, autonomic factors like play a predominate role. These factors may include peri-ictal tachycardia, bradycardia/asystole, cardiac repolarization abnormalities, reduced HRV, hypoxemia/apnea, and/or PGES. Given that each of these phenomena occur more frequently than SUDEP, it is likely one alone is not enough to result in sudden death. Rather, SUDEP may result from several precipitating factors coming together in a "perfect storm" during the peri-ictal period [53].

If autonomic dysfunction is further implicated in SUDEP, clinicians may one day be able to intervene to alleviate such dysfunction, reducing the risk of sudden unexpected death. However, given how much time and resources must be utilized to measure ictal autonomic disturbances, it would be advantageous to determine if such disturbances can reliably be measured interictally. Previous researchers have explored interictal parasympathetic dysfunction in epilepsy patients by examining HRV. Sympathetic dysfunction could similarly be investigated by recording electrodermal activity. Further research is needed to determine if such signs of autonomic dysfunction can be detected in larger numbers of adults outside of the ictal period and whether such tests yield similar findings in children.

Future SUDEP research should also explore whether interictal epileptiform activity is responsible for autonomic dysfunction.

Although it typically occurs immediately following seizures, some cases of SUDEP have been reported in patients with no evidence of seizures prior to death. It has been argued that interictal discharges can activate sympathetic and parasympathetic centers and lead to alterations in the parasympathetic-sympathetic balance [54]. Previous studies have documented transient increases in heart rate, altered heart rate variability, and hypoxemia in association with interictal discharges [55-57]. If true, it is possible treatments which reduce interictal discharges (such as vagal nerve and deep brain stimulation) may alleviate autonomic dysfunction in such patients.

Most importantly, larger, prospective gathering of in-hospital, pre-surgical monitoring data is needed to assess the mechanisms of and risk factors for SUDEP. Examples of recent prospective endeavors include the North American SUDEP Registry and the Mortality in Epilepsy Monitoring Unit Study (MORTEMUS) [23]. Finally, further explorations of ion channelopathies co-expressed in the heart and brain are needed. The SUDEP Tissue Donation (STOP SUDEP) Program is one study aimed at answering whether such channelopathies predispose to both epilepsy and cardiac rhythm disturbances. This is particularly pertinent given that the risk of death in such circumstances could be mitigated with antiarrhythmic medications and/or pacemaker implantation. It is only by working together and sharing our observations that we will hopefully one day understand the mechanisms behind SUDEP enough to fully prevent it. The lives of many future patients diagnosed with epilepsy depend on it.

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