Abstract: Sudden unexpected death in epilepsy (SUDEP) is a devastating yet overlooked complication of epilepsy. The rare and complex nature of SUDEP makes it challenging to study. No prediction or prevention of SUDEP is currently available in a clinical setting. In the past decade, significant advances have been made in our knowledge of the pathophysiologic cascades that lead to SUDEP. In particular, studies of brain, heart, and respiratory functions in both human patients at the epilepsy monitoring unit and animal models during fatal seizures provide critical information to integrate computational tools for SUDEP prediction. The rapid advances in automated seizure detection and prediction algorithms provide a fundamental framework for their adaption in predicting SUDEP. If a SUDEP can be predicted, then there will be a potential for medical intervention to be administered, either by their caregivers or via an implanted device automatically delivering electrical stimulation or medication, and finally save lives from fatal seizures. This article presents recent developments of SUDEP studies focusing on the pathophysiologic basis of SUDEP and computational implications of machine learning techniques that can be adapted and extended for SUDEP prediction. This article also discusses some novel ideas for SUDEP prediction and rescue including principal component analysis and closed-loop intervention.

Keywords: automated prediction; epilepsy; machine learning; pathophysiology; sudden unexpected death in epilepsy.

Introduction

Epilepsy is a spectrum of clinically heterogeneous neurological disorders characterized by spontaneous recurrent seizures. Over 1% of the general population have active epileptic seizures, which adversely affect patients’ life quality and increase the risk of psychiatric comorbidities, hospitalization, and mortality (Devinsky et al. 2018; Zack and Kobau 2017). Among the deaths that are attributable to seizures, sudden unexpected death in epilepsy (SUDEP) is the leading cause (Devinsky et al. 2016; Friedman 2017). SUDEP refers to deaths in people with epilepsy that are not caused by injury, drowning, or status epilepticus, in which the postmortem examination does not reveal a clear cause of death (Nashef et al. 2012). SUDEP rates vary depending on the patient cohort, and the population-based studies of SUDEP suggest a pooled estimate of 1.3–1.65/1000 epileptic individuals/year (Einarsdottir et al. 2019; Kløvgaard et al. 2021; Saetre and Abdelnoor 2018). SUDEP also constitutes to ~30% of young adult epilepsy-related deaths (Mbizvo et al. 2021). SUDEP is considered to be the most catastrophic complication of epilepsy and poses a substantial public health burden (Thurman et al. 2014). However, the cause of SUDEP is still largely unknown, and there is no method to predict or prevent SUDEP in a clinical setting.

A computer-aided automated brain states detection and prediction system can be developed through adroit integration of signal processing methods such as EEG wavelet transforms (Moradi et al. 2020; Sharma et al. 2014) and machine-learning techniques (Li et al. 2020a, b; Liu et al. 2020; Nogay and Adeli 2020). In the past two decades, many authors have employed machine learning to develop algorithms for automated epilepsy diagnoses (Thomas et al. 2021), seizure detection (Abbasi and Goldenholz 2019; Baumgartner et al. 2018; Boonyakitanont et al. 2020; Ma et al. 2021; O’Shea et al. 2021; Zhao et al. 2021), and seizure prediction (Acharya et al. 2018; Peng et al. 2021; Zhang et al. 2020). In these studies, the electroencephalogram (EEG), brain imaging such as magnetic resonance imaging (MRI), and other forms of data collected from epileptic patients are fed into a computer model for preprocessing, featurization, model learning, testing, and validation. The good performance (>90% accuracy, sensitivity, and
specifi
city) of many machine-learning algorithms in seizure detection and prediction provides the opportunity to adapt similar approaches for SUDEP risk assessment and prediction (Figure 1). This article presents a state-of-the-art review of recent articles studying pathophysiology and predicting algorithms of SUDEP in both humans (Table 1) and animal subjects in the past five years. The genetic, molecular, and cellular mechanisms of SUDEP have been well-reviewed elsewhere (Bagnall et al. 2017; Chahal et al. 2020; Glasscock 2014; Massey et al. 2014).

Pathophysiology and biomarkers of SUDEP

Human studies

Converging lines of evidence collected from limited SUDEP and near-SUDEP cases at the epilepsy monitoring unit (EMU) suggest that SUDEP primarily follows the severe impairment of respiratory and cardiac functions induced by generalized tonic-clonic seizures (GTCS), which are commonly associated with postictal generalized EEG suppression (PGES) (Lhatoo et al. 2010; Rajakulendran and Nashef 2015; Ryvlin et al. 2013). PGES has been linked to postictal sympathetic and parasympathetic dysregulations including seizure-related respiratory inhibition. Thereby, PGES is considered a major contributor to SUDEP (Bruno et al. 2020a, b, c; Kuo et al. 2016; Poh et al. 2012; Sarkis et al. 2015). However, it remains unclear whether PGES is a reliable biomarker of SUDEP. The conclusion is controversial in terms of the association between the presence or duration of PGES and SUDEP (Kang et al. 2017). The association between PGES and SUDEP also failed to be replicated in other studies (Lamberts et al. 2013; Surges et al. 2011). Hence, the measurements of duration and magnitude of PGES may not be sufficient to address the relationship between the postictal EEG state and the SUDEP risk. Beyond the time-domain analysis, frequency-domain features including cross-frequency coupling are also studied in the context of SUDEP. EEG recordings from a single SUDEP case suggested the loss of ictal phase-amplitude coupling dynamics from the frontal temporal lobe, which are consistently observed in epileptic survivors (Grigorovsky et al. 2020).

In contrast to scalp EEG routines, intracranial EEG (iEEG) allows direct recording of specific brain regions that are critical in regulating seizure-related mortality. iEEG recordings in near-SUDEP cases revealed that the onset of ictal and postictal apnea was highly correlated with seizure spreading to the amygdala (Johnson et al. 2021; Nobis et al. 2019). Consistently, electrical amygdala stimulation also produced apnea in human subjects (Nobis et al. 2018; Rhone et al. 2020). Together these studies suggest a critical role of the amygdala in regulating breathing during seizures, with implications for SUDEP pathophysiology (Vilella et al. 2019). However, in a separate iEEG study, the amygdala seizure spread was neither necessary nor sufficient to cause spontaneous seizure-related apneas, suggesting an inconsistent linkage between these two events (Park et al. 2020).

Compared to EEG, brain imaging techniques including MRI offer a better spatial resolution for deciphering structural and functional brain alterations in epilepsy. In particular, MRI allows a comprehensive examination of distinct neural structures and networks that are crucial for cardiac and respiratory regulations in patients who succumb to SUDEP (Allen et al. 2019). In serial retrospective volumetric MRI studies, SUDEP cases exhibited increased...
gray matter volume in the right anterior hippocampus, parahippocampus, and amygdala, whereas decreased
volume in medial and lateral cerebellum, posterior thalamic gray matter, and medulla oblongata compared to
controls (Mueller et al. 2018; Wandschneider et al. 2015). A postmortem volumetric MRI study found a lower volume of
the rostral medulla reticular formation zone but a higher volume of the caudal medulla in SUDEP compared to
epileptic and nonepileptic controls (Patodia et al. 2021). Together, these observations indicate that the anatomical
alteration of specific brain regions including medulla oblongata is a potential risk factor for SUDEP.

In addition to structural changes, functional imaging
tools facilitate our understanding of the physiology and
network dynamics underlying this fatal event. A resting-
state functional MRI study revealed multiple alterations of

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AUC, area under the curve; GCS, generalized convulsive seizures; GTCS, generalized tonic-clonic seizures; ROC, receiver operating characteristic; PGES, postictal generalized EEG suppression.
network properties including disrupted thalamic connectivity in SUDEP cases compared to low-risk subjects who did not experience any GTCS (La et al. 2019). Positron emission tomography studies identified several unique metabolic patterns including hypometabolism in frontal lobe, hypermetabolism in midbrain and pons in the high SUDEP risk compared to the low SUDEP risk subgroup (Kumar et al. 2021; Whatley et al. 2021). In sum, these SUDEP studies in humans unveil dysfunctional changes and interactions that can be used to further generate discriminative representations using machine-learning and deep-learning tools (Abrol et al. 2021; Davatzikos 2019).

**Animal models of SUDEP**

The rare and unexpected nature of SUDEP limits data from the EMU that is available for studying its pathophysiology in humans (Ryvlin et al. 2013). Animal models offer a complementary tool with rich resources to study SUDEP under the control of genetic and/or environmental variables. Currently available animal models of SUDEP not only recapitulate many key features of human cases of SUDEP including autonomic dysregulation, apnea, hyperventilation, cardiac arrhythmia, and postictal EEG suppression, but also suggest potential genetic and molecular mechanisms of SUDEP such as channelopathies and impairment of serotonergic and adenosinergic systems.

A wide range of model organisms including mice, rats, sheep, and baboons have been used to study SUDEP. Among them, the house mouse (Mus musculus) has been developed into the premier mammalian model organism of SUDEP. Several single-gene manipulations as monogenic causes of developmental and epileptic encephalopathies (e.g., SCN1A, SCN8A, SCN1B, and DEPDC5) and long-QT syndromes (e.g., KCNQ1 and KCNA1) have been used to model SUDEP in mice (Griffin et al. 2018). In these studies, transgenic mice are maintained on a single genetic background; thereby, the importance of isolated genes to SUDEP sensitivities has been demonstrated without consideration of the effect of genetic complexity (e.g., genetic modifiers and polygenicity) on SUDEP response (Goldman et al. 2016).

DBA/1J and DBA/2J mice are classic laboratory inbred mouse strains commonly used in the study of SUDEP given their susceptibility to audiogenic seizure-related respiratory arrest (Pansani et al. 2016). However, their SUDEP sensitivity requires acoustic “priming” at a younger age (Faingold et al. 2010) to maximize the severity of the acoustic seizure response. Compared to DBA/1J and DBA/2J, a recent study showed that 129/SvTer mouse is a more versatile model of SUDEP because it has a wider age range of susceptibility without the need for “priming” (Martin et al. 2020). Utilizing a genetic reference population, the recombinant inbred Collaborative Cross mice, our group identified four strains of Collaborative Cross mice (i.e., CC003/Unc, CC008/GeniUnc, CC009/Unc, and CC029/Unc) that succumbed to sudden death immediately following a transient episode of generalized seizure induced by flurothyl, which is otherwise nonfatal to other inbred mouse strains (Gu et al. 2020).

In sum, these animal models of SUDEP provide basic scientists essential tools for studying mechanisms and treatment strategies of SUDEP. However, the translational value of the knowledge that we gained using animal models of SUDEP requires further evaluation.

**Pathophysiology and biomarkers of SUDEP in animal models**

The implementation of a time-locked behavior-brain-heart-respiratory simultaneous recording system in both anesthetized and freely moving animals offers means to investigate the alterations of the nervous, cardiac, and respiratory functions that lead to seizure-induced sudden death in greater detail. In particular, animal models allow direct recordings from brainstem — the cardiorespiratory pacemaker center which is hard to access in a clinical setting.

Mounting evidence suggests that altered brainstem function is associated with respiratory and cardiac dysfunction, followed by terminal apnea and asystole leading to death in animal models of SUDEP (Lertwittayanon et al. 2020). For example, a slow, negative direct current (DC) potential shift, also known as spreading depolarization, was located in the brainstem of anesthetized mouse models of SUDEP carrying mutation in Kcnat, Scn1a, Ryr2, or Cacna1a (Aiba and Noebels 2015; Aiba et al. 2016; Loonen et al. 2019). A recent study also pinpointed superior colliculus hyperexcitability as a key regulator of brainstem spreading depolarization using diffusion-weighted MRI in a mouse model of SUDEP (Cain et al. 2022). Together, data from DC recordings point to a critical role of brainstem spreading depolarization in mediating the postictal cardiorespiratory collapse that leads to SUDEP. Negative DC field potential shifts of the brainstem were also observed following the final breath in a rat model of status epilepticus. However, the timing suggests that, in the case of a prolonged seizure, the DC shift is a consequence rather than the cause of the respiratory collapse (Jefferys et al. 2019). Although traditional alternating current (AC)-coupled techniques used in clinics are unable to reliably detect spreading depolarization, the rapid development of
intracranial unfiltered DC-coupled recordings in humans improves the translational value of using spreading depolarization in SUDEP prediction (Hartings et al. 2017). A recent study from our group utilizing AC-coupled local field potential recordings directly from dorsal raphe in a mouse model of SUDEP revealed strong ictal brainstem suppression preceding asystole and death (Gu et al. 2022).

In addition to the nervous system, the importance of cardiac and respiratory functions as well as their interplay with the brain have been demonstrated using animal models of SUDEP. Peri-ictal and tonic-phase central apnea co-occurring or preceding terminal asystole was directly associated with SUDEP across DBA/1J mouse models of SUDEP and mice carrying *Scn8a, Scn1a, Kcna1*, or *Cacna1a* mutation (Dhaibar et al. 2019; Kim et al. 2018; Schilling et al. 2019; Wenker et al. 2021). A combination of electrophysiology and fast MRI scans in a rat model of seizures showed laryngospasm-preceded esophageal reflux during fatal seizures suggesting that obstructive apnea is associated with subsequent sudden death in rats (Mandal et al. 2021). Consistent with human studies, the amygdala also plays a fundamental role in respiratory regulation in the animal model of SUDEP. Electrolytic lesions of the amygdala of DBA/1J mice significantly reduced the incidence of seizure-induced respiratory arrest without affecting the seizures, baseline breathing, or chemoreception (Marincovich et al. 2021).

Besides respiratory impairments, cardiac dysfunction and failure are equally important to SUDEP pathology. Cardiac dysfunctions are common in patients with SUDEP as many SUDEP-related genetic mutations are associated with cardiac arrhythmia (Chahal et al. 2020; Friedman et al. 2018). Cardiac dysfunctions including reduced heart rate variability, cardiac myocytes hyperexcitability, increased atrioventricular conduction blocks, bradycardia, and cardiac arrhythmias have also been demonstrated in various transgenic mouse models of SUDEP (Frasier et al. 2016; Glasscock et al. 2010; Kalume et al. 2013; Lin et al. 2015).

After the demonstration of the importance of the isolated system in SUDEP, the multimodal recordings can reveal the potential interplay between each system in regulating SUDEP. Hutson et al. conducted the first directional connectivity analysis of multimodal data collected from SUDEP model mice. Their elegant work showed impairment in the afferent and efferent pathways in the holistic neurocardio-respiratory network in *Kcnal* deletion mice compared to wild-type controls suggesting that effective connectivity measures among brain, heart, and lung could serve as novel biomarkers of SUDEP (Hutson et al. 2020).

**Toward automated SUDEP prediction**

Though seizure control is still the best practice for SUDEP prevention, special measures and algorithms need to be developed to prevent SUDEP when seizure control is not possible or optimal. The discovery of surrogate biomarkers that can be quantitatively measured and computed to identify individuals at risk and determine which seizure is fatal enables automated SUDEP prediction (Figures 1 and 2).
Although it is still controversial whether PGES is an EEG biomarker for the risk of SUDEP, major efforts have been focused on automated detection of PGES as a potential SUDEP prediction practice. Serial machine-learning tools including both traditional machine-learning and deep-learning algorithms have been employed for automatic detection of the start, end, and duration of PGES based on EEG recordings (Bauer et al. 2017; Lamichhane et al. 2020; Li et al. 2020a, b; Mier et al. 2020; Theeranaew et al. 2018; Zhu et al. 2020). In addition to standard EEG routines, features extracted from other forms of data such as video, ECG, electrodermal, and muscular activities can also be used for assisting the computer-aided assessment of SUDEP risks (Chen et al. 2022; Gutierrez et al. 2018). For example, automated video-based nocturnal convulsive epileptic events detection algorithms offer a great predictive value for SUDEP (Geertsema et al. 2018; van Westrhenen et al. 2020) (Table 1).

Wearable devices open a new avenue for continuous monitoring of seizures and biological signals reflecting seizure severity in outpatients with epilepsy (Beniczky et al. 2020; Bruno et al. 2020a, b; Burns and Adeli 2017; Onorati et al. 2017; Ryvlin et al. 2018; van Westrhenen et al. 2021). A case study using a smartwatch to record wrist motion and an electrodermal activity revealed sympathetic hyperactivity and hypoventilation before probable SUDEP (Picard et al. 2017). The accelerometer silence detected by wearables reliably identified the postictal immobility, which has been associated with SUDEP (Bruno et al. 2020a, b). The automated processing of quantitative surface electromyography (EMG) accurately detected the key features of GTCS, which is a major risk factor for SUDEP (Beniczky et al. 2018; Cardenas et al. 2020; Zibrandtsen et al. 2018).

Besides the motion and electrophysiological signals directly collected from patients, electronic medical records contain a wealth of information that can be analyzed to predict the risks of SUDEP. Implementation of natural language processing on text search in electronic medical records was used for the automated identification of SUDEP risk factors (Barbour et al. 2019). A similar tool for individualized prediction of SUDEP was developed using a Bayesian logistic regression model based on 29 common clinical predictor variables (Jha et al. 2021).

To date, major efforts have been focused on using EEG, body motion, and medical records for SUDEP prediction. Algorithms that are specifically designed for cardiac and respiratory feature extraction and classification have not been widely explored in SUDEP prediction. Less attention has been received to other systems that also play a fundamental role in SUDEP such as arousal (Buchanan 2019), vasculature (Szczurkowska et al. 2021), and microbiome (Lum et al. 2020; Olson et al. 2018). Compared to human studies, the current automated SUDEP prediction research in animals is still in paucity and needs to receive more attention.

In sum, published literature on both humans and animal subjects suggests there is a list of surrogate biomarkers and features that can be leveraged to achieve automated SUDEP prediction via machine-learning techniques. Notably, unsupervised machine-learning algorithms can also uncover hidden structures and patterns that have not been previously associated with SUDEP (Figure 2).

**Challenges and opportunities in SUDEP prevention**

The central question of SUDEP prevention is why a particular seizure causes death while others do not. Many challenges including clinical variables such as genetics, treatment history, and other comorbid health conditions as well as inconsistent methodology in data collection and interpretation are inherent in the implication of machine learning in seizure and SUDEP prediction in humans. For EEG-based algorithms, in particular, the artifacts from movement, breathing, and muscle activity can negatively affect the quality of data and linear measures. To resolve this issue, artifacts from EEG signals can be filtered before signal processing or the advantages of nonlinear analyses should be robust against the noise present in the EEG signals.

Large amount of data are required to train a computer to achieve highly sensitive performance in predicting the SUDEP using a deep-learning approach, which is challenging given the rare nature of SUDEP even with the integration of near-SUDEP and high-risk SUDEP cases. To tackle the challenge of accumulating large clinical datasets, many cloud-based repositories have been established to facilitate data sharing and quality control across institutions and countries (Cui et al. 2016). The Center for SUDEP Research (CSR) is an initiative that has been established by the National Institute of Neurological Disorders and Stroke to investigate SUDEP. The major goal of CSR clinical research focuses on the examination of the complex interplay between postictal suppression of brain function, disordered peri-ictal breathing, and autonomic dysfunction (Lhatoo et al. 2015). Accumulating recordings of physiologic parameters including EEG, ECG, breathing,
oxygen saturation, CO₂, and biochemical measures in SUDEP and epileptic controls provide valuable information for multimodal data integration and analysis. For example, one study combined diverse elements of the dataset including EEG, blood pressure, ECG, and baroreflex sensitivity to discover temporal patterns of transitions in network connectivity as potential biomarkers of SUDEP (Threeanaew et al. 2019). In addition to connectivity analysis of multimodal data, other multivariate statistics including principal component analysis (Torres-Espín et al. 2021) can be performed for interpreting, visualizing, and studying the robustness of the main components that characterize SUDEP. Future work can extract underlying principal components that reflect disease states (i.e., SUDEP) as the center of a Venn diagram (Figure 3).

Final remarks

In this article, the authors reviewed different aspects of SUDEP pathologies in both humans and animal models, potential SUDEP prediction algorithms, and their challenges and opportunities. The rapid advances of wearable devices and machine-learning techniques provide viable tools to improve the accuracy and reliability of the SUDEP prediction, which can further revolutionize SUDEP prevention and reduce the likelihood of this tragic event and familial loss.

Epileptiform activities emerge unpredictively and intermittently, and therefore, a feedback brain manipulation that leaves other normal episodes and aspects of brain functions unaffected is desirable (Berényi et al. 2012). Closed-loop therapy has been proposed for better seizure control and has been receiving increasing attention (Lasemidis 2011; Nagaraj et al. 2015). A responsive neurostimulation device has been approved by FDA for treating focal seizures using on-demand electrical brain stimulation. Similarly, the detection of triggers of SUDEP in real time will allow the development of tunable algorithms to identify and rapidly respond to fatal seizures. With better knowledge of the cellular and circuit regulation of SUDEP pathologies (Faingold et al. 2016; Petrucci et al. 2021; Zhang et al. 2016), the idea of a feedback system that can accurately detect and quickly respond to fatal seizures can be first tested in animal models of SUDEP by constructing a real-time rescuing system using the closed-loop electrical and on-demand optogenetic approaches (Armstrong et al. 2013; Tafazoli et al. 2020) (Figure 4).
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References


Faingold, C.L., Randall, M., and Tupal, S. (2010). DBA/1 mice exhibit chronic susceptibility to audiogenic seizures followed by sudden


with seizures correlate with postictal EEG suppression. Neurology 78: 1868–1876.


