An explanation for sudden death in epilepsy (SUDEP)

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Abstract
This review traces the examination of autonomic, cardiovascular, and respiratory derangements associated with seizure activity in the clinical and preclinical literature generally, and in the author’s animal model specifically, and concludes with the author’s views on the potential mechanisms for sudden death in epilepsy (SUDEP). An animal model that employs kainic acid-induced seizures on a background of urethane anesthesia has permitted unprecedented access to the behavior of autonomic, cardiovascular, and respiratory systems during seizure activity. The result is a detailed description of the major causes of death and how this animal model can be used to develop and test preventative and interventional strategies. A critical translational step was taken when the rat data were shown to directly parallel data from definite SUDEP cases in the clinical literature. The reasons why ventricular fibrillation as a cause of death is so rarely reported and tools for verifying that seizure-associated laryngospasm can induce obstructive apnea as a cause of death are discussed in detail. Many details of the specific kinetics of activation of brainstem neurons serving autonomic and respiratory function remain to be elucidated, but the boundary conditions described in this review provide an excellent framework for more focused studies. A number of studies conducted in animal models of seizure activity and in epilepsy patients have contributed information on the autonomic, cardiovascular, and respiratory consequences of seizure activity spreading through hypothalamus and brainstem to the periphery. The result is detailed information on the systemic impact of seizure spread and the development of an understanding of the essential mechanistic features of sudden unexpected death in epilepsy (SUDEP). This review summarizes translation of data obtained from animal models to biomarkers that are useful in evaluating data from epilepsy patients.

Keywords Seizure · Laryngospasm · Ventricular fibrillation · Obstructive apnea

Definition of SUDEP
Sudden unexpected death in epilepsy (SUDEP) is the sudden, unexpected death of someone with epilepsy, who was otherwise healthy. Attention to the condition in the last decade has resulted in refinements in the definition (“... a non-traumatic, non-drowning death that occurs in benign circumstances in an individual with epilepsy…” see e.g., [1, 2]), more detailed calculations of incidence (from about 1–9 deaths per 1000 patient years) [2–4], and the identification of key cardiopulmonary events that contribute to an overall pattern ending with death [3]. Qualifiers of “definite”, “probable”, and “possible” depend on the availability of autopsy or direct observations/recordings of terminal event and the presence or absence of a competing cause of death. “Definite” is used when competing causes of death are ruled out by autopsy or having directly observed/recorded the terminal event. “Probable” is used in the absence of autopsy data or likely alternative cause of death and confidence that the circumstances surrounding the death were otherwise benign. “Possible” is used when a competing cause of death exists and autopsy data are unavailable. A “plus” designation attached to the “definite” or “probable” definitions is used “when a concomitant condition other than epilepsy is identified before or after death, if the death may have been due to the combined effect of both conditions, and if autopsy or direct observations/recordings of terminal event did not prove the concomitant condition to be the cause of death” [1].
While the incidence of sudden deaths is < 10/1000 [2–4], the highest risk occurs in patients whose seizures are poorly controlled, and SUDEP is the leading cause of death in young adults with uncontrolled seizures. With an estimated 65 million people worldwide currently living with epilepsy, and hundreds of thousands of new diagnoses annually, SUDEP is a significant concern—especially if preventative or interventional strategies could be made available.

**Utility of animal models for SUDEP studies**

A wide range of animal models has been used to explore cardiac and/or respiratory derangements due to or associated with seizure activity that may contribute to an individual’s death (for wide-ranging reviews: [5, 6]). For example, research employing transgenic mouse models has suggested critical contributions from genetic mutations impacting serotonergic neurotransmission and function in brainstem respiratory centers [2, 7–9]. However, over a dozen mouse strains show audiogenic seizures [10].

Complicating the development and accepted value of animal models is that what is known and what is unknown about the circumstances of each human death has been used to question the appropriateness of particular animal models for the study of SUDEP. As examples, because of data that the majority of deaths occur at night (suggesting a circadian variance in some parameter) and when the individual was in bed (suggesting that, as with some infants, the airway might become obstructed by bedding) (reviewed in [2]), data from animal models not specifically incorporating these details are often dismissed as incomplete. Identification of linkages between the animal model and human pathophysiology has been challenging.

In audiogenic seizure-prone mice, death typically accompanies an extreme tonic phase that includes hindlimb extension (e.g., [8, 11–15]). The parallels of this convulsive activity to aspects of human motor convulsions and the systemic physiological impact of this seizure type have not been fully established, but the audiogenic seizure phenotype has been extremely valuable in epilepsy research.

Our approach to the SUDEP mechanism has been different. Having used urethane as an anesthetic for work on hippocampal theta rhythm, one of the best-studied EEG signals reflecting synchrony in the limbic system [16], we found that seizure activity could be induced under urethane, but remarkably, motor convulsions were absent [17, 18]. This preparation has permitted an extraordinary range of recordings during seizure activity [19]. Some recordings, in fact, such as continuous and direct visualization of the larynx during seizure activity, have not been possible previously [20]. The seizure activity induced by kainic acid is of limbic cortical origin, thus resembling temporal lobe seizures, and follows a similar pattern to that seen when administered to unanesthetized animals, namely a period of seizure activity that can be long lasting enough to meet the definition of status epilepticus, followed by much briefer discrete seizures over. The pronounced metabolic derangements associated with status epilepticus are also not present, due to the absence of motor convulsions (e.g., [21, 22]).

**Panautonomic activation during limbic cortical seizure activity**

Access to autonomic premotor and preganglionic neurons from limbic cortical regions is relatively direct, with projections from subiculum into paraventricular nucleus of the hypothalamus (PVN; there are also projections where limbic cortical and insular cortical outputs are relayed through the amygdala) [23–26], and projections from PVN into medullary areas for both sympathetic premotor and parasympathetic preganglionic activation. Projections also engage respiratory rhythm generation and motor areas (e.g., [7, 8, 11]). Many of these projections are reviewed in [27, 28] and highly schematized in Fig. 1.

Clinical reports and experimental studies have demonstrated changes in cardiac, respiratory, gastrointestinal, and genitourinary function before, during, and after a seizure (see e.g., [29–41]). Significant autonomic effects of seizures more commonly occur in association with generalized tonic–clonic seizures or partial seizures originating in the temporal lobe [31, 42, 43] than in association with absence seizures or focal seizures that minimally impact limbic or insular cortices. With a starting view that a seizure that causes death must do so by spreading to autonomic brain regions to ultimately impact cardiovascular or respiratory function, we began by looking for such spread in recordings from autonomic peripheral nerves.

Each seizure was able to increase parasympathetic activity by about tenfold and sympathetic tone by nearly as much [36]. Although both divisions of the autonomic nervous
system showed significant increases in activity, the resulting change in heart rate and rhythm, which could be either brady- or tachy-arrhythmia, depended upon the relative levels in each division and the baseline conditions (Fig. 2).

Multiple studies have sought to define the extent to which seizures alter cardiac rhythm (e.g., [43–45]). Seizures that produce sinus arrhythmias provoke tachycardia in up to 99% of cases [46], with HR increases to 120–150 bpm [45, 47, 48]. Episodes of ictal bradycardia to a HR of 20–40 bpm have been reported [48]. Other changes to cardiac rhythm have been noted during seizures, including premature atrial and ventricular contractions [44] and ST-segment changes indicating cardiac ischemia [49, 50]. The main finding from many of the clinical and animal studies was that seizure-induced autonomic changes were transient: when the seizure abated, ANS activity reverted to normal pre-seizure levels.

Although less common, bradyarrhythmias, including periods of asystole, have been reported in epilepsy patients [51–58]. In our animal studies of seizure-induced bradyarrhythmia, extremes significantly impacted cardiac output and we showed in physiological simulations that the resulting decrease in brain blood flow would terminate any ongoing seizure activity (Fig. 3) [59, 60]. Similar examples of seizure termination have been reported in the clinical literature [61, 62]. The resulting conclusion with regard to a mechanism of sudden death was that it may not be possible for severe autonomic derangements to be lethal. If the seizure was the stimulus for increased vagal tone and bradyarrhythmia, terminating the seizure would end the stimulus and permit a return to baseline conditions. A seizure-induced overdrive of the vagal output to the heart might never be lethal because it would be self-terminating.

**Ventricular fibrillation**

Cardiac fibrosis and hypertrophy, increased QT interval lengths and dispersion, evidence for increased sympathetic tone and decreased parasympathetic tone, and the commonly acknowledged observations of ictal tachycardia all raise the question of whether ventricular fibrillation (VF) may be a cause of SUDEP (e.g., [63], see also [64]). Generally, decreased vagal protection increases the risk for ventricular fibrillation (VF; [65]). To date, four cases of VF arising from seizures [66, 67], plus one case of VF in relation to seizure-induced takotsubo cardiomyopathy [68] have been documented. In addition, epilepsy has been shown to be a risk factor for sudden cardiac arrest ending in ventricular fibrillation [69, 70].

We looked at conditions that might favor ventricular fibrillation, a condition which when initiated would be lethal whether a precipitating seizure continued or not. Briefly, we found that entry into ventricular tachycardia and ventricular fibrillation could occur spontaneously under narrow conditions of moderate, but not severe hypoxia, sympathetic overdrive, and minimal vagal activity.

![Simplified schematic of pathways from cortical regions to the brainstem to influence autonomic outflow. Adapted from [105] with permission. Lines denote bidirectional connections, and arrows denote monodirectional projections. The key point is that pathways exist for seizure spread from limbic cortical areas (via subiculum) to hypothalamus (including paraventricular nucleus, PVN) and to brainstem regions serving as parasympathetic motor and sympathetic premotor functions. Relayed projections through the amygdala are even more prominent. Projections from neocortical regions, including insular cortex, have their own access to the hypothalamus and brainstem nuclei. The result is a multitude of pathways for seizure spread to impact autonomic and respiratory brainstem regions. NTS nucleus of the tractus solitarius, RVLM rostral ventrolateral medulla](image)
Even small amounts of vagal activity were protective. Most interesting was the finding that repeated seizure activity in rats led to cardiac dilatation that actually lowered the already small risk for ventricular fibrillation [72]. Enlargement of the overall dimension of the heart by increasing ventricular cavity size and not increasing ventricular wall thickness is eccentric hypertrophy, and this increases the path length for conduction within the ventricular myocardium. The longer path length might explain the increased difficulty in initiating ventricular fibrillation in

**Fig. 2** Recordings from peripheral autonomic nerve and ganglion to demonstrate seizure-induced increases in both divisions of the ANS. a Increases in vagus nerve activity during a single discrete seizure (shown divided into for sequential segments where each segment shows arterial blood pressure, hippocampal EEG, and vagus nerve multi-unit activity). Note that the massive vagal activity increases by the second and third segments. b Increases in multi-unit activity recorded in superior cervical ganglion, even during a very brief seizure. a and b were taken from [36] with permission. c Percent change in mean activity (EEG autonomic peripheral nerve or ganglion) and hear rate from the beginning of bradycardic and tachycardic seizures to the peak autonomic activity during the seizure. The peak-to-peak amplitude of seizure EEG (black) tended to be larger when seizures were associated with bradycardia in ECG (green). Parasympathetic (blue) and sympathetic (red) activity was always increased, but the relative levels of the sympathetic and parasympathetic activity changes (and the starting heart rate—not shown) contribute to the final condition of bradycardia or tachycardia. Adapted from the doctoral thesis of Isaac Naggar with permission (Stewart, mentor). d Portion of a schematic diagram (full diagram is shown in Fig. 9) to emphasize the sequence of events: seizure activity changes autonomic activity; seizure ends; autonomic activity returns to pre-seizure levels. EEG electroencephalogram, ECG electrocardiogram
dilated hearts, i.e., a lower incidence of reentrant arrhythmias. Protection by the vagus and the very specific conditions necessary for destabilizing the ventricular conduction pathways suggested that seizure-induced ventricular fibrillation was not the most likely cause of sudden death due to seizure activity.

Whereas the most common cause of VF in humans is regional cardiac ischemia in the setting of myocardial infarction, global hypoxemia has been implicated in some conditions to produce arrhythmias (e.g., obstructive apnea; [73], cf. [74]). The closest we came to triggering a run of VF with a “vagal storm” supports the notion that global
hypoxemia can destabilize the conduction pathways of the heart: a 50-Hz vagal stimulus train initiated a run of ventricular tachycardia in our rat model, but this was relatively quickly suppressed by the continuation of the vagal stimulus train (Fig. 4c). We suspect that periods of severe bradyarrhythmia or asystole may disable some regions of the intrinsic conduction system or ventricular myocardium thereby disrupting the normal sequential activation of myocytes and favoring VF.

Airway occlusion by laryngospasm

As the conditions for VF are highly constrained and appear to disfavor VF with repeated seizures, we sought a more likely explanation for sudden death. Seizure activity significantly alters respiratory rhythm, causing an irregular, but increased respiratory rate and an irregular, but decreased tidal volume, leaving a relatively unchanged minute ventilation [20].
Respiratory changes during seizures can be significant (reviewed in [2, 7, 75]). Reports of ictal tachypnea, bradypnea, and apnea (e.g., [3, 20, 76–82]) all point to an impact of seizure activity on respiratory rhythm generation and thereby a role in oxygen desaturation during seizures [77, 80].

Animal studies involving rats [18, 20, 36], mice [11, 83], cats [84, 85], and sheep [86, 87] have all contributed to a demonstration of the importance of ictal hypoxemia in seizure-induced death.

Laryngospasm sufficient to produce partial airway occlusion was also typical [20]. High-frequency “convulsive” activity of the vocal folds was described as a feature of seizure activity, but occasionally, the spasm of laryngeal musculature was such that complete airway occlusion with obstructive apnea occurred [20].

Interestingly, in our experiments, animals with a protected airway (tracheal implant, endotracheal tube, or tracheal window) never died during seizure activity, but animals without airway protection died more than 20% of the time [20].

We found during seizure activity that episodes of central apnea (defined as periods of no airflow and no evidence of respiratory effort) and obstructive apnea (defined as periods of no airflow with evidence of inspiratory effort) were both observed [20, 88], but only the periods of obstructive apnea were associated with severe systemic consequences and death (Fig. 5). The basis for the airway obstruction was demonstrated to be seizure-induced laryngospasm [20]. This was sufficient to completely prevent airflow and precipitated rapid desaturation, ischemic cardiac rhythm and functional changes, respiratory arrest, cardiac arrest, and finally death. Other, indirect evidence has supported laryngospasm, most significantly, pulmonary edema (e.g., [14, 89–91]).

Central apneic episodes were associated with smaller changes in oxygen saturation (e.g., Fig. 6) and were argued to result from seizure-triggered activation of the diving reflex [88], a “normal” response that results from co-activation of both divisions of the autonomic nervous system (Fig. 7) [92–96].
The mammalian diving response is an extremely powerful reflex response to nasopharyngeal stimulation that results in apnea, bradycardia, and increased systemic blood pressure, highlighting the integration of these systems. The strongest evidence that the diving reflex is not the mechanism for airflow cessation during seizure-induced periods of central apnea is the fact that the HR changed in our animals by less than 10% [88], whereas other studies have reported HR changes over 50% in rats (e.g., [97–99]). In fact, we initially compared seizure-induced central apneic episodes to breath holding [20] because periods of seizure-induced central apnea were relatively free of the intense autonomic response that comes during attempts to breathe against a closed airway or during asphyxiation (e.g., [100–102]).

The sympathetic response to airway occlusion is severe (e.g., [101]). We also find that seizure activity drives sympathetic outflow to the adrenal gland (Nobuhiro Watanabe and Mark Stewart, unpublished), amplifying the sympathetic impact of hypoxia during seizure activity. In fact, the sympathetic activity is critical for many of the cardiac performance changes (e.g., [59]).

![Diagram of laryngeal states for obstructive and central apneas](image)

**Fig. 6** Illustration of the active laryngeal states for both obstructive apnea due to laryngospasm and the seizure-associated periods of central apnea. Each panel shows a segment of EEG, multi-unit recurrent laryngeal nerve activity (RLN), and ECG. The RLN, which carries motor output for both laryngeal abductors and adductors, is active during both types of apnea. Note the significant slowing and ST changes associated with obstructive apnea, but no ECG changes associated with central apnea. Shown to the right are three ECG sweeps for each type of apnea to illustrate the pronounced ST segment elevation and slowing during obstructive apnea and the uniform PQRST complexes during central apnea. The asterisks above the ECG recording mark the times of the high-resolution sweeps shown to the right (also marked with asterisks). The recording illustrating obstructive apnea is taken from the end of a seizure; seizure activity is present from the beginning of the illustrated data and an estimate of seizure offset (based on a complete flatlining of EEG) is marked by an arrow. Calibrations on the figure. Taken from [20] with permission.
Translation to the bedside

As detailed as our studies have been, how could it be possible to translate results from rats, which are anesthetized, and induced to have seizures with a chemical convulsant to epilepsy patients?

The detailed publication of results from the MORTality in Epilepsy Monitoring Unit Study (MORTEMUS) [3] presented a sequence of events between seizure and death that included the onset of “terminal apnea” followed by cardiac...

Fig. 7 Illustration of respiratory rhythm reset and evidence that seizure-associated central apneic episodes result from a partial activation of the diving reflex brainstem circuitry. Taken from [88] with permission. Raw data record shows two events, the first associated with a flat head-out plethysmogram and the second showing a small ripple present in the plethysmogram. Both events are similarly associated with brief bursts in the EEG that can be isolated by high-pass filtering (top sweep). When non-flat plethysmogram periods are superimposed using the brief bursts to align the records, the plethysmograms superimpose, indicating a reset of the respiratory rhythm with each burst. The periods of no air movement are consistent with activation of the diving reflex efferent pathways and resemble responses induced by actual activation of the diving reflex with nasopharyngeal mist or irrigation with water (data not shown). a Example record of two events, one event that includes complete cessation of breathing effort as evidenced by flatline plethysmograph, and a later event where respiratory effort did not stop. Records from top to bottom are high-pass filtered EEG (top EEG channel was filtered), plethysmograph, ECG, and two EEG recordings, one from each hemisphere over dorsal hippocampus. The pronounced artifacts evident on the filtered EEG trace are associated with the central apneic episode lasting about 1.5 s (onset indicated by arrow), and a later event that does not include cessation of airflow. High-frequency events are evident in the full bandpass EEG records. Segment of raw data is taken from a longer seizure episode; the onset and offset of the seizure itself are not illustrated. Calibrations are 0.025 mV filtered EEG, 0.2 ml plethysmograph, 0.05 mV ECG, and 0.2 mV for both EEG channels. Time calibration is 2 s. b Twenty superimposed sequential non-apneic events from a single animal to highlight the complete alignment of the pre- and post-artifact plethysmograph records. This alignment, given the broader range of phases leading up to the event onset, indicates a resetting of the respiratory rhythm, but the rhythm after about 1–1.5 s becomes highly variable. Calibrations are 0.05 mV filtered EEG and 0.2 ml plethysmograph. Time calibration is 1 s
arrest. A supplement to the paper showed raw data from the key cases that led to this overall sequence. In analyzing our data, we found that during inspiratory attempts against an occluded airway, EMG signals from the effort mixed with the ECG recordings [20, 103]. The MORTEMUS paper interpreted these signals as evidence of actual breathing, and we could show with certainty that these events also reflected effort during airway occlusion and, further, that the amplitude of these signals correlated with the effort [103, 104].

In fact, two complementary biomarkers can be derived from ECG records (Fig. 8). The first is the EMG-based signal described above and the second biomarker is an abrupt increase in RR interval variance due to both the bradycardia and conduction block as well as the development of very short intervals associated with attempts to inspire during obstruction. We believe that this linkage between our model and the clinical data argues strongly for airway obstruction in the human cases and that seizure-induced laryngospasm may link the ictal state to postictal terminal events. Further, we argue that these biomarkers can...
be applied to past cases to subclassify possible causes of death and used to monitor patients to improve outcomes by signaling times of airway obstruction.

**Prevention and intervention**

The challenge for identifying the mechanism of a clinical condition that occurs rarely and under circumstances where physiological data are rarely available is daunting. The availability of a small animal model that can be extensively manipulated and monitored opens a number of doors for accelerating advances in SUDEP research. Our animal model has been manipulated to offer experimental access to many of the points on the path from seizure to death (Fig. 9). This or equivalent models can be studied to define the critical window of opportunity for resuscitation, specific poor ejection fraction will lead to decreased brain blood flow and terminate the seizure). Once the point of respiratory arrest is reached, relaxation of the laryngospasm or artificially opening the airway will not be sufficient for resuscitation. There is clearly a window of opportunity for cardiopulmonary resuscitation (CPR) to resuscitate patients at this point, but resuscitation depends on how quickly CPR can be applied [3]. As a preventative measure, the best prevention remains good control of seizures. As interventions, the opportunity for resuscitation after VF or laryngospasm is short. Attention to differentiating between these two possibilities will save additional time. Critically, access to an animal model such as ours will permit the exploration of additional preventative or interventional approaches resuscitation interventions, and approaches that can lead to prevention.

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