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Sudden Unexpected Death in Epilepsy

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Abstract

Purpose of review—Sudden unexpected death in epilepsy (SUDEP) is a leading cause of death in patients with epilepsy. This review highlights the recent literature regarding epidemiology on a global scale, putative mechanisms, and thoughts toward intervention and prevention.

Recent findings—Recently, numerous population-based studies have examined incidence of SUDEP in many countries. Remarkably, incidence is quite consistent across these studies, and is commensurate with the recent estimates of about 1.2 per 1000 patient years. These studies further continue to support that incidence is similar across the ages and that comparable factors portend heightened risk for SUDEP. Fervent research in patients and animal studies continue to hone the understanding of potential mechanisms for SUDEP, especially those regarding seizure-induced respiratory dysregulation. Many of these studies and others, have begun to lay out a path toward identification of improved treatment and prevention means. However, continued efforts are needed to educate medical professionals about SUDEP risk and the need to disclose this to patients.

Summary—SUDEP is a devastating potential outcome of epilepsy. More is continually learned about risk and mechanism for clinical and preclinical studies. This knowledge can hopefully be leveraged into preventive measures in the near future.

Keywords

Mortality; Respiration; Cardiac; Sleep; Serotonin

Introduction

Epilepsy is a common neurological disorder. Approximately one in 26 individuals will develop epilepsy within their lifetime [1]. Anti-seizure medications (ASM) are the mainstay for seizure control. While medications provide seizure freedom for many patients, ~35%

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Conflicts of interest

None.

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of patients will not achieve seizure freedom with ASMs [2;3] and have refractory epilepsy. Poor seizure control associated with refractory epilepsy puts an individual at increased risk of premature death [4]. Over the last decade-and-a-half, there has been an explosion of research with an emphasis on understanding SUDEP, including its mechanisms, risk factors, and potential biomarkers. While there are many ways epilepsy can result in fatality, including accidents, drowning, status epilepticus, suicide, and others, SUDEP is a leading cause death in patients with epilepsy attributing for up to 50% of epilepsy-related deaths [5]. Several pathophysiological mechanisms have been proposed for SUDEP. What is coming to light recently is that there is probably not one etiology for SUDEP, but rather different mechanisms may contribute to death in different patient populations or epilepsy syndromes.

Epidemiology of SUDEP

Incidence

Incidence of SUDEP has proven challenging to determine. SUDEP is not always listed as the cause of death, making it difficult to capture all SUDEP [6]. This is especially true in children and the elderly, leading to a probable underestimation of SUDEP risk in these populations [7]. Great strides have been made in partnership with medical examiners to accurately label deaths as SUDEP when appropriate. Recently, several population-based studies have been conducted in many different countries to evaluate incidence of SUDEP. The most prominent of these is from patients with epilepsy in Sweden in whom the incidence is approximately 1.2 per 1000 patient-years [8]. A reprise of this study in a Canadian cohort reported a similar incidence in children [9]. Remarkably, several newer studies in a variety of countries and patient populations reveal similar incidences as those reported in the Swedish and Canadian studies[6;10–19].

Of note, there are several patient populations that demonstrate a higher incidence of SUDEP, such those with the epileptic encephalopathy, Dravet Syndrome, which is due to mutations in the *Scn1a* gene encoding the voltage gated sodium channel $Na_V1.1$ [20], and others such as *Scn8a* encephalopathy impaired $Na_V1.6$ channel function [21].

Risk Factors

Several risk factors for SUDEP have been identified, including having frequent generalized convulsive seizures (GCS), nocturnal seizures, being found prone, and being male, among others [7]. Importantly, these same themes emerged in most of the studies conducted in other countries and published in the last year or so [6;10–19;22]. Many of these risk factors have been combined into a new risk assessment scale, the SUDEP clinical risk score (SUDEP-CARE) [23]. This is refinement of the previously employed SUDEP-7 [24] inventory. In addition, it may prove valuable to extract data from electronic seizure diaries to assess risk [25].

Several measures have been purported to portend increased risk for SUDEP including reduced heart rate variability (HRV), as an indicator of general autonomic function [26], and postictal generalized EEG suppression (PGES) [27–30]. These measures, especially HRV, were the subject of intense investigation in the last year and were found to be differentially

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affected by seizures occuring from wake versus sleep [31–33]. Duration and regularity of the QT interval may also be emerging as a risk indicator for SUDEP [34], and may be a useful tool for assessing risk at the initial visit [35]. In addition, indicators of respiratory function are also emerging, including incidence of ictal and postictal apnea [36–39], and reduction of the sensitivity of the hypercapnic ventilatory response [40;41]. It is clear from studies such as the multi-center retrospective Mortality in Epilepsy Monitoring Units Study (MORTEMUS), that multifactorial monitoring will be important to continue to understand and stratify SUDEP risk in patients with epilepsy. Such multimodal monitoring has begun to be implemented in some centers and is producing valuable information [42–45].

Mechanisms for SUDEP

There is continued ongoing discussion regarding the mechanisms for SUDEP. There is general consensus that there is cardiorespiratory dysfunction triggered by a convulsive seizure that leads to death. While breathing [46;47] and other cardiorespiratory function can be profoundly affected by focal seizures [48], SUDEP is thought to occur more commonly following GCS. It is becoming apparent that there are likely to be different primary mechanisms for SUDEP in different given patients depending on their seizure type and semiology. Both patient data and animal studies indicate that seizures can impair respiratory function, which contributes to seizure-related death, or SUDEP. This respiratory dysregulation contributes to cardiac dysregulation in many cases [20]. In MORTEMUS, all nine patients for which peri-ictal cardiac and respiratory activity could be discerned experienced terminal apnea prior to terminal asystole [49]. How seizures affect breathing has been a subject of intense study recently [20;50].

Breathing is a complex process involving central and peripheral components. Breathing is automatic, but it can be modulated by higher centers. Central pattern generators for breathing reside in the brainstem and drive inspiration/expiration through control of the diaphragm and other downstream components. These breathing centers include the pre-Bötzinger complex [51] and parafacial nucleus [52]. Apnea can be central, resulting from loss of the control signals from brainstem, or obstructive resulting from blockade of the airflow system (e.g., loss of airway tone/pharyngeal muscle tome, tonic activation of diaphragm, laryngospasm, etc.). There is evidence from human studies that seizures are associated with central apnea [53]. This is generally ictal, but can also be post-convulsive, and in some instances occur prior to the seizure [38;39]. Obstructive mechanisms such as laryngospasm have also been identified in patients with epilepsy [54].

Seizure-induced respiratory arrest has been identified in several seizure and epilepsy models including audiogenic seizures in DBA/1 and DBA/2 mice [55;56], maximal electroshock (MES)-induced seizures in C57BL/6J mice [57–61], *Lmx1b* conditional knockout mice [62] that lack serotonin (5-HT) neurons in the central nervous system [57], mouse models of Dravet syndrome[63–65], and *Kcna1* knockout mice lacking the $K_V1.1$ voltage gated potassium channel [66;67].

Considerable work has been done recently to try to understand how seizures lead to breathing impairment. Elegant studies in humans [68–71] and in animals [72;73] suggest

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involvement of forebrain structures such as amygdala. Recently, a large effort has been made to map connectivity of the amygdala, which paved the way for further unveiling of specific network mechanisms [74]. There is also evidence from animal models that seizures must be detected in brainstem before cardiac and respiratory effects manifest [75], and that when there is impaired breathing, activity in brainstem neurons (e.g., 5-HT neurons in the medullary raphe) is reduced [76]. Additional recent work in animal models has focused on determining ways to circumvent airway and/or respiratory muscle impairment, including stimulation of the diaphragm to reduce tonic activation [77], and carotid body/carotid sinus nerve stimulation to reduce airway constriction by laryngospasm [78–80]. Findings from some studies evaluating effects of seizures on breathing, mortality, and other factors should be interpreted carefully, as some of these are models of prolonged seizures. Prolonged seizures, or status epilepticus (SE), are dangerous and a significant cause of mortality. Mechanisms for death from SE need to be further elucidated; however, SE, by definition, excludes the death from being labelled SUDEP [81].

There may be central and obstructive mechanisms occurring concomitantly to contribute to seizure-related apnea. If there is cause for obstruction, removing the obstruction will only be useful if there is a central drive to breathe; conversely, restoration of a central drive to breathe will only be effective if there is no obstruction (i.e., airway is patent, respiratory muscles are not tonically activated, there is no laryngospasm, etc.). There is likely a critical window of time following a seizure for homeostatic mechanisms to come back online. The non-pharmacological means for circumventing some forms of obstruction mentioned above are attractive potential avenues for intervention because they require stimulation of peripheral systems, and do not require invasive intracranial hardware. As noted above, though, these will only be useful in cases where there is no centrally mediated apnea, or in which the central component is brief. For instance, during a period of concomitant central apnea and tonic activation of diaphragm, diaphragmatic pacing can overcome the tonic activation to allow phasing pumping of the lungs to circulate enough oxygen to temper the hypoxia and hypercapnia and allow resumption of normal breathing once the central apnea ends.

There is the question of how seizures reach central respiratory components to impair cardiorespiratory function. There are direct synaptic connections from cortex to the aforementioned forebrain and brainstem structures controlling breathing. Certainly, seizures could propagate along these channels to impair breathing and cardiac activity. Seizures can also trigger spreading depolarization (SD) [82–84] which is a traveling wave of depolarization that moves in a mass-like fashion through contiguous tissue inhibiting everything in its path [85;86]. It has long been known to underlie pathophysiology in migraine and has more recently been implicated in traumatic brain injury, epilepsy and SUDEP [82]. Recent studies in a hyperexcitable mouse model demonstrate that when SD reaches superior colliculus it is more likely to be fatal [87–89]. In certain syndromic epilepsies, ion channel mutations could also be present in key control regions and directly impair cardiorespiratory function in this manner [50].

Impairment of arousal has also been implicated in SUDEP [90]. Arousal generally speaks to a level of alertness ranging from fully alert/vigilant to coma with many states on a

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continuum in between [91]. Arousal can also be used to describe awakening from sleep. Seizures can lead to PGES. Seizures can also lead to impairment of arousal ranging from mild confusion to profound obtundation [90;92;93]. Following this, patients may become somnolent and fall asleep. PGES and arousal impairment can occur concomitantly, but they do not have to, necessarily. Impairment in arousal can be associated with other features such as immobility [30;94]. It is clear that external stimulation can hasten recovery from the post-ictal state [95]. Indeed, the majority of patients that received rapid intervention in the MORTEMUS study did not die, but rather experienced near-SUDEP [49].

Considerable work has been done recently to evaluate anatomical and pathological changes in patients who died from SUDEP compared to cohorts with or without epilepsy. This has included examining 5-HT receptor subtypes in hippocampus and temporal cortex [96], 5-HT transporter in brainstem and amygdala [97], evaluating proteomic changes [98;99], and evaluating for anatomical changes in central autonomic regions [100–102]. Changes in 5-HT and serotonergic nuclei in brainstem have been evaluated previously [103]. More needs to be done looking for changes more broadly. Serotonergic neurons and autonomic sites are a good starting place, but more careful examination of brainstem respiratory centers, amygdala, and other forebrain and limbic structures is warranted.

Neurotransmitters involved in SUDEP

Perhaps the largest body of evidence implicates dysfunction of the 5-HT system in SUDEP. 5-HT modulates seizures, breathing, and cardiac activity, and is involved in sleep wake regulation [104;105]. 5-HT is implicated in another sudden death entity, sudden infant death syndrome (SIDS). There are many parallels between SIDS and SUDEP [20;106]. Much work on the role of 5-HT in SUDEP comes from animal studies [104;107]. Enhancing 5-HT transmission with reuptake inhibitors or receptor agonists reduces seizure-induced respiratory arrest following audiogenically-induced seizures in DBA/1 mice [56;108–112] and following MES-induced seizures in C57BL/6J mice [57]. Elimination of 5-HT neurons increases mortality following chemically or electrically induced seizures [57]. Optogenetic stimulation of 5-HT neurons in the dorsal raphe nucleus (DRN) reduces seizure-induced respiratory arrest in DBA/1 mice [113]. Chemical or optogenetic stimulation of DRN also reduces PGES and hastens termination of immobility following seizures induced by amygdala kindling and reduces mortality following MES-induced seizures [30]. PGES and prolonged immobility have been correlated with SUDEP risk in some studies [27;94;114]. Genetic elimination of *htr2c*, the gene encoding the 5-HT_{2C} receptor, in mice leads to development of adult-onset epilepsy with a high risk of mortality [115].

A number of serotonergic abnormalities have been identified in patients that died of SUDEP, including in the medullary 5-HT neurons [100;103] and reduced volume on MRI in brainstem serotonergic regions [116]. Serum 5-HT level has been shown to inversely correlate with PGES duration [117]. This is commensurate with the findings in animal studies. However, serum 5-HT may not be the optimal measure of 5-HT concentration as 5-HT does not typically cross the blood brain barrier. More work will be needed to determine if the blood brain barrier disruption induced by seizures is sufficient to cause serum 5-HT levels to reflect 5-HT levels in the brain in these circumstances [118;118].

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Recently, as noted above, transcriptomic and proteomic variations have been identified in patients who died from SUDEP [96–98]. Among the many properties of 5-HT neurons is that they are CO_2 chemosensors that modulate breathing in response to elevated CO_2, the hypercapnic ventilatory response (HCVR) [119], and are involved in regulating arousal in response to CO_2 [120–123]. Since there are profound change in CO_2 with seizures, it is intriguing to consider that altered 5-HT neuron chemosensor function could pay a role in SUDEP, as it has been proposed to do in SIDS [122].Recent functional magnetic resonance imaging (fMRI) studies demonstrate altered activation in these regions in response to CO_2 in patients with epilepsy compared to healthy controls [124]. More will need to be done to understand whether this reflects a true alteration in chemosensitivity of the neurons or whether this reflects a change in sensitivity of the vasculature in these regions to CO_2-induced vasodilation.

Other neurotransmitters, including adenosine (ADO), norepinephrine (NE), and orexin (ORX) have also been implicated in SUDEP. Most evidence comes from studies in animal models. All these transmitters affect seizures, breathing, and sleep and wakefulness, and they interact with each other in various circumstances. ADO levels rise during seizures as adenosine triphosphate (ATP) energy stores are depleted. The ADO rise contributes to seizure cessation; however, ADO also suppresses breathing. ADO kinase deficient mice demonstrate increased seizure-related death rate [125;126]. Studies of audiogenic seizures in DBA/1 mice and with MES-induced seizures in C57BL/6J mice have implicated the norepinephrine (NE) system in seizure-related death. In both models, the NE reuptake inhibitor (NRI), atomoxetine, reduces seizure-induced respiratory arrest and mortality [60;127;128]. In the MES model another NRI, reboxetine also reduces mortality. Toxin-mediated destruction of NE neurons increases mortality [60]. In the MES model, the effect of the NRI was mediated through an α_1-noradrenergic receptor dependent mechanism, and there was interaction between the NE and 5-HT systems [60]. Work examining a role for orexin has been primarily undertaken in *Kcna1* knockout mice. Dual orexin receptor antagonism improves seizures, positively affects seizure-induced cardiorespiratory effects, and reduces mortality in this model [129;130]. Many pharmaceutical agents are available that target these neurotransmitter mechanisms. These represent attractive avenues for investigating pharmacological reduction of SUDEP risk. Very recent work in mice indicates that analogs of the neuropeptide, galanin, can prevent seizure-induced respiratory arrest and death in kindled mice [131], which may occur through action in the amygdala [132].

Association between sleep, circadian rhythms, the night and SUDEP

There is a strong bidirectional interaction between sleep and epilepsy [133]. There is also a well-described influence of circadian rhythms and time of day on epilepsy and seizures [134]. A large proportion, if not most, SUDEP occurs during the night [135]. Since SUDEP is generally unwitnessed, if the patient is found in or near the bed, they were presumed to be asleep [136]. In MORTEMUS, SUDEP followed a seizure that occurred during sleep in 7 of the 10 patients for which there was sufficient data to determine sleep-wake state [49]. Animal studies demonstrate a differential role for sleep and wake in seizure-induced mortality and on effects of seizures on breathing, cardiac function, and PGES

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[30;58;61;107;137–139], and progressive sleep dysregulation preceding death in certain genetic models for seizures and seizure-related death [138;140]. Death is more common during the night in several animal models including a model of Dravet Syndrome [64], *Kcna1* knockout mice [141], audiogenic seizures in DBA/1 mice, and MES-induced seizures in C57BL/6J mice [61]. It is somewhat surprising that the preponderance of death from seizures occurs during the night in both diurnal humans and nocturnal rodents. This suggests a conserved mechanism, one of which could be the circadian oscillation in 5-HT which is similar in some brain loci between species [134;135;142]. The relative importance of sleep state versus time or day/circadian pattern is yet to be determined.

Prevention and Intervention

The most comprehensive method for SUDEP prevention remains eradication of epilepsy. Short of that, since the majority of SUDEP is associated with GCS, eliminating GCS is next best, with aggressive medical management of GCS, compliance with and adherence to the seizure treatment plan, avoiding triggers and other lifestyle modifications, and early work up for surgery and surgery if indicated. Given that SUDEP occurs commonly at night, nighttime supervision, either directly or via monitoring devices, with the ability to intervene in some way is helpful. Devices will not be foolproof, and just having a device will not eradicate SUDEP, but devices have the potential to reduce the likelihood of SUDEP. The choice of which device and how it will be monitored is a personal one [143–145]. Many encounters with bereaved family members of those who died from SUDEP begin with the bereaved saying that they were not told about the risk of SUDEP. While it is clear that patients and families want to know about SUDEP [146–148], continued efforts are needed to educate all medical professionals, including specialists and non-specialists, who care for patients with epilepsy about SUDEP. This will allow them to disclose the risk of SUDEP to patients and to educate patients and caregivers about SUDEP, and thus make a stronger effort to best reduce SUDEP likelihood [149].

Conclusion

Much continues to be learned about SUDEP from both patients and animal models, with many consistent findings discovered between them. Now, after assessment of many populations of people with epilepsy, the recent estimates of SUDEP incidence remain remarkably consistent. While working towards seizure-freedom is always a goal of epilepsy therapy, this can be challenging. Further reductions in seizure frequency can come at the cost of burdensome side effects. Refined SUDEP risk assessment scales may be useful in deciding which patients to be more aggressive with despite risks of additional medication trials, surgery, or neuromodulation. Certainly, mechanisms for SUDEP are likely to be heterogeneous, with many factors coming into play in varying combinations. That said, cessation of breathing is a primary etiology of SUDEP in many, if not most, cases. Recent work to delineate neurotransmitter, circuit, and network mechanisms leading to seizure-induced respiratory arrest have been fruitful with many potential avenues uncovered with which to explore treatments/preventions. Additional recent work has even presented ways to circumvent death in some models. As a field, we are getting better at informing patients and caregivers about SUDEP, identifying those individuals at highest risk, and implementing

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tools at hand to attempt to mitigate risk. We need to continue to improve in these realms, and also continue advancing research into mechanisms so that we can exploit these to best intervene, prevent, and eradicate SUDEP.

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Key Points

- SUDEP is a major cause of death in patients with epilepsy.
- SUDEP rates are comparable in numerous recent population-based studies.
- Mechanisms for respiratory dysregulation caused by seizures and contributing to SUDEP are emerging.
- Potential network mechanisms for SUDEP are emerging.
- Sleep-wake state and time of day are important factors in SUDEP.