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REVIEW ARTICLE

Autonomic aspects of sudden unexpected death in epilepsy (SUDEP)

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Abstract

Sudden unexpected death in epilepsy (SUDEP) is a major cause of epilepsy-related mortality. SUDEP is highly linked to seizures, with most deaths occurring after convulsive seizures in sleep. In most cases of SUDEP, convulsive seizures appear to directly trigger catastrophic cardiorespiratory dysfunction leading to death. In the last few decades, many pathophysiological mechanisms have been proposed to explain the sequence of events leading to death. Patients with epilepsy often have underlying autonomic dysfunction, as measured by heart rate variability and other testing modalities. Additionally, seizures often trigger acute cardiac and respiratory dysfunction. While sinus tachycardia is the most common cardiac finding during seizures, asystole and malignant tachyarrhythmias may also occur. Seizures can also lead to respiratory dysfunction, including central ictal and obstructive apnea related to laryngospasm. Available data suggest that there could be underlying autonomic dysfunction, potentially related to genetic, medication, and other factors that might predispose individuals to sudden catastrophic cardio-respiratory dysfunction in the setting of a seizure, resulting in SUDEP. Further exploration of this possible link is needed. Patients with medically refractory epilepsy are at the highest risk, and adequate management via medical therapy to control convulsive seizures, or surgical intervention may decrease the SUDEP risk. Recently, many automated seizure detection systems have been developed to detect convulsive seizures, which may enable caregivers to more closely monitor individuals with epilepsy. Improved identification of seizures may be important for patients with refractory epilepsy as close supervision and timely intervention after a seizure could potentially reduce the risk of SUDEP.

Keywords SUDEP · Epilepsy · Mortality · Cardiac · Respiratory

Introduction

Sudden unexpected death in epilepsy (SUDEP) is a major cause of epilepsy-related mortality. SUDEP is defined as the "sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death, occurring in benign circumstances, in an individual with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which postmortem examination does not reveal a cause of death" [1]. The risk of sudden death is higher in those individuals with uncontrolled seizures, especially when they have frequent convulsive seizures, particularly when there are greater than 2–3 convulsive seizures/year [2, 3].

Most deaths occur in sleep, with the patient in the prone position (which might exacerbate seizure-related respiratory dysfunction), and are unwitnessed, though there is often evidence of a recent seizure (e.g., tongue bite, urinary incontinence, or body positioning to suggest a recent seizure) at the time of death [4–6]. Most witnessed cases of SUDEP occur immediately after convulsive seizures [4, 7].

In epilepsy, mortality is 2–3 times that of the general population [8, 9]. This increased risk is due to multiple causes, including seizure-related trauma/drowning, status epilepticus, and associated neurologic conditions [10]. The risk of sudden unexpected death is 24 times that in the general population, which accounts for an average of 17% of deaths in patients with epilepsy [11]. Patients who die due to SUDEP are most often young adults with uncontrolled epilepsy, particularly with convulsive seizures. For the general epilepsy population, the incidence of SUDEP is

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approximately 0.35–2.3/1000 person-years [12, 13]. Patients with refractory epilepsy, particularly those who are epilepsy surgery candidates or continue to have seizures despite epilepsy surgery, are at the highest risk for SUDEP with an incidence of approximately 6.3–9.3 SUDEP deaths per 1000 people with epilepsy per year [12].

Other associations with SUDEP include antiepileptic drug (AED) polytherapy, young age of epilepsy onset, low antiepileptic medication levels, cognitive disability, and high seizure frequency [14, 15]. While some studies implicate specific AEDs as increasing the risk for SUDEP, other studies show no specific AED association with SUDEP [16]. Elimination of seizures by epilepsy surgery may confer reduced risk [3]. And seizure reduction via vagal nerve stimulation or responsive neurostimulation (RNS) may also reduce the risk of SUDEP [17, 18]. Increased seizure surveillance and early intervention may also reduce risk for SUDEP [19].

Human cardiorespiratory function in SUDEP and near-SUDEP

Available data from witnessed and monitored SUDEP cases suggest that, in most cases, a convulsive seizure triggers catastrophic cardio-respiratory dysfunction that results in death [20, 19].The MORTEMUS study, which is the largest study to date describing cardiorespiratory function at the time of death in epilepsy, reported all SUDEP deaths occurring after a convulsive seizure [19]. In those cases, a seizure appeared to trigger progressive bradycardia and apnea beginning during the immediate post-ictal period. Terminal apnea occurred before terminal asystole in all cases. Notably, cardiopulmonary resuscitation was delayed by > 13 min or did not occur at all in the monitored cases of SUDEP. There were no cases of ventricular tachyarrhythmia as a cause of death in any of the patients in this series. In contrast, in the same series, patients who had near-SUDEP (due to prolonged apnea, asystole, or ventricular arrhythmia) received cardiopulmonary resuscitation within 3 min, at the latest. These data suggest that when there is significant cardiorespiratory dysfunction after a seizure, rapid intervention with cardiorespiratory support might prevent death in some cases.

However, there are cases of non-seizure related SUDEP, which reveal that a seizure is not necessary to trigger severe terminal cardiorespiratory dysfunction resulting in death [21]. In this series of three patients with refractory epilepsy, all patients died in the epilepsy monitoring unit during continuous video-EEG monitoring. There was no clinical seizure and no ictal change on EEG preceding death. Similar to other cases of monitored SUDEP, the deaths were not due to a primary cardiac (ventricular tachyarrhythmia) cause. In all cases there was progressive cardiorespiratory dysfunction associated with suppression of the EEG. In two cases there was tachycardia and tachypnea preceding bradypnea and bradycardia followed by terminal apnea, which was then followed by terminal asystole, a pattern that is similar to the progression of cardiorespiratory dysfunction noted in the MORTEMUS study. These data, along with data from seizure-related SUDEP, suggest that catastrophic autonomic dysfunction may occur due to severe brainstem dysfunction, which may be responsible for the highly abnormal cardiorespiratory patterns seen in all of these cases. In these non-seizure SUDEP cases, there was no evidence of cortical activation (via a seizure) causing this dysfunction, again supporting possible initial brainstem dysfunction as a cause of death. More recently, there was another case of SUDEP that occurred without evidence of an electrographic seizure on electrocorticography stored in the patient's implanted responsive neurostimulator, but cardiorespiratory function was not available in that case [17].

While severe combined cardiorespiratory dysfunction appears to be the most common finding in SUDEP, there are some cases of ventricular tachyarrhythmia in near-SUDEP or SUDEP patients. Espinosa et al. reported near-SUDEP in a 51-year-old woman with refractory temporal lobe epilepsy. During video-EEG monitoring, the patient had a right temporal focal to bilateral tonic–clonic seizure, which triggered ventricular tachycardia, requiring placement of an implantable cardiac defibrillator [22]. Ferlisi et al. also reported ventricular tachycardia at the end of a convulsive seizure occurring outside the hospital setting [23]. Ventricular arrhythmia occurred at the time of SUDEP in one case but underlying ischemic heart disease may have contributed, and only the emergency medical report of ventricular fibrillation was available in another case [24, 25]. There are additionally rare cases of patients with long QT syndrome who also have epilepsy [26, 27]. Animal data also suggests that an ion channelopathy may cause both epilepsy and alter the autonomic control of the heart [28]. Additionally, ventricular tachyarrhythmias may occur more frequently in patients with epilepsy (possibly related to increased risk of cardiovascular disease in this population) and could be an underestimated cause of SUDEP [29–31]. The data thus far suggest that ventricular arrhythmia might be a rare cause of SUDEP.

Ictal and interictal cardiac function

Seizures commonly alter respiratory and cardiac function. Most seizures cause an increase in heart rate, which generally resolves spontaneously and is not clinically significant. However, seizures may also cause significant bradycardia or potential high-risk arrhythmias. In multi-day recordings in patients admitted to epilepsy monitoring units, almost

40% of patients had ictal cardiac arrhythmias or repolarization abnormalities, including bundle branch block, atrial fibrillation, supraventricular tachycardia, asystole, and other abnormalities [32, 33]. Convulsive and longer seizures may increase the risk for ictal EKG abnormalities [32].

Long-term EKG recording (between 4 and 22 months) via implantable loop recorders in patients with refractory epilepsy suggest that ictal and interictal bradycardia may occur relatively commonly in this population, with 8/39 patients in both studies combined having bradycardia or asystole [34, 3]. None of the 39 patients had ventricular tachyarrhythmias. There were 4/39 patients who had cardiac pacemaker implantation due to asystole found on their long-term cardiac recordings. However, the utility of cardiac pacemaker implantation in preventing death in this population remains questionable. While it is clear that pacemaker implantation can be very helpful in preventing ictal syncope (i.e., syncope due to ictal asystole with subsequent hypotension and cerebral hypoperfusion) and falls, it is not clear that pacemaker implantation can prevent SUDEP. Schuele et al. found that when pacemakers were implanted in patients with ictal asystole and followed for 5 years, the risk of recurrent asystole appears to be low and that asystole may be a benign event [35, 36]. However, one caveat is that ictal asystole is likely to be a rare event, since rare or intermittent pacing occurring only during seizures may be below the detectable threshold of pacing. Additionally, while post-ictal asystole occurred in monitored SUDEP cases, it always followed apnea. Thus, it is not clear that cardiac pacing could prevent terminal asystole in the setting respiratory failure. In a review of ictal and post-ictal cardiac arrhythmias, there were no deaths related to ictal asystole though there was one case of prolonged asystole terminated by resuscitation [37].

Retrospective analysis of multi-day ECG data obtained during video-EEG monitoring from patients who subsequently died due to SUDEP found that SUDEP patients had greater increases in heart rate during seizures than in other refractory control epilepsy patients [25]. The changes in heart rate from baseline to seizure were particularly marked during sleep-onset seizures in the SUDEP group. However, while 56% of SUDEP patients had ictal cardiac rhythm and/or repolarization abnormalities, this was not significantly higher than the 39% rate of abnormalities seen in the refractory control population. More recently, a case–controlled study compared the electrocardiographic features of twelve SUDEP cases with 22 age and sex matched controls. An abnormal ventricular conduction pattern was more common in cases than controls (58% vs 18%, $p = 0.04$), but the rates of early repolarization (which may indicate increased risk for sudden death) was similar among cases and controls [38].

In a non-SUDEP epilepsy population, Lamberts et al. found that early repolarization abnormalities and severe QTc interval prolongation were more common in a cohort of patients with refractory epilepsy than in a control non-epilepsy group. Of note, severe QTc prolongation was found only in patients with epilepsy who were on depolarization-blocking drugs, which primarily included antiepileptic drugs (AEDs). In this study, since only epilepsy patients had severe QTc prolongation, it was not possible to separate whether the QTc prolongation was related to epilepsy or to the AED effect. In peri-ictal QTc evaluation, Brotherstone et al. found that the QTc interval significantly increased during some seizures in 9 out of 39 patients admitted for video-EEG monitoring [39]. While individual transient seizure-related QTc interval prolongation may occur in epilepsy, as a group, QTc intervals are not prolonged in the SUDEP population as compared with a refractory epilepsy control population [25]. Consistent with the findings from these studies, another study found that the post-ictal QTc was prolonged in some SUDEP cases but not more commonly than in a control epilepsy group [40]. Another study reported that early repolarization on EKGs may be more common in epilepsy patients than in healthy controls [41]. In that same study, one of two patients who subsequently died due to SUDEP had abnormal early repolarization. To date, studies evaluating SUDEP compared to other patients with epilepsy have failed to find any reliable cardiac marker that is specific for SUDEP.

Heart rate variability and electrodermal activity

Patients with epilepsy often have interictal autonomic dysfunction, with many studies reporting decreased heart rate variability (HRV) [42]. Interictal HRV abnormalities have been reported in various populations of epilepsy, including in focal (particularly in temporal lobe epilepsy) and generalized epilepsy [43–45]. Additionally, other forms of autonomic testing, including baroreflex function and Valsalva maneuver tests, also show interictal dysfunction in epilepsy. HRV studies reveal variable findings, with some showing parasympathetic dominance and others showing sympathetic dominance or combined sympathetic and parasympathetic dysfunction [42]. Some studies correlate specific antiepileptic medication use with greater degrees of autonomic dysfunction [46, 47]. Decreased HRV may also correlate with atrophy of specific brain stem regions involved in autonomic control in patients with focal epilepsy [48]. In the same study, a separate group of patients who subsequently died due to SUDEP had progressive atrophy of these brainstem regions in serial MRI scans prior to death, suggesting a possible link between structural and functional autonomic pathology. It is possible that when there is already underlying autonomic dysfunction, related to genetic, medication, and other factors, these abnormalities may predispose

individuals to sudden autonomic dysfunction in the setting of a seizure, resulting in SUDEP.

Most HRV studies have focused on living patients with epilepsy, with many studies evaluating HRV parameters in relation to SUDEP risk factors, but there are limited HRV data directly from SUDEP patients. Decreased HRV strongly correlates with increased risk of sudden death, presumably due to lethal cardiac tachyarrhythmias in most cases, in some non-epilepsy populations, particularly in those with underlying cardiovascular disease [49]. However, thus far, there are no clear specific HRV biomarkers for SUDEP. Surges et al. 2009 investigated the HRV in seven patients with SUDEP with HRV in seven control patients and found no significant differences in interictal HRV measures between the groups [50]. More recently, Myers et al., noted that the awake HRV was lower and the sleep:awake HRV ratios were either extremely high or very low in a group of patients with sodium channel mutations who died due to SUDEP, as compared with refractory epilepsy controls [51]. Patients with Dravet syndrome, which is highly associated with SUDEP, also have reduced HRV [52, 53]. There is also one case report of a man with refractory epilepsy and SUDEP in whom serial studies showed a sudden increase in parasympathetic activity, as measured by high-frequency (HF) power and the ratio between cardiac vagal index (CVI) and cardiac sympathetic index (CSI) during the 1 day to 30 min preceding death [54]. Although the MORTEMUS and other available SUDEP data suggest that primary cardiogenic causes of SUDEP are rare, it is still possible that abnormal HRV might contribute to SUDEP in a minority of cases.

Of course, it is possible that HRV may also be abnormal due to overall autonomic dysfunction and thus may be related to SUDEP independently from a potential cardiogenic pathomechanism of death. Additional evaluation from larger populations of patients with SUDEP is needed to clarify whether specific HRV parameters may correlate with risk of SUDEP and whether there might be a specific pattern of progressive HRV changes over time that may predict SUDEP.

Electrodermal activity (EDA) measures changes in the electrical conductance of the skin due to sympathetic neuronal activity [55]. One study evaluating primarily children found that there is a surge of EDA (correlating with increased sympathetic activation) and suppression of high frequency power of HRV (correlating with parasympathetic suppression) after tonic–clonic seizures [56]. This post-ictal autonomic dysregulation correlated to increased duration of PGES in this study. These data suggest that PGES, which may be a biomarker for SUDEP, could be associated with significant autonomic dysfunction during the critical post-ictal period, when SUDEP most often occurs. A recent case report of a SUDEP patient showed significant elevation in peri-ictal electrodermal response recorded by a commercially available wrist device suggesting uninhibited sympathetic surge [57]. Such autonomic dysregulation could potentially contribute to the risk of SUDEP. Additional investigation showed that age may affect the degree of sympathetic and parasympathetic activity following seizures [58]. Adults tend to have longer durations of PGES [59, 60]. Sarkis et al. also found that adults had longer durations of PGES and that the duration of PGES correlated with the degree of sympathetic activation as measured by EDA [58]. However, after controlling for PGES duration, pediatric patients were found to have stronger sympathetic activation as well as greater parasympathetic suppression than adults. These age-dependent findings may correlate with the variable incidence of SUDEP seen in different age groups.

Blood pressure and heart rate

The resting awake interictal heart rate (HR) and blood pressure (BP) in SUDEP cases and control epilepsy groups (refractory and controlled) are similar but there is a trend toward a higher diastolic BP and more stable (less variable) HR over time in individuals who subsequently died due to SUDEP [61]. These data suggest that patients who subsequently die due to SUDEP may have increased resting sympathetic tone as well as impaired normal heart rate regulation. While these findings need to be confirmed in larger populations, they again support the possibility that patients at risk for SUDEP may have underlying autonomic dysfunction, which may increase their risk for death in the setting of a seizure. Such abnormalities may serve as markers for SUDEP.

Jaychandran et al. evaluated peri-ictal HR and BP in patients undergoing video-EEG monitoring and found that ictal hypertension occurred in 26.3% of 57 seizures in 42 patients [62]. Ictal hypotension was less common, occurring in 8.7% of seizures in that same series. Hampel et al. found that increases in HR and BP varied depending on seizure type and were more marked during seizures with impaired awareness or convulsive activity [63]. More recently, ictal data utilizing continuous noninvasive blood pressure monitoring found that post-ictal hypotension lasting more than 60 s was closely correlated with post-ictal generalized EEG suppression [64]. Lacuey et al. recently found that stimulation of Brodman area 25 (subcallosal region) causes hypotension, suggesting that involvement of this area during seizures might cause peri-ictal hypotension, which might contribute to SUDEP [65].

Respiratory system and SUDEP

Ictal respiratory dysfunction is common and is often closely linked to cardiac dysfunction. Cortical centers of respiratory control have been known as early as the 1950s. Jasper

noted that electrical stimulation of the human insular cortex, ventromedial prefrontal cortex, hippocampus, and amygdala affects autonomic control and may cause respiratory arrest [66]. Ictal central apnea strongly correlates with focal epilepsy, particularly temporal lobe epilepsy. In 56 patients with focal epilepsy, Bateman et al. found that approximately one-third of focal seizures with or without generalization were accompanied by desaturations below 90% [67]. More recently, Lacuey et al. found that ictal central apnea occurred in 47% of 109 patients (36.5% of 312 seizures), most notably in temporal lobe epilepsy [68]. Dlouhy et al. 2015 found that electrical stimulation of the amygdala in patients undergoing intracranial EEG monitoring resulted in central apnea [69]. An increase in end tidal Co_2 is also reported with seizures. Seyal et al. studied one hundred and eighty-seven seizures in 33 patients with focal epilepsy and found that one third of patients had seizures with $ETCO_2$ elevation above 50 mm Hg. Ictal/postictal ETCO(2) increase above baseline was recorded for a significant duration (Mean 424 s). The peak $ETCO_2$ value was significantly associated with ictal spread to the contralateral hemisphere [70]. Study of regional cerebral perfusion with near-infrared spectroscopy has shown decreased regional cerebral oxygenation with ictal onset [71]. Another study focusing on the same technique noted that generalized tonic–clonic seizures were significantly associated with lower values of ictal and post ictal regional cerebral oxygen saturation. Patients who had more than 20% decrease in the periictal regional cerebral perfusion from baseline were also found to have higher scores on the SUDEP-7 Inventory [72].

Animal models have been studied to identify the basic neurobiological mechanisms of respiratory arrest with seizures. It has been well studied that 5-hydroxytryptamine (5-HT) neurons play a critical role in maintaining respiratory drive. Provoked audiogenic seizures in DBA/2 mice which lack several 5 HT receptor proteins in the brainstem lead to death due to respiratory arrest, which can be prevented with oxygenation [73]. It is notable that seizure-related death is reduced by use of selective serotonin reuptake inhibitors (SSRI) [74, 75]. Additionally, adenosine antagonists may also significantly reduce ictal apnea [76]. Reduced 5-HT levels and immature 5-HT neurons in the medulla have also been noted in infants who died of Sudden Infant Death Syndrome (SIDS), which suggests a possible role of 5-HT axis dysfunction as a cause of sudden unexplained death [77]. Further investigation is needed to evaluate whether SSRIs and adenosine antagonists might have a role in reducing ictal apnea in humans.

Recent studies with a kainic acid rat model showed that seizure activity caused increased firing of the recurrent laryngeal nerve resulting in laryngospasm and airway occlusion. Seizures induced ictal central apnea in some rats, but others had obstructive apnea due to severe laryngospasm causing obstruction and cessation of airflow followed by ST-segment elevation, bradycardia, and death [78]. The same group also recently identified two biomarkers of obstructive apnea: (1) EMG-based signal or muscle artifact detectable on the EKG produced by the attempt to breathe and (2) an abrupt increase in RR interval. They noted that these two biomarkers of obstructive apnea were also seen in patients from MORTEMEUS study. They suggested that both might be potential biomarkers of obstructive apnea and possibly for risk of SUDEP [79].

Latreille et al. reported that nocturnal seizures are more likely to be associated with both PGES as well as with greater desaturation as compared with wake-related seizures [80]. PGES additionally correlates with the both the nadir and duration of desaturation as well as with the duration of postictal immobility [81]. These data suggest that PGES, desaturation, and post-ictal immobility may be related and could be related to risk of SUDEP. The MORTEMUS study provides clear evidence of respiratory dysfunction in SUDEP. In patients with SUDEP in the MORTEMUS series, convulsive seizures were followed by terminal apnea and then asystole [19]. In a study by Park et al., focal to bilateral tonic–clonic seizures or generalized tonic–clonic seizures which caused ictal/post-ictal hypoxemia more than 125 s had a statistically significant association with high-risk cardiac arrhythmias (nonsustained ventricular tachycardia, bradyarrhythmia, and sinus pauses). The odds ratio for occurrence of arrhythmia was 7.86 for desaturation durations ≥ 125 s versus desaturations < 125 s ($p = 0.005$). The odds ratio increased to 13.09 for desaturation durations ≥ 150 s ($p < 0.001$) [82]. These studies show that the peri-ictal respiratory decline may be the critical initial node in the series of terminal events resulting in sudden death.

Pulmonary edema has been reported in the autopsy of SUDEP cases [83]. It is important to note that hypercapnia and oxygen desaturation often extends into the post-ictal period, during which time respiratory effort has been reported to be normalized, and that also suggests the possibility of intrinsic pulmonary dysfunction [84]. The mechanism of pulmonary edema due to seizure is poorly understood.

Prevention of SUDEP

Seizure control is the most important potentially modifiable risk factor of SUDEP. In order to best participate with their care, patients should be knowledgeable about potential risks of seizures, including SUDEP. The American Academy of Neurology and American Epilepsy Society recommend that clinicians counsel epilepsy patients regarding SUDEP. Survey studies of epilepsy patients and family members of SUDEP patients have shown that they prefer to know about

the risk factors of SUDEP during the early phase of management [85, 86]. Unfortunately, some data suggest that only a small minority of neurologists counsel all of their patients about SUDEP [87]. Non-adherence to medications often results in breakthrough seizures and may lead to both status epilepticus as well as SUDEP. Patient counseling efforts should include the importance of medication compliance [88]. A meta-analysis by Ryvlin reported that an adjunctive AED treatment might reduce the SUDEP risk by seven times when given to patients with intractable epilepsy [89]. Antiepileptic medication adherence and surgical interventions, when appropriate, may reduce the risk of SUDEP.

Prone position and post-ictal immobility are often cited in SUDEP cases, and some data suggests that nocturnal supervision might reduce the risk of SUDEP [90]. Nursing interventions such as stimulating and turning the patient to the lateral position and suction with or without supplemental oxygenation have been reported to shorten the duration of peri-ictal hypoxemia and seizure duration [91, 92]. However, currently, no guidelines exist on the use of supplemental oxygen with seizures, and the potential benefits must be weighed against the significant cost and risks of home oxygen. The MORTEMUS data suggests that early peri-ictal intervention might be important in preventing SUDEP. Use of SSRIs has been noted with reduced severity of oxygen desaturation after focal seizures without secondary generalization in comparison to patients who were not taking SSRIs; however, additional data are needed to determine if SSRIs can reduce SUDEP [93]. At this time, the data suggests that close supervision during the post-ictal period and judicious use of mild stimulation and maneuvers to aide respiration, if needed, may be reasonable recommendations for caregivers. Caregivers might also consider training in basic cardiopulmonary resuscitation as a precaution; however, additional data are needed to determine whether this would be beneficial in preventing deaths in the outpatient setting.

Automated seizure detection systems (ASDS)

Many automated seizure detection devices are now available in the market which may help facilitate early peri-ictal intervention. A patient survey found that there is significant interest in using ASDS and that patients would be willing to use it regularly [94]. Most patients felt that an acceptable ratio of false positive to false negative seizure alerts was 25% and that alerting should be within 1 min. Patients expected that these devices should be covered by insurance.

Video-EEG monitoring is the gold standard tool for seizure detection. However, it is not practical for long-term daily use for seizure detection. The ideal portable/wearable device should have high sensitivity and specificity and be comfortable for daily use. Non- EEG based devices are now available commercially, but these products primarily detect convulsive seizures and have variable specificity, limiting their use. One device utilizing a pressure sensor mat which detects abnormal movement or absence of movement was studied in an inpatient setting. A total of 51 patients were included, and a total of eighteen generalized tonic–clonic seizures were recorded with video EEG. The pressure sensor mat detected 89% of tonic–clonic seizures with a positive predictive value (PPV) of 43% [95]. Accelerometer-based devices, which can be similar to smartwatches, can have a high sensitivity up to 90% [96, 97]. However, the data for specificity varies significantly in the reported literature and positive predictive value remains on the low side (57%) for these devices [97, 98]. One EMG-based detection system was studied in 33 patients who were admitted for video-EEG monitoring. The device detected 95% of GTCs within 20 s of electroclinical onset with only one false positive detection [99]. A device monitoring galvanic skin resistance and accelerometers detected 94% of the generalized tonic–clonic seizures in 80 study patients with a false positive rate of 0.74 per 24 h [100]. Another multimodal approach with monitoring of heart rate, respiration, and EMG detected 100% of GTCS and 94% of myoclonic seizures [101]. A wearable device over the trachea reported 88% sensitivity of sleep apnoea detection in ten subjects and a specificity of 99% which may be of potential utility for SUDEP prevention [102]. It is vital to note that all these studies were done on limited patient populations and often done by the same team developing the devices. Additional studies, particularly in outpatient settings, are needed to further evaluate the utility and practicality of these devices.

Conclusions

Both cardiac and respiratory dysfunction occur in epilepsy. Convulsive seizures strongly correlate with SUDEP as well as with PGES and autonomic dysregulation, particularly during the peri-ictal period. Current data suggests that the most common scenario for SUDEP is a sleep-onset convulsive seizure which triggers catastrophic cardiorespiratory dysfunction. Additionally, there are rare cases of primary cardiac tachyarrhythmias in epilepsy which may also play a role in some cases of SUDEP. Most of the data to date are from patients with epilepsy who are at uncertain risk for SUDEP and animal data. There are still limited autonomic data directly from patients who died due to SUDEP. Ongoing prospective multicenter studies may yield additional clues regarding possible biomarkers for SUDEP and effective preventative therapy.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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