UAB
Universitat Autònoma de Barcelona

# ELECTROCLINICAL FEATURES AND CARDIORESPIRATORY DYSFUNCTION IN GENERALIZED CONVULSIVE SEIZURES

**Laura Vilella Bertran**

UAB
Universitat Autònoma de Barcelona

# ELECTROCLINICAL FEATURES AND CARDIORESPIRATORY DYSFUNCTION IN GENERALIZED CONVULSIVE SEIZURES

**TESI DOCTORAL**

**Author**
Laura Vilella Bertran

**Directors**
Dr. Samden D. Lhatoo, MBBS. MD. FRCP (Lon)
Dr. Nuria Lacuey Lecumberri, MD. PhD

**Tutor**
Estevo Santamarina Pérez, MD. PhD

**Doctorate Program in Medicine**
**Department of Medicine**
**Universitat Autònoma de Barcelona**
**Barcelona, 2024**

UAB
Universitat Autònoma
de Barcelona

**TESI DOCTORAL**

# ELECTROCLINICAL FEATURES AND CARDIORESPIRATORY DYSFUNCTION IN GENERALIZED CONVULSIVE SEIZURES


**Author**

Laura Vilella Bertran

**Directors**

Dr. Samden D. Lhatoo, MBBS. MD. FRCP (Lon)

Dr. Nuria Lacuey Lecumberri, MD. PhD

**Tutor**

Estevo Santamarina Pérez, MD. PhD



**Doctorate Program in Medicine**

**Department of Medicine**

**Universitat Autònoma de Barcelona**

**Barcelona, 2024**

A la meva família, pel seu suport incondicional.

A les persones afectes d'epilèpsia, la nostra font de motivació i sense la participació de les quals aquesta tesi no seria possible.

# ABBREVIATIONS

Afib: atrial fibrillation
ASM: antiseizure medications
AVB: atrioventricular block
CI: confidence interval
EEG: electroencephalogram
ESA: exaggerated sinus arrhythmia
ESAWB: exaggerated sinus arrhythmia with bradycardia
Est: beta estimate
GCS: generalized convulsive seizures
GEPR-9: genetically epilepsy-prone rats 9
HFP: high-frequency power
HRV: heart rate variability
IBE: International Bureau Against Epilepsy
ICA: ictal central apnea
ILAE: International League Against Epilepsy
LFP: low-frequency power
MRI: magnetic resonance imaging
NSVT: non-sustained ventricular tachycardia
OR: odds ratio
PAG: periaqueductal gray
PCCA: postconvulsive central apnea
PGES: Postictal Generalized Electroencephalographic Suppression
SEGP: Supressió Electroencefalogràfica Generalitzada Postictal (catalan)
$SpO_2$: peripheral capillary oxygen saturation
SUDEP: Sudden Unexpected Death in Epilepsy
SVT: supraventricular tachycardia
VEEG: video-electroencephalography
VF: ventricular fibrillation
VNS: Vagus Nerve Stimulation

# TABLE OF CONTENTS

# ABSTRACT

Generalized convulsive seizures (GCS) have been consistently associated with Sudden Unexpected Death in Epilepsy (SUDEP) in case-control studies. Animal studies have shown that GCS may produce cardiorespiratory collapse through seizure-induced brainstem dysfunction, affecting crucial structures for cardiorespiratory homeostasis. Moreover, semiology observed during GCS in humans can resemble the decerebrate and decorticate posturing seen in comatose patients, suggesting varying degrees of cerebral and brainstem compromise.

We hypothesized that peri-ictal brainstem semiology might predict the severity of a GCS, based on cardiorespiratory dysfunction and postictal generalized electroencephalographic suppression (PGES). To test our hypothesis, we conducted a multicentric and prospective analysis of GCS-induced cardiorespiratory dysfunction and PGES and their relationship with peri-ictal brainstem semiology in adult patients admitted for VEEG monitoring.

The results of our study show that peri-ictal brainstem semiology is a biomarker of GCS severity defined by PGES and variables of respiratory dysfunction but not of cardiac arrhythmias of interest (exaggerated sinus arrhythmia with bradycardia [ESAWB], asystole, bradycardia, atrioventricular block [AVB], supraventricular tachycardia [SVT], atrial fibrillation [Afib], non-sustained ventricular tachycardia [NSVT] and, ventricular fibrillation [VF]). Specifically, any ictal brainstem semiology (decerebration, decortication, or hemi-decerebration) during GCS increases the risk of PGES and is associated with larger $SpO_2$ desaturations. Moreover, ictal decerebration is associated with longer PGES. Regarding postictal brainstem semiology, this is associated with a sixfold increased risk of PCCA and longer hypoxemia and $SpO_2$ recovery after GCS. Potentially fatal cardiac arrhythmias such as asystole, bradycardia, AVB, SVT, Afib, NSVT, and VF are rare, and along with ESAWB, are unrelated to peri-ictal brainstem semiology, PGES, and respiratory dysfunction. This suggests that arrhythmias caused by GCS are unrelated to cortical suppression or hypoxia and may be due to underlying cardiac occult abnormalities.

# RESUM

Les crisis convulsives generalitzades són el factor de risc més consistent en tots els estudis de casos i controls sobre la mort sobtada en epilèpsia. Els estudis animals han demostrat que les crisis convulsives generalitzades són capaces de provocar el col·lapse cardio-respiratori mitjançant la inducció de disfunció tronc-encefàlica en estructures crucials per l'homeòstasi cardio-respiratòria. A més a més, la semiologia observada durant les crisis convulsives generalitzades en humans és similar a la postura de decerebració i decorticació que presenten els pacients en coma, suggerint diferents graus d'afectació cortical i del tronc de l'encèfal.

La hipòtesi d'aquest treball és que la semiologia tronc-encefàlica peri-ictal pot predir la severitat d'una crisi convulsiva generalitzada, basada en el grau de disfunció cardio-respiratòria i de la supressió electroencefalogràfica generalitzada post-ictal (SEGP). Per tal de validar aquesta hipòtesi, s'ha dut a terme una anàlisi prospectiva i multicèntrica sobre la disfunció cardio-respiratòria i la SEGP produïda per les crisis convulsives i la seva relació amb la semiologia tronc-encefàlica peri-ictal, en pacients admesos per video-monitorització EEG.

Els resultats d'aquesta tesi doctoral mostren que la semiologia tronc-encefàlica peri-ictal és un marcador de severitat de les crisis convulsives generalitzades, definida per la SEGP i el grau de disfunció respiratòria, però no de les arrítmies cardíaques d'interès (arrítmia sinusal exagerada amb bradicàrdia, asístole, bradicàrdia, bloqueig auriculo-ventricular, taquicàrdia supraventricular, fibril·lació auricular, taquicàrdia ventricular no sostinguda i fibril·lació ventricular). Concretament, qualsevol tipus de semiologia tronc-encefàlica ictal (decerebració, decorticació o hemi-decerebració) durant les crisis convulsives generalitzades, augmenta el risc de SEGP i s'associa a un major grau de dessaturació. A més a més, la decerebració ictal, s'associa a una major duració de la SEGP. Pel que fa a la semiologia tronc-encefàlica post-ictal, aquesta s'associa a sis cops més risc d'apnea central post-convulsiva i a una major duració de la hipoxèmia i de la recuperació de la dessaturació després de les crisis convulsives generalitzades. Les arrítmies potencialment fatals, com l'asístole, la bradicàrdia, el bloqueig auriculo-ventricular, la taquicàrdia supraventricular, la fibril·lació auricular, la taquicàrdia ventricular no sostinguda i la fibril·lació ventricular són infreqüents, i juntament amb l'arrítmia sinusal exagerada amb bradicàrdia, no s'associen a la semiologia peri-ictal tronc-encefàlica, a la SEGP ni a la disfunció respiratòria. Aquests resultats suggereixen que les arrítmies produïdes per les crisis convulsives generalitzades no estan relacionades amb la supressió cortical ni amb la hipòxia i probablement siguin degudes a anomalies cardíaques ocultes subjacents.

# 1. INTRODUCTION

## 1.1. Epilepsy and epileptic seizures

### 1.1.1. Definition of epilepsy and epileptic seizure

The terms epilepsy and epileptic seizure had commonly been used interchangeably in literature until 2005 when the International Bureau for Epilepsy (IBE) and the International League Against Epilepsy (ILAE) unequivocally defined these terms.(1, 2) According to this consensus document, an *epileptic seizure* is the clinical presentation of an abnormal excessive or synchronous neuronal activity in the brain. In contrast, *epilepsy* is a brain disease characterized by a tendency to have recurrent epileptic seizures. Neurobiological, cognitive, and psychological consequences accompany the diagnosis of epilepsy.(2)

The conceptual definition of epilepsy set the grounds for a practical (operational) definition of epilepsy in 2014, applicable to clinical diagnosis.(3) According to the ILAE official report, *epilepsy* is a disease defined by any of the following conditions: 1) Two or more unprovoked (or reflex) seizures occurring at least 24 hours apart 2) One unprovoked (or reflex) seizure and a likelihood of additional seizures comparable to the general recurrence risk ($\geq$60%) after two unprovoked seizures within the following ten years 3) When fulfilling diagnostic criteria for an epileptic syndrome.(3)

### 1.1.2. Epidemiology of epilepsy

At least 5-10% of the population will have an epileptic seizure during their lifetime.(4) According to population-based studies, the point prevalence of active epilepsy is 6.38/1,000 persons, and the lifetime prevalence is 7.60/1,000 persons.(5) The incidence rate of epilepsy is 61.4/100,000 person-years.(5) Overall, it is estimated that there are 400,000 people with epilepsy in Spain and 3.4 million patients in the United States.(6, 7)

The incidence of epilepsy has a biphasic distribution, with peaks during the first year of life and above 75 years of age.(8) In contrast, epilepsy prevalence peaks during adolescence and early adulthood, decreasing after the age of 30 and becoming fairly constant for the remainder of life, likely due to increased mortality in the older age groups.(5) The lifetime prevalence and incidence rate of epilepsy have been reported to be higher in low to middle-income countries.(5)

### 1.1.3. Seizure classification

The first seizure classification proposal was led by Gastaut in 1964 and formally established in 1969.(9, 10) Over time, with an increasing understanding of seizure physiopathology, this classification has faced further revisions. The most recent operational seizure classification by the ILAE in 2017 is based on determining whether the initial manifestations of the seizure are indicative of a *focal*, *generalized*, or *unknown onset*. These seizure types can be subdivided into *motor* and *non-motor onset* seizures, depending on whether motor features are predominant at seizure onset. Focal onset seizures can be further classified based on the retention of awareness into *focal aware* seizures and *focal* seizures *with impaired awareness*.(11)

According to this classification, tonic-clonic seizures can evolve from focal-onset seizures (focal to bilateral tonic-clonic seizures) or be classified as generalized-onset motor seizures or as having an unknown onset. Tonic, clonic, and myoclonic seizures can also be a subcategory of focal and generalized motor onsets. Myoclonic-tonic-clonic seizures are classified as generalized-onset motor seizures but not as focal-onset seizures.(11)

### 1.1.4. Generalized convulsive seizures: clinical features and pathophysiology

Gastaut and Broughton provided one of the most exquisite observations on generalized tonic-clonic seizures in 1972.(12) In this work, they described in great detail generalized tonic-clonic seizure phases with the sequence of motor involvement in each of them. First, there is the *tonic phase*, characterized by a sustained muscle contraction, initially of the flexor muscles in the axis and proximal arms. This results in abduction, external rotation, and elevation of the arms with semiflexed elbows and an overall body posture of *emprosthotonos*. This is followed by tonic extension beginning again in the axial muscles, producing a contraction of the thoracic and abdominal muscles against a tonic glottis, which results in the “epileptic cry.” Tongue-biting is expected during this phase. The arms progressively lower in adduction until they are crossed in the chest and finally extend at the elbow and pronate. The legs, feet, and big toes also extend, resembling Babinski’s sign. The overall body posture is of *opisthotonos*. After 10-20 seconds, the muscle tone decreases recurrently, predominantly in the peripheral muscles, resulting in a fine tremor called the *vibratory period*. Finally, the relaxation periods become prolonged enough to intermittently disrupt the tonic contraction, producing the violent jerks of the *clonic phase,* which lasts for 45-50 seconds. Patients can also bite their tongue during this period and may have clonic cries with each recurrent contraction. In the *immediate postictal period*, Gastaut and Broughton observed what had been underreported by classical authors. Instead of complete relaxation and recovery, they described a new phase of tonic muscle contraction within five seconds

of the last clonic jerk. This *postictal tonic contraction* predominantly affects the face and masticatory muscles. Still, if the limbs participate, the posture resembles a "functional decerebrate state" and may last from seconds to less than 5 minutes. Patients persist with loss of consciousness during this phase; pupillary and cutaneous reflexes are usually absent, whereas deep tendon reflexes are brisk. Finally, there is complete muscle atonia and progressive reactivity to stimuli until full recovery of consciousness or falling asleep. After that, patients complain of headache and tiredness and are amnestic for the event.(12)

Despite the stereotyped sequence, the authors acknowledged the existence of variations, such as seizures with a very brief tonic phase (resembling clonic seizures at onset) and seizures with asynchrony between the right and left sides of the body, raising the question of whether these are indeed two independent seizures occurring almost simultaneously.(12) The term generalized convulsive seizure (GCS) is often used for seizures that have a bilateral clonic phase, regardless of the presence of a preceding tonic phase, likely reflecting different physiopathology (generalized vs focal onsets).(13)

Lhatoo and Lüders provided further descriptions of semiology during focal onset GCS.(13) For this, they analyzed the semiology of 24 seizures (14 patients) from the point where motor bilateral involvement of the arm and/or leg was seen concurrently with complete loss of consciousness. During the tonic phase, they observed four types of posturing: 1) Arms flexed at the elbows with an extension of the lower limbs, seen in 35% of the seizures. 2) Arms extended at the elbow with an extension of the lower limbs in 26% of the seizures. 3) Similar to type 1 but with flexion of the lower limbs, in 9%. 4) Bilateral asymmetric tonic posturing, with flexion in the limbs of one side and extension of the contralateral limbs, seen in 30%. In 17% of the seizures, seizures started in the clonic phase.

Gastaut and Broughton also elegantly described the autonomic changes accompanying tonic-clonic seizures by analyzing electrocardiography, sphygmomanometry, electrodermography, electromyography, pupillary measurement, and intravesical pressure measurements.(12, 13) At seizure onset, they described a sudden decrease in skin resistance, increased blood and intravesical (bladder) pressures, and tachycardia. These continue during the seizure proper, along with apnea, mydriasis (which is rhythmical with the clonic jerks, resulting in hippus), glandular hypersecretion, and skin changes. Apart from apnea, all the autonomic changes peak in the tonic phase and decrease during the clonic phase. In the immediate postictal period, they described complete electroencephalogram (EEG) silence, recurrence of mydriasis, tachycardia sometimes with cardiac arrhythmia, tachypnea, stertorous breathing, urinary incontinence, and rarely, ejaculation and fecal incontinence. During the recovery phase, EEG shows slow wave activity, and vegetative functions return to normal.(12)

The physiopathology of GCS is still a matter of debate in epileptology. The EEG pattern at onset shows a brief period of attenuation or low-voltage fast activity progressively evolving into a 10 Hz rhythm that increases and modulates in amplitude, known as the *epileptic recruiting rhythm*.(12) This has been compared to the rhythms obtained by Dempsey and Morrison in 1942 when stimulating thalamic nuclei.(12, 14) In fact, Penfield and Jasper conceptualized the "centrencephalic" system, which includes the brainstem and the diencephalon and integrates the function of the cerebral hemispheres. Under the centrencephalic theory, seizures would originate deep in the "centrencephalon" or involve the whole system due to diffuse projections. According to this, GCS semiology results from the activation of the reticulospinal and sympathetic fibers arising from the brainstem modulated by thalamic-reticular connections.(12, 14)

Most of the studies about GCS physiopathology come from animal models, with divergent observations among studies. One of the models that supports the "centrencephalic" hypothesis is audiogenic kindling in genetically epilepsy-prone rats (GEPR-9). Before kindling, the epileptogenic network is limited to the brainstem, and semiology resembles epileptic spasms. After kindling, the semiology consists of tonic seizures followed by clonus, with accompanying epileptiform EEG activity.(15) In other animal models, tonic-clonic seizures have been reproduced with brainstem stimulation prior to or after brainstem kindling.(15-18) Moreover, the dorsal periaqueductal gray kindling has been shown to transfer to the amygdala.(18)

However, in other studies, neocortical or systemic injection of bicuculline in cats produces a neocortical seizure pattern similar to the tonic pattern in GCS, while the thalamus continues to show EEG spindles. Similar neocortical activity is seen when the injection is performed in the neocortex of athalamic rats, suggesting that the neocortex is the essential foundation for GCS generation.(19-23)

## 1.2. Sudden Unexpected Death in Epilepsy (SUDEP)

### 1.2.1. Definition of SUDEP and SUDEP classification

Sudden Unexpected Death in epilepsy was first described more than a century ago.(24) However, SUDEP was not systematically studied until the late 1970s and 1980s. In 1997, two definitions for SUDEP were published.(25, 26) These were unified in 2012 to facilitate SUDEP identification and harmonize SUDEP research.(27)

*Sudden Unexpected Death in Epilepsy* describes a category of death in a person with epilepsy in which postmortem examination does not identify a pathologic or toxicologic cause of death. Documented status epilepticus, trauma, or drowning exclude the diagnosis of SUDEP according to the unified definition.(27)

Since autopsies are not systematically performed and other comorbidities may mask the cause of death, many SUDEP might be underreported using the definition above. For this reason, depending on the availability of postmortem examination as well as the presence of other comorbidities that may have contributed to death, SUDEP can be classified into several categories:(27)

*Definite SUDEP*: fulfills the unified definition explained above. A postmortem examination was conducted and did not identify the cause of death.

*Definite SUDEP Plus*: postmortem examination was performed, fulfilling the criteria for definite SUDEP, although there is a concurrent condition other than epilepsy. Death could be due to the combined effect of both illnesses, but there is no evidence for the coexistent condition to be responsible for the death.

*Probable SUDEP/Probable SUDEP Plus*: same as definite SUDEP/definite SUDEP plus, respectively, but without an autopsy.

*Possible SUDEP*: there is a competing cause of death.

*Near-SUDEP/Near-SUDEP Plus*: a person with epilepsy survives at least one hour (arbitrarily set) of resuscitation after a cardiorespiratory arrest that has no etiology after investigation.

*Not SUDEP*: there is an identified cause of death.

*Unclassified*: It is not possible to classify because of lacking information.

### 1.2.2. Epidemiology of mortality in epilepsy and SUDEP

Patients with epilepsy face a risk of death that is 2-5 folds higher than the general population, with an increased risk of sudden death up to 27 folds.(28-30)

Death in patients with epilepsy can be *epilepsy-related or not epilepsy-related*. Epilepsy-related deaths are the most common cause of death in patients with epilepsy.(31) These can

be further classified as *directly due to epilepsy*, *indirectly due to epilepsy,* and *due to the underlying neurological disease*.(32) The first cause of death in patients with epilepsy is the underlying neurological disease, specifically brain tumors.(31) SUDEP is the commonest category of death directly related to epilepsy.(31)

Sudden Unexpected Death in Epilepsy has an incidence of 1.2/1,000 patient-years in the general adult epilepsy population and 0.22/1,000 in children.(33, 34) The incidence of SUDEP has been reported to be the highest among surgical candidates or patients who do not become seizure-free after epilepsy surgery, with an incidence of 6.3 to 9.3/1,000 people-years in this group.(35) Considering the prevalence of active epilepsy, SUDEP claims the lives of ~ 3,000 people in the United States and 230 people in Spain every year.(5)

Sudden Unexpected Death in Epilepsy typically affects young adults (21-50 years old).(36) For this reason, although SUDEP is rare, it is the second leading cause of potential years of life loss of neurological etiology, only after stroke.(36) Therefore, SUDEP represents a significant public health burden.

### 1.2.3. Risk factors for SUDEP

Numerous studies assessing potential SUDEP risk factors have been conducted throughout the years.(37-39) Across all these studies, the most consistent risk factor for SUDEP has been the presence of GCS.

In the most recent case-control study, a positive history for GCS was associated with a 10-fold SUDEP risk (OR 9.60 [95% CI 3.44–26.82]) compared to those patients without GCS. SUDEP risk was 27-fold increased (OR 26.81 [95% CI 14.86–48.38]) when GCS had occurred in the preceding year (compared to patients who did not have any seizures at all the prior year), whereas no excess risk of SUDEP was seen in those patients experiencing only non-GCS seizures in the year prior. Risk of SUDEP was higher among those patients with 4-10 GCS per year (OR 31.87 [95% CI 15.95–63.67]) than in those with 1-3 GCS per year (OR 22.14 [95% CI 12.74–38.46]). In the same study, SUDEP risk was increased in those patients who did not share a household (OR 5.01 [95% CI 2.93–8.57]) or their bedroom (OR 2.28 [95% CI 1.14–4.58]). An interaction analysis showed that not sharing a bedroom and having GCS conferred a SUDEP OR of 67.10 (95% CI 29.66–151.88), with an estimated proportion attributable to interaction of 0.69 (95% CI 0.53–0.85), meaning that sharing a bedroom or not having had GCS in the year prior could have avoided 69% of SUDEP cases.(39)

In contrast to other studies, no association between age at epilepsy onset and SUDEP risk was found. However, in patients with more than three GCS per year, the risk was higher within the first five years after the diagnosis of epilepsy and declined afterwards, suggesting that certain patients would be less sensitive to GCS effects.(40) Patients with unknown epilepsy types faced a threefold SUDEP risk (OR 3.51 CI 95% [1.44–8.55]) compared to those with generalized epilepsies.(39) Although it seemed that patients with focal epilepsies had a higher risk of SUDEP when compared to patients with generalized epilepsies, no differences were found when adjusting by the number of GCS during the year prior, indicating that it is the GCS part of seizures that poses the patient at risk for SUDEP.(40)

Regarding comorbidities, a history of intellectual disability or a psychiatric condition did not increase SUDEP risk when adjusted for GCS frequency. In contrast, a history of substance abuse and alcohol dependence did.(39)

Antiseizure medications (ASM), either monotherapy or polytherapy, were associated with a protective effect against SUDEP when adjusted for GCS frequency, which aligns with prior publications.(39, 41, 42) Despite recent safety concerns regarding the *in vitro* pro-arrhythmogenic properties of lamotrigine, no individual ASM, including lamotrigine, has consistently been associated with an increased SUDEP risk.(39, 43-45)

Lastly, vagus nerve stimulation (VNS) was associated with a protective effect against SUDEP after adjusting for GCS frequency, living conditions, and ASM treatment. In contrast, no association was seen between epilepsy surgery and SUDEP.(39) However, conflicting data exists in this regard since other studies have shown that epilepsy surgery may reduce overall mortality and SUDEP risk in patients with pharmacoresistant epilepsy.(46, 47) Therefore, larger studies are needed to investigate the role of epilepsy surgery in SUDEP.

### 1.2.4. Physiopathology of SUDEP

The exact physiopathology underlying SUDEP still needs to be elucidated. However, there is current evidence of functional and structural damage in essential brain structures responsible for cardiorespiratory control and arousal in patients with epilepsy, which will be reviewed in the following sections.

#### 1.2.4.1. Respiratory dysfunction

The MORTEMUS study, a retrospective and multicentric study of cardiorespiratory arrests in epilepsy monitoring units, demonstrated for the first time that SUDEP is due to seizure-in-

duced cardiorespiratory collapse and not to extrinsic circumstances.(48) This study analyzed 16 SUDEP cases (eight definite and eight probable) and nine near-SUDEP cases (two fatal). In all the monitored SUDEP (11 patients) and near-SUDEP cases, the terminal event was preceded by a seizure, a GCS in all the monitored SUDEP cases, and seven out of the nine near-SUDEP cases. A stereotyped sequence was identified in all the monitored SUDEP cases to which researchers could reliably analyze breathing and heart rates (ten patients). This was characterized by cardiorespiratory dysfunction within three minutes after the seizure ended, with intermittent periods of apnea and bradycardia. In all these cases, terminal apnea ended up preceding terminal asystole, suggesting that seizure-induced respiratory dysfunction, rather than cardiac dysfunction, was crucial for the deadly event.(48)

Peri-ictal central respiratory dysfunction, characterized by transient periods of breathing arrest, has been reported during focal seizures and after GCS. It has been named ictal central apnea (ICA) and postconvulsive central apnea (PCCA), respectively. (49-52)

*Ictal central apnea* occurs in approximately one-third of epileptic seizures. It has been described exclusively in focal epilepsies and is particularly associated with temporal lobe epilepsy.(50) In up to 16% of the cases, it may be the only manifestation of an epileptic seizure, and in half of the cases, it can precede the ictal pattern on scalp EEG.(50) If ICA duration extends beyond 60 seconds duration, it can produce severe hypoxemia ($SpO_2$ <75%). ICA was not seen in association with cardiac arrhythmias.(50) Cortical electrical stimulation studies have elicited ICA with intracranial stimulation of the amygdala, hippocampal head and body, temporal tip, parahippocampal gyrus, and the anterior-mesial part of the fusiform gyrus.(53) Therefore, ICA has been postulated as a semiological feature of mesial temporal lobe seizures, only posing the patient at risk if prolonged enough to produce severe hypoxemia.(49, 50, 54)

*Postconvulsive central apnea* has been reported in approximately one-fifth of epileptic seizures, and, as opposed to ICA, it has been observed in both focal and generalized epilepsies. In one study, PCCA was seen in association with postictal asystole in two near-SUDEP cases and in a patient without postictal asystole who succumbed to possible SUDEP at home during follow-up.(51) For this reason, PCCA has been proposed as a potential biomarker of seizure severity and SUDEP risk.(51, 52) Although the exact physiopathology of PCCA is unknown, it is suspected to reflect seizure-induced brainstem dysfunction.(51, 55)

Besides central respiratory dysfunction, peri-ictal obstructive respiratory dysfunction manifested as laryngospasm has also been reported in humans and SUDEP animal models. (56-61) Nevertheless, the incidence of peri-ictal laryngospasm in humans is unknown, given the inherent technical challenge of assessing it.

### 1.2.4.2. Cardiovascular dysfunction

The occurrence of peri-ictal cardiac arrhythmias is widely reported.(62, 63) Sinus tachycardia is the most common of these, occurring in more than 80% of epileptic seizures.(64) It is commonly seen in both focal and generalized seizures, and it is usually asymptomatic and self-limited.(64) Much less frequent are peri-ictal bradycardia and asystole, occurring in less than 1% of epileptic seizures.(64) Ictal bradycardia and asystole have only been reported in patients with focal epilepsies, but there is no consistency among studies regarding their exact symptomatogenic zone.(65) Other rare arrhythmias in the peri-ictal period are atrioventricular conduction block (AVB), atrial flutter/fibrillation (Afib), and ventricular fibrillation (VF).(64) Contrary to peri-ictal sinus tachycardia, they may have a significant clinical impact since they can produce falls with subsequent injuries.(66, 67) Moreover, whereas peri-ictal tachycardia and ictal arrhythmias have not been definitely related to SUDEP, postictal AVB, postictal atrial or ventricular fibrillation, and postictal asystole have been associated with GCS and observed in (near) SUDEP cases, pointing towards a different physiopathology and prognosis for ictal and postictal arrhythmias.(64)

In GCS, hypoxemia duration, but not hypoxemia severity, has been associated with potentially high-risk arrhythmias.(68) Moreover, in GCS, there is a significant increase in postictal levels of blood catecholamines and high-sensitive troponin T, which could be biomarkers of cardiac stress and, at the same time, contribute to cardiovascular dysfunction in both the acute phase and in the long run due to repeated exposure.(69) Nonetheless, the definite contribution of cardiac arrhythmias in SUDEP has not been established, given the MORTEMUS study findings.(48) Moreover, two patients have been reported to succumb to SUDEP despite well-functioning pacemakers at the time of death, suggesting that peri-ictal cardiac arrhythmias are not the ultimate or the sole mechanism responsible for death.(70, 71)

Heart rate variability (HRV), a measurement of beat-to-beat time-interval variation, has been postulated as a measurement of neural cardiac control.(72) As a general rule, increased HRV reflects a higher parasympathetic tone, whereas decreases in HRV suggest a shift towards a sympathetic tone, although the relationship is not linear.(73) Significantly, low HRV has been linked to a higher risk of overall mortality and cardiovascular events in individuals with cardiovascular conditions.(74) Heart rate variability can be analyzed by measuring time-domain and frequency-domain (spectral) components.(75) The frequency-domain component is assessed by determining low-frequency power (LFP), a surrogate for sympathetic drive, and high-frequency power (HFP), representing parasympathetic outflow.(73) Heart rate variability changes have been observed in patients with epilepsy during the interictal, peri-ictal, and ictal periods, and many studies have attempted to establish an

association between such changes and SUDEP risk.(73) However, methodological variations have led to inconsistent results.(73) Overall, patients with epilepsy have been found to have a decreased interictal HRV, indicating a shift towards sympathetic drive, with higher derangements in temporal lobe epilepsy patients compared to those with generalized epilepsy.(73) Interestingly, patients with Dravet syndrome, who are highly susceptible to SUDEP, have shown a severely depressed parasympathetic drive compared to healthy controls and patients with other epilepsy syndromes.(76) However, patients with paroxysmal non-epileptic events have also been found to have lower HRV, comparable to HRV in patients with pharmacoresistant epilepsy.(77) Therefore, it is unclear if HRV imbalance towards sympathetic tone in patients with epilepsy is derived from the epileptic activity itself or from psychosocial comorbidities of epilepsy.(73) Conflicting data exists regarding the effect of VNS and ASM on HRV.(73) Regarding peri-ictal HRV changes, a similar trend towards sympathetic predominance has been seen, although with some inconsistent results.(73) Finally, there is conflicting data regarding HRV changes and SUDEP risk. Some studies have found an association between HRV and SUDEP risk factors, whereas others have not.(78-82) Recently, in a case-control study, the authors found a significantly decreased normalized LFP during wakefulness (but not during sleep) in SUDEP cases, although no differences were found when adjusting by treatment with sodium channel blockers or beta-blockers.(83)

Changes in blood pressure have also been described in the peri-ictal period. An increase in blood pressure is usually seen in patients with focal seizures, with the highest magnitude of change in those patients with impaired awareness. However, there is conflicting data regarding the postictal values being statistically significant from preictal values.(84, 85) Hypertension (systolic arterial pressure [SAP] >140 and/or diastolic blood pressure [DBP]>90) has been reported in 26% of patients with focal seizures, whereas hypotension (SAP<90mm Hg and/or DAP<60mm Hg), in 9% of patients.(86) There is a shortage of data regarding blood pressure changes in the GCS peri-ictal period due to artifact generation during GCS, although a significant increase in blood pressure in the postictal period compared to baseline has been described.(85) Nevertheless, life-threatening decreases in blood pressure after a GCS have also been reported.(87) Hypotension has been elicited in humans after cortical electrical stimulation of Broadman area 25, and insular stimulation can produce a decrease in cardiac output and heart rate and an increase in systolic volume without changes in blood pressure or breathing rate.(88, 89) These findings suggest that peri-ictal blood pressure changes may be due to seizure-mediated direct cortical stimulation of the central autonomic network.(90) Other potential explanations for cardiovascular changes in the peri-ictal period are immediate muscular hyperemia and catecholamine release, which may activate adrenergic receptors in the heart, potentially altering cardiac contractility, and blood vessels.(91)

### 1.2.4.3. Postictal Generalized Electroencephalographic Suppression (PGES)

Postictal generalized electroencephalographic suppression refers to the diffuse absence of electroencephalographic activity above 10 μV within the first 30 seconds following a seizure.(92) Postictal generalized electroencephalographic suppression is seen after GCS in 23-76% of cases, but not in focal seizures that do not evolve into GCS.(93) Postictal generalized electroencephalographic suppression has been suggested as a potential SUDEP biomarker, although with inconsistent results.(92, 94-96) It was seen in all monitored SUDEP cases in the MORTEMUS study, as well as in a case of monitored near-SUDEP.(48, 97) Moreover, in a SUDEP case-control study, PGES longer than 50 seconds was associated with a 9-fold (OR 8.9; CI 95% 1.47-53.46) increase in SUDEP risk.(92) However, other studies have failed to find an association between PGES and SUDEP risk, and have postulated that PGES is a mere signature of GCS.(96) Nevertheless, PGES has been associated with the postictal immobility period and markers of seizure-induced breathing dysfunction, including hypoxemia (magnitude and duration), and rise in end-tidal $CO_2$. In contrast, early $O_2$ administration during GCS has been associated with a lower incidence and shorter duration of PGES as well as shorter hypoxemia duration.(98-101)

The physiopathology underlying PGES has yet to be fully understood. It has been more frequently observed in seizures arising from sleep.(98, 102) Postictal generalized electroencephalographic suppression has been linked to tonic phase duration (but not total GCS duration) and bilateral tonic symmetric extensor posturing.(103-105) Moreover, PGES duration is positively correlated with electrodermal activity, sympathetic drive, and tonic postictal electromyographic (EMG) duration.(80, 106)

The analysis of PGES has two main limitations. One is derived from significant interrater variability, for which automated methods for PGES analysis have been developed.(107) The other is derived from the fact that focal cerebral activity may continue in unrecorded regions despite PGES on scalp EEG. However, data is conflicting on this aspect.(108-110)

### 1.2.4.4. Brainstem functional disruption

#### 1.2.4.4.1. Spreading depolarization

Spreading depolarization is a pathological, self-regenerating wave of depolarization in neurons and glia associated with excess glutamate release and extracellular potassium elevation. (111) Spreading depolarization can produce profound reversible or irreversible loss of neuronal activity, and it may be responsible for focal neurological deficits during migraines

and cerebral ischemia. Animal models of SUDEP (knocked out Kv1.1, Scn1a, and Cacna 1a mice) have a lower threshold for brainstem spreading depolarization after seizures induced by cortical injection of 4-aminopiridine in the cortex or cortical electrical stimulation, and it is associated with cardiorespiratory arrest, phenocopying the monitored SUDEP cases in the MORTEMUS study.(111, 112)

### 1.2.4.4.2. Serotoninergic axis dysfunction

Serotoninergic neurons in the central nervous system lie in the brainstem, within the raphe nuclei. These neurons send projections to the cortex, hippocampus, and other brainstem nuclei that are critical respiratory centers. Serotoninergic neurons act as chemoreceptors to decreased pH induced by hypercapnia. In such circumstances, midbrain serotoninergic neurons activate thalamocortical pathways to promote arousal, and the medullary neurons project to the preBotzinger nuclei and nucleus of the solitary tract to enhance ventilation. Therefore, serotoninergic neurons play a protective role against hypercapnia. (113) In fact, mice that lack serotoninergic neurons have a lower threshold for seizures induced by pilocarpine injection and maximal electroshock. Moreover, they have an increased mortality due to respiratory failure compared to controls, which can be prevented by mechanical ventilation and premedication with a serotoninergic agent.(114) Similar results have been reproduced in other animal models of SUDEP, which reinforces the protective role of the serotoninergic pathway. (115-117)

In patients with epilepsy, the ventilatory response to hypercapnia directly correlates with the degree of dyspnea and shows an inverse correlation with baseline $ETCO_2$ and duration and increase in transcutaneous $CO_2$ after a GCS.(118) This suggests that patients with baseline hypoventilation or those with profound hypoventilation after a GCS may have an insufficient response to hypercapnia in terms of activation of arousal and ventilation, potentially increasing their SUDEP risk.(118) Considering serotonin's role in promoting arousal and respiratory drive, a dysfunction of the serotonergic axis might be responsible for the inadequate response observed in these patients.

### 1.2.4.4.3. Role of adenosine

Epileptic seizures trigger a surge in adenosine, an inhibitory modulator of neuronal excitability. This response has protective effects by promoting seizure termination. Additionally, adenosine induces vasodilation, serving as a neuroprotector against hypoxia. However, adenosine's suppression of breathing and its potential to prolong spreading depolarization and PGES contribute to peri-ictal breathing and arousal dysfunction.(119, 120)

### 1.2.4.5. Brainstem structural damage

Autopsy studies of SUDEP patients have shown a significant reduction of neuropeptides and serotoninergic neurons in the medullar raphe.(121) Moreover, in MRI studies, SUDEP patients exhibit widespread brainstem volume loss, with the extension of damage correlating with a shorter survival time since MRI.(122)

### 1.2.4.6. Genetics

Specific genes expressed in both brain and cardiac tissue, such as KCNQ1, KCNH2, and SCN5A, are associated with long QT syndrome and epilepsy.(123) In 80% of Dravet syndrome cases, patients exhibit a mutation in SCN1A, which may increase the risk of peri-ictal arrhythmia.

While no single gene directly causes SUDEP, some genes, such as SCN1A, SCN2A, SCN8A, and STXBP1 in genetic developmental encephalopathies, may elevate the risk.(124, 125)

# 2. HYPOTHESIS AND RATIONALE

Sudden Unexpected Death in Epilepsy is the first category of death directly due to epilepsy and the second cause of years of potential life lost from a neurological disease, second only to stroke.(31, 36) Therefore, it represents a concerning public health burden worthy of study. A history of GCS is the most consistent SUDEP risk factor across studies.(39, 41) Both cardiac and respiratory mechanisms in the setting of impaired arousal likely contribute to SUDEP pathophysiology. However, monitored VEEG deaths have shown that terminal cardiac arrest is consistently preceded by terminal central apnea.(48) Animal models suggest that cardiorespiratory collapse leading to SUDEP may be mediated through seizure-induced brainstem dysfunction affecting critical structures for respiratory control.(111, 112, 126) Moreover, semiology observed during GCS in humans can resemble the decerebrate and decorticate posturing seen in comatose patients, suggesting varying degrees of cerebral and brainstem compromise.(48)

There is a dearth of literature about the extent of cardiorespiratory disturbances in GCS in humans and their potential contribution to SUDEP. Effective measures to prevent SUDEP are currently lacking. A better understanding of SUDEP´s physiopathology and identification of SUDEP biomarkers will help identify those patients at high SUDEP risk to conduct clinical trials, as well as to develop targeted interventions.

We *hypothesize* that:

- Generalized convulsive seizures can produce severe cardiorespiratory dysfunction.

- Different semiological features may indicate different anatomical pathways involved in seizure generation and spread, with crucial cardiorespiratory centers potentially involved.

- Seizure semiology may predict the degree of seizure severity in GCS defined by cardiorespiratory dysfunction and PGES, and therefore be used as a surrogate of seizure severity biomarker.

# 3. OBJECTIVES

The *main objective* of this thesis is:

- To describe the electroclinical features of GCS, focusing on peri-ictal brainstem semiology, and seizure severity biomarkers, defined by PGES, PCCA, hypoxemia, and cardiac arrhythmias.

The *secondary objectives* of the thesis are:

- To determine the incidence of brainstem semiology during the tonic phase of GCS and its association with PGES and variables of breathing dysfunction, including hypoxemia duration, $SpO_2$ recovery, and change in $SpO_2$.

- To analyze the incidence of postictal brainstem semiology and its association with PGES and variables of breathing dysfunction.

- To assess if seizure-induced cardiac arrhythmias of interest are associated with peri-ictal brainstem semiology, PGES, and variables of respiratory dysfunction.

# 4. COMPENDIUM OF PUBLICATIONS

**4.1. Association of Peri-ictal Brainstem Posturing With Seizure Severity and Breathing Compromise in Patients With Generalized Convulsive Seizures. Neurology. 2021 Jan 19;96(3):e352-e365. Epub 2020 Dec 2.**

PMID: 33268557.
DOI: 10.1212/WNL.0000000000011274

ARTICLE CLASS OF EVIDENCE

# Association of Peri-ictal Brainstem Posturing With Seizure Severity and Breathing Compromise in Patients With Generalized Convulsive Seizures

Laura Vilella, MD, Nuria Lacuey, MD, PhD, Johnson P. Hampson, MSBME, Liang Zhu, PhD, Shirin Omidi, MD, Manuela Ochoa-Urrea, MD, Shiqiang Tao, PhD, M.R. Sandhya Rani, PhD, Rup K. Sainju, MBBS, Daniel Friedman, MD, Maromi Nei, MD, Kingman Strohl, MD, Catherine Scott, MPhil, Luke Allen, PhD, Brian K. Gehlbach, MD, Norma J. Hupp, REEGTCLTm, Jaison S. Hampson, MD, Nassim Shafiabadi, MD, Xiuhe Zhao, MD, Victoria Reick-Mitrisin, MS, Stephan Schuele, MD, MPH, Jennifer Ogren, PhD, Ronald M. Harper, PhD, Beate Diehl, MD, PhD, FRCP, Lisa M. Bateman, MD, Orrin Devinsky, MD, George B. Richerson, MD, PhD, Philippe Ryvlin, MD, PhD, Guo-Qiang Zhang, MS, PhD, and Samden D. Lhatoo, MD, FRCP

**Correspondence**
Laura Vilella
Lvilellabertran@gmail.com

*Neurology*® 2021;96:e352-e365. doi:10.1212/WNL.0000000000011274

## Abstract

### Objective
To analyze the association between peri-ictal brainstem posturing semiologies with postictal generalized electroencephalographic suppression (PGES) and breathing dysfunction in generalized convulsive seizures (GCS).

### Methods
In this prospective, multicenter analysis of GCS, ictal brainstem semiology was classified as (1) decerebration (bilateral symmetric tonic arm extension), (2) decortication (bilateral symmetric tonic arm flexion only), (3) hemi-decerebration (unilateral tonic arm extension with contralateral flexion) and (4) absence of ictal tonic phase. Postictal posturing was also assessed. Respiration was monitored with thoracoabdominal belts, video, and pulse oximetry.

### Results
Two hundred ninety-five seizures (180 patients) were analyzed. Ictal decerebration was observed in 122 of 295 (41.4%), decortication in 47 of 295 (15.9%), and hemi-decerebration in 28 of 295 (9.5%) seizures. Tonic phase was absent in 98 of 295 (33.2%) seizures. Postictal posturing occurred in 18 of 295 (6.1%) seizures. PGES risk increased with ictal decerebration (odds ratio [OR] 14.79, 95% confidence interval [CI] 6.18–35.39, $p < 0.001$), decortication (OR 11.26, 95% CI 2.96–42.93, $p < 0.001$), or hemi-decerebration (OR 48.56, 95% CI 6.07–388.78, $p < 0.001$). Ictal decerebration was associated with longer PGES ($p = 0.011$). Postictal posturing was associated with postconvulsive central apnea (PCCA) ($p = 0.004$), longer hypoxemia ($p < 0.001$), and $Spo_2$ recovery ($p = 0.035$).

### Conclusions
Ictal brainstem semiology is associated with increased PGES risk. Ictal decerebration is associated with longer PGES. Postictal posturing is associated with a 6-fold increased risk of PCCA, longer hypoxemia, and $Spo_2$ recovery. Peri-ictal brainstem posturing may be a surrogate biomarker for GCS severity identifiable without in-hospital monitoring.

### Classification of Evidence
This study provides Class III evidence that peri-ictal brainstem posturing is associated with the GCS with more prolonged PGES and more severe breathing dysfunction.

RELATED ARTICLE

**Editorial**
Peri-ictal Brainstem-Driven Posturing and Its Meaning
Page 89

MORE ONLINE

**→ Class of Evidence**
Criteria for rating therapeutic and diagnostic studies
NPub.org/coe

**Videos**

From the NINDS Center for SUDEP Research (L.V., N.L., S.O., M.O.-U., S.T., M.R.S.R., R.K.S., D.F., M.N., C.S., L.A., B.K.G., J.S.H., S.S., J.O., R.M.H., B.D., L.M.B., O.D., G.B.R., P.R., G.-Q.Z., S.D.L.) and Department of Neurology (L.V., N.L., J.P.H., S.O., M.O.-U., S.T., M.R.S.R., N.J.H., J.S.H., G.-Q.Z., S.D.L.), McGovern Medical School, and Biostatistics and Epidemiology Research Design Core (L.Z., G.B.R.), Division of Clinical and Translational Sciences, University of Texas Health Science Center at Houston; Departament de Medicina (L.V.), Universitat Autonoma de Barcelona, Spain; University of Iowa Carver College of Medicine (R.K.S., B.K.G.), Iowa City; NYU Langone School of Medicine (D.F., O.D.), New York; Sidney Kimmel Medical College (M.N.), Thomas Jefferson University, Philadelphia, PA; Division of Pulmonary (K.S.), Critical Care and Sleep Medicine, University Hospitals Medical Center, Cleveland, OH; Institute of Neurology (C.S., L.A., B.D.), University College London, UK; Case Western Reserve University (N.S., X.Z., V.R.-M.), Cleveland, OH; Feinberg School of Medicine (S.S.), Northwestern University, Chicago, IL; Department of Neurobiology and the Brain Research Institute (J.O., R.M.H.), University of California, Los Angeles; Department of Neurology (L.M.B.), Columbia University, New York, NY; and Department of Clinical Neuroscience (P.R.), Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

## Glossary

**CI** = confidence interval; **EST** = β estimate; **GCS** = generalized convulsive seizures; **GEE** = generalized estimating equation; **ICA** = ictal central apnea; **MORTEMUS** = Mortality in Epilepsy Monitoring Unit Study; **OR** = odds ratio; **PAG** = periaqueductal gray; **PCCA** = postconvulsive central apnea; **PGES** = postictal generalized electroencephalographic suppression; **PRISM** = Prevention and Risk Identification of SUDEP Mortality; **SUDEP** = sudden unexpected death in epilepsy; **VEEG** = video-EEG.

Sudden unexpected death in epilepsy (SUDEP) is the leading category of death in patients with refractory epilepsy, with an incidence of 6.3 to 9.3 per 1,000 person-years in this population.[1,2] Frequent generalized convulsive seizures (GCS) in patients with long-standing, early-onset epilepsy have the most significant risk.[3] Recent studies have focused on determining pathophysiology and electroclinical risk factors for SUDEP as well as markers of GCS severity. These factors include prolonged ictal central apnea (ICA), postconvulsive central apnea (PCCA), hypoxemia severity, postictal blood catecholamine rise, and prolonged (>50 seconds) postictal generalized electroencephalographic suppression (PGES).[4–9] PGES was observed in all monitored SUDEP cases in the Mortality in Epilepsy Monitoring Unit Study (MORTEMUS) along with cardiorespiratory instability.[10] Although its role as a risk marker of SUDEP has not been prospectively confirmed, prolonged PGES is seen with severe GCS, cardiorespiratory compromise, and delayed arousal.[6,10–12] GCS tonic phase semiology and duration are strongly linked to PGES incidence, particularly when characterized by bilateral symmetric tonic arm extension (decerebrate) posturing.[13–15] Tonic or dystonic posturing can also be postictal, although its symptomatogenic brain areas and its relationship to postictal cardiorespiratory compromise are unknown.[16] Brainstem seizure spread may potentially explain both.[14,17] Semiologic clinical features such as posturing can be recognized without the need for multimodal monitoring and thus may have value in seizure severity assessment. We sought to precisely study GCS features, including tonic phase semiology and postictal posturing and their association with potential SUDEP biomarkers such as PGES and peri-ictal breathing dysfunction.

## Methods

The primary research question is to determine the association between peri-ictal brainstem posturing and presence of PGES and its duration as well as breathing compromise.

### Standard Protocol Approvals, Registrations, and Patient Consents

Written informed consent was obtained prospectively from all the participants in the National Institute for Neurological Disorders and Stroke Center for SUDEP Research's Autonomic and Imaging Biomarkers of SUDEP multicenter project (U01-NS090407) and its preliminary phase, the Prevention and Risk Identification of SUDEP Mortality (PRISM) project (P20NS076965). These studies were approved by the Institutional Review boards of the participating centers.

### Patient Selection

Patients with intractable epilepsy (failure of adequate trials of ≥2 antiepileptic medications)[18] who were ≥18 years of age and were undergoing video-EEG (VEEG) evaluation in the adult epilepsy monitoring units of participating centers from February 2011 until April 2018 were selected. We included patients with recorded GCS that were successfully analyzed until April 2018, including generalized tonic-clonic seizures, focal to bilateral tonic-clonic seizures, and focal-onset motor bilateral clonic seizures.[19] Exclusion criteria were status epilepticus and obscured or unavailable video. Demographic and clinical data were collected, including epilepsy duration, seizure type and frequency, semiologic seizure features, awake or asleep states at seizure onset, and presence of major cardiac (cardiac ischemic disease, known arrhythmia, valvulopathy) or respiratory (obstructive sleep apnea, asthma, chronic obstructive pulmonary disease, bronchiectasis, cystic fibrosis) disease. We considered the use of serotonin or serotonin-noradrenaline reuptake inhibitors. We assessed the impact of antiepileptic drug regimen during admission on tonic phase semiology. Epilepsy type was classified as generalized (genetic generalized epilepsy in all cases), focal, both, or unknown.[20] GCS duration was defined as time from onset of bilateral motor signs of tonicity or clonicity to clinical seizure end, and GCS phases were classified as tonic, jittery, and clonic.

### Data Collection

#### Semiology Classification

Tonic phase semiology was classified into 4 categories based on a modified classification proposed by previous authors[13]: (1) ictal decerebration (bilateral symmetric tonic arm extension), (2) ictal decortication (bilateral symmetric tonic arm flexion without progression to decerebration), (3) ictal hemi-decerebration (tonic extension of 1 arm with flexion of contralateral arm without progression to decortication or decerebration), and (4) absence of ictal tonic phase. Examples of brainstem posturing are provided in videos 1 through 3 .

Postictal posturing referred to patients adopting decerebration or decortication after the last clonic jerk of the GCS. An example is provided in video 4.

#### Cardiorespiratory Monitoring and VEEG Monitoring

All patients underwent prolonged surface VEEG monitoring with the 10-20 International Electrode System. EEG and ECG were acquired with Nihon Kohden (Tokyo, Japan), Micromed (Modigliani Veneto, Italy), and Xtlek and Nicolet (Natus

Medical Inc, Pleasanton, CA) acquisition platforms. Peripheral capillary oxygen saturation ($Spo_2$) was monitored with pulse oximetry (Nellcor OxiMax N-600x [Covidien, Dublin, Ireland], Masimo Radical-7 [Irvine, CA], and SenTec Digital Monitoring System [Therwil BL, Switzerland]), and chest wall and abdominal excursions were recorded with inductance plethysmography (Ambu [Ballerup, Denmark] Sleepmate and Perfect Fit 2 [Dymedix, Shoreview, MN]).

Breathing analysis for apnea used a composite analysis of inductance plethysmography, EEG breathing artifact, and visually inspected thoracoabdominal excursions 2 minutes before seizure onset (clinical or electrographic, whichever occurred first) and up to 3 minutes after clinical seizure end. Central apnea (cessation of thoracoabdominal breathing movements) was defined as >1 missed breath without other explanation (i.e., speech or intervention), with a minimum duration of 5 seconds. ICA referred to apnea occurring in the preconvulsive phase of GCS. PCCA referred to apnea after GCS; we preferred this term to post-ICA because apnea could occur after convulsions but with ongoing EEG seizure discharges. Incidences and durations of ICA and PCCA were determined. Apnea was not assessed during the GCS phase because of invariable artifact in breathing channels.

Baseline $Spo_2$ was determined as the mean value in a 15-second page at 2 minutes before EEG onset or clinical onset, whichever occurred first. We defined change in $Spo_2$ as the difference between baseline and the lowest $Spo_2$ value (nadir $Spo_2$) recorded during or up to 3 minutes after clinical seizure end. Hypoxemia was defined as $Spo_2$ <95%. When baseline $Spo_2$ was already <95%, a >1% drop was considered significant. If transient loss of $Spo_2$ signal occurred during monitoring but hypoxemia persisted after signal recovery, hypoxemia duration was determined but not $Spo_2$ nadir (and thus change in $Spo_2$). If $Spo_2$ signal did not return or hypoxemia had resolved, we made no comment on change in $Spo_2$ or hypoxemia duration. Finally, to avoid the effect of seizure duration and following previous studies, we determined time to recovery to mild hypoxemia ($Spo_2$ 90%) after clinical seizure end, which we called $Spo_2$ recovery.[7] We considered early oxygen administration when it was applied during the seizure or within 5 seconds of seizure termination.[13]

Presence and duration of PGES[6] were determined by a validated automated EEG suppression detection tool[21] and supplemented by visual analysis by the same 2 epilepsy neurophysiologists in all cases when the tool gave no solution. The visual inspection was masked to VEEG results for 1 neurophysiologist but not for the other one.

## Statistical Analysis

Descriptive statistics (mean, SD, frequency, percentage, etc) were provided for demographic and clinical variables based on patients and seizures (table 1). Descriptive statistics for continuous outcomes (PGES duration, change in $Spo_2$, hypoxemia duration, and $Spo_2$ recovery) are provided in tables 2 and 3. Mean and SD of the continuous outcomes across seizures were provided for categorical demographic and clinical variables. Considering that the outcomes are repeated measures, $p$ values were obtained from the generalized estimating equation (GEE) method to account for within-participant correlation. For continuous demographic and clinical variables, covariate coefficient estimates, standard error, and corresponding $p$ values from the GEE method were provided.

**Table 1** Demographic and Phenotypic Variables

| | Patients (n = 180) | Seizures (n = 295) |
|---|---|---|
| **Age at study, $\bar{x}$ ± SD (median; range), y** | 36.7 ± 13.3 (34; 18–77) | — |
| **Age at epilepsy onset, $\bar{x}$ ± SD (median; range), y** | 19.6 ± 15.5 (16; 1–68) | — |
| **Epilepsy duration, $\bar{x}$ ± SD (median; range), y** | 16.8 ± 12.1 (15; 0.08–45) | — |
| **GCS frequency the year prior, n (%)** | | |
| **0** | 21 (11.7) | 32 (10.8) |
| **1–2** | 35 (19.4) | 51 (17.3) |
| **3–12** | 47 (26.1) | 81 (27.5) |
| **>12** | 57 (31.7) | 99 (33.6) |
| **Unknown** | 20 (11.1) | 32 (10.8) |
| **Cardiac comorbid conditions, n (%)** | 6 (3.3) | 8 (2.7) |
| **Unknown** | 7 (3.4) | 8 (2.7) |
| **Respiratory comorbid conditions, n (%)** | 20 (11.1) | 29 (9.8) |
| **Unknown** | 7 (3.9) | 8 (2.7) |
| **Epileptogenic zone, n (%)** | | |
| **Temporal** | 78 (43.3) | 125 (42.4) |
| **Generalized** | 29 (16.1) | 40 (13.5) |
| **Frontal** | 26 (14.4) | 41 (13.9) |
| **Lateralized** | 19 (10.6) | 40 (13.5) |
| **Multifocal** | 18 (10) | 37 (12.5) |
| **Parietal** | 2 (1.1) | 2 (0.7) |
| **Insular** | 2 (1.1) | 2 (0.7) |
| **Both focal and generalized** | 1 (0.6) | 2 (0.7) |
| **Unknown** | 5 (2.8) | 6 (2.0) |
| **Neuroimaging, n (%)** | | |
| **Negative** | 95 (52.8) | 164 (55.6) |
| **Positive** | 69 (38.3) | 105 (35.6) |
| **Unavailable** | 16 (8.9) | 26 (8.8) |

Abbreviations: GCS = generalized convulsive seizure; $\bar{x}$ = mean.

Descriptive statistics for dichotomous outcomes (PGES, PCCA) are provided in table 4. Frequency and percentage and mean and SD were provided for categorical and continuous variables, respectively. The $p$ values were obtained from GEE as well, with the binomial distribution and logit link. Based on the univariate analysis shown in tables 2 through 4, the multivariable analysis is presented in tables 5 and 6. Variables from the univariant analysis with $p < 0.1$ were included in the final models, and age at study and sex were treated as force-in variables. A value of $p < 0.05$ in the final models was considered significant. All analyses were performed in SAS 9.4 (SAS Institute Inc, Cary, NC).

### Data Availability

The datasets used and analyzed during the current study are available from the corresponding author on request.

## Results

### Demographics and Clinical Phenotype

We identified 307 GCS in 187 patients. VEEG recordings meeting study criteria were available in 295 seizures in 180 patients (90 female). Two hundred thirty-seven seizures were included in 2 previous publications on peri-ictal breathing dysfunction.[5,22] Mean age at monitoring was 36.7 ± 13.3 years (median 34; range 18–77 years). Mean age at epilepsy onset was 19.6 ± 15.5 years (16; 1–68 years), and mean epilepsy duration was 16.8 ± 12.1 years (15; 1 month–45 years). Epilepsy type was generalized in 29 patients (16.1%), focal in 145 (80.6%), and unknown in 5 (2.8%). One patient had both focal and generalized epilepsy. Details regarding demographic and phenotypic characteristics are summarized in table 1.

### Seizure Characteristics

One hundred forty-eight seizures occurred during wakefulness; 144 occurred during sleep; and 3 occurred during postictal stupor in a seizure cluster in 1 patient.

Total GCS duration was 52.3 ± 17.9 seconds (51; 5–154 seconds). Tonic phase was present in 197 of 295 (67%) seizures (mean duration 7.9 ± 4 seconds [7; 1–22 seconds]), and jittery phase was present in 238 of 295 (80.7%) seizures (mean duration 9.5 ± 7.3 seconds [7; 1–55 seconds]). All seizures had a clonic phase, with a duration of 39.3 ± 17.7 seconds (36; 5–123 seconds). Ictal decerebration was observed in 122 of 295 (41.4%) seizures; ictal decortication was seen in 47 of 295 (15.9%) seizures; and ictal hemi-decerebration was observed in 28 of 295 (9.5%) seizures. We found no association between antiepileptic drug regimen or medication reduction/cessation and tonic phase semiology ($p > 0.05$).

Postictal posturing occurred in 18 of 295 (6.1%) seizures in 12 patients (6.6%). In 16 of 18 (88.8%) seizures in 10 of 12 patients (83.3%), tonic flexion of the upper extremities, identical to ictal decortication, was observed. In the remaining 2 of 18 seizures (2 of 10 patients), tonic extension of the upper extremities was noted, similar to ictal decerebration. Electrographic burst discharge was simultaneous with decortication in 2 seizures (2 patients) followed by PGES. In the remainder, this occurred concurrently with PGES. Posturing occurred 7 ± 7.9 seconds (4; 1–30 seconds) after the last clonic jerk.

PGES was present in 197 of 293 (67%) GCS in 132 patients, with a mean duration of 36.5 ± 21.4 seconds (35; 1–169 seconds); it could not be assessed in 2 seizures due to electrode artifact.

ICA was observed in 83 of 205 (40.4%) seizures in 48 patients (mean duration 14.7 ± 8.6 seconds [12; 5–39 seconds]), and PCCA was seen in 45 of 285 (15.8%) seizures in 34 patients (mean duration 11.2 ± 12 seconds [8; 5–85 seconds]). No comment could be made on the incidence of ICA in 90 seizures and the incidence of PCCA in 10 seizures due to movement artifact or loss of polygraphic data.

Hypoxemia duration, available in 127 seizures, was 142.6 ± 65.5 seconds (124; 25–314 seconds). In analysis of $Spo_2$ recovery from clinical seizure end, available in 120 seizures, it was 43.2 ± 34.2 seconds (35.5; −27 to 179 seconds). Finally, $Spo_2$ change (baseline to nadir), available in 119 seizures, was 34.4 ± 14.5% (33%; 2–77%).

### Association of Peri-Ictal Semiology With PGES and Breathing Dysfunction

In univariate analyses, tonic phase semiology was related to PGES presence ($p = 0.000$), PGES duration ($p = 0.034$), and change in $Spo_2$ ($p = 0.024$). Tonic phase semiology was not related to the presence of ICA ($p = 0.906$) or PCCA ($p = 0.546$). In the univariate analysis, for the subset of patients with tonic phase, its duration was associated with total hypoxemia duration ($p = 0.027$) and $Spo_2$ recovery ($p = 0.049$). However, there was no significant association of tonic phase duration with PGES presence ($p = 0.376$) or duration ($p = 0.791$) or with change in $Spo_2$ ($p = 0.822$). There was also no association of tonic phase duration with ICA ($p = 0.965$) or PCCA ($p = 0.712$). Postictal posturing was associated with PGES ($p = 0.001$, tables 2–4).

In multivariate analysis, the presence of ictal decerebration (odds ratio [OR] 14.79, 95% confidence interval [CI] 6.18–35.39, $p < 0.001$), ictal decortication (OR 11.26, 95% CI 2.96, 42.93, $p < 0.001$), or ictal hemi-decerebration (OR 48.56, 95% CI 6.07–388.78, $p < 0.001$) was associated with increased risk for PGES compared to the absence of any tonic phase. PGES duration was significantly longer in those seizures with ictal decerebration (β estimate [Est] 20.45 seconds, 95% CI 4.74–36.15, $p = 0.011$) compared to seizures without tonic phase. No differences were noted in PGES duration between seizures with ictal decortication (Est 11.09, 95% CI −4.41 to 26.59, $p = 0.161$) or hemi-decerebration (Est 5.22, 95% CI −10.16 to 20.61, $p = 0.506$) and those seizures without tonic phase. PGES duration was also longer with increasing age at the time of study (Est 0.51 second, 95% CI 0.13–0.89, $p = 0.008$, table 5).

**Table 2** Univariate Analysis for Continuous Variables With Categorical Independent Variables

| | PGES Duration, s | | Change in $Spo_2$, % | | Hypoxemia Duration, s | | $Spo_2$ Recovery, s | |
|---|---|---|---|---|---|---|---|---|
| | x̄ ± SD | *p* Value | x̄ ± SD | *p* Value | x̄ ± SD | *p* Value | x̄ ± SD | *p* Value |
| **Sex** | | 0.377[a] | | 0.032[a] | | 0.014[a] | | 0.406[a] |
| **Male** | 35.1 ± 22.2 | | 31.2 ± 12.7 | | 159.8 ± 70.2 | | 46.9 ± 35.4 | |
| **Female** | 38.0 ± 20.7 | | 36.8 ± 15.4 | | 129.0 ± 58.5 | | 40.4 ± 33.2 | |
| **State** | | 0.551 | | 0.845 | | 0.072[a] | | 0.058[a] |
| **Awake** | 37.5 ± 23.8 | | 34.9 ± 15.2 | | 154.0 ± 69.2 | | 49.5 ± 38.6 | |
| **Asleep** | 35.7 ± 18.4 | | 34.4 ± 14.2 | | 130.1 ± 60.3 | | 37.1 ± 28.0 | |
| **Epilepsy type** | | 0.359 | | 0.096[a] | | 0.818 | | 0.525 |
| **Focal** | 35.8 ± 22.5 | | 32.6 ± 13.3 | | 143.3 ± 64.0 | | 43.8 ± 36.1 | |
| **Generalized** | 39.0 ± 15.6 | | 38.2 ± 16.3 | | 139.4 ± 69.9 | | 39.3 ± 27.3 | |
| **MRI** | | 0.168 | | 0.311 | | 0.405 | | 0.554 |
| **Negative** | 38.9 ± 22.4 | | 35.4 ± 14.7 | | 146.7 ± 65.7 | | 43.2 ± 32.2 | |
| **Positive** | 33.8 ± 22.3 | | 32.4 ± 14.2 | | 134.8 ± 70.0 | | 38.7 ± 33.7 | |
| **Tonic phase semiology** | | 0.034[a] | | 0.024[a] | | 0.093[a] | | 0.657 |
| **Decerebrate** | 40.1 ± 22.7 | | 36.9 ± 14.4 | | 155.4 ± 65.5 | | 46.1 ± 36.2 | |
| **Decorticate** | 38.9 ± 21.8 | | 37.6 ± 14.8 | | 115.3 ± 47.2 | | 40.2 ± 29.1 | |
| **Hemi-decerebration** | 31.3 ± 17.5 | | 38.4 ± 13.2 | | 126.0 ± 46.7 | | 36.4 ± 19.2 | |
| **No tonic phase** | 26.4 ± 15.4 | | 26.2 ± 12.2 | | 144.7 ± 76.2 | | 42.8 ± 39.1 | |
| **Postictal posturing** | | 0.261 | | 0.989 | | 0.075[a] | | 0.075[a] |
| **No** | 35.8 ± 19.3 | | 34.4 ± 14.8 | | 139.4 ± 65.5 | | 40.1 ± 30.2 | |
| **Yes** | 46.2 ± 36.7 | | 34.4 ± 9.3 | | 179.3 ± 54.7 | | 81.4 ± 55.0 | |
| **Early $O_2$ administration** | | 0.076[a] | | 0.343 | | 0.130 | | 0.029[a] |
| **No** | 40.4 ± 23.7 | | 36.7 ± 14.7 | | 157.3 ± 64.8 | | 56.3 ± 41.4 | |
| **Yes** | 34.8 ± 20.0 | | 33.6 ± 14.4 | | 136.5 ± 65.1 | | 38.2 ± 29.8 | |
| **ICA** | | 0.091[a] | | 0.840 | | 0.800 | | 0.324 |
| **No** | 34.1 ± 15.8 | | 35.2 ± 14.9 | | 146.9 ± 70.9 | | 42.5 ± 32.0 | |
| **Yes** | 41.3 ± 29.6 | | 35.8 ± 13.4 | | 150.1 ± 56.6 | | 51.6 ± 41.1 | |
| **PCCA** | | 0.653 | | 0.453 | | 0.608 | | 0.126 |
| **No** | 35.9 ± 19.7 | | 33.6 ± 13.6 | | 144.9 ± 70.1 | | 38.8 ± 30.3 | |
| **Yes** | 38.4 ± 27.6 | | 36.6 ± 16.9 | | 139.1 ± 40.9 | | 58.3 ± 42.0 | |
| **Cardiac comorbid conditions** | | 0.384 | | 0.114 | | 0.861 | | 0.960 |
| **No** | 36.6 ± 21.6 | | 34.9 ± 14.3 | | 142.4 ± 65.4 | | 43.2 ± 34.3 | |
| **Yes** | 44.5 ± 21.3 | | 19.5 ± 14.2 | | 148.3 ± 75.7 | | 42.3 ± 37.1 | |
| **Respiratory comorbid conditions** | | | | 0.024[a] | | 0.615 | | 0.944 |
| **No** | 36.5 ± 21.8 | 0.535 | 35.2 ± 14.4 | | 141.6 ± 65.2 | | 43.3 ± 34.2 | |
| **Yes** | 39.5 ± 20.0 | | 25.9 ± 12.6 | | 154.0 ± 71.0 | | 42.3 ± 35.3 | |

Continued

**Table 2** Univariate Analysis for Continuous Variables With Categorical Independent Variables *(continued)*

| | PGES Duration, s | | Change in $Spo_2$, % | | Hypoxemia Duration, s | | $Spo_2$ Recovery, s | |
|---|---|---|---|---|---|---|---|---|
| | x̄ ± SD | *p* Value | x̄ ± SD | *p* Value | x̄ ± SD | *p* Value | x̄ ± SD | *p* Value |
| **GCS frequency the prior year, n** | | 0.624 | | 0.055[a] | | 0.301 | | 0.191 |
| **0** | 36.4 ± 15.3 | | 31.8 ± 9.6 | | 160.9 ± 81.9 | | 40.0 ± 26.5 | |
| **1–2** | 39.5 ± 22.2 | | 29.4 ± 13.6 | | 148.2 ± 73.5 | | 30.1 ± 28.9 | |
| **3–12** | 38.6 ± 24.0 | | 40.5 ± 17.7 | | 124.2 ± 60.3 | | 40.1 ± 26.7 | |
| **>12** | 33.7 ± 21.9 | | 33.7 ± 12.3 | | 148.2 ± 60.9 | | 52.3 ± 40.4 | |
| **Long-term SRI treatment** | | | | | | | | |
| **No** | 36.3 ± 21.8 | 0.845 | 34.1 ± 15 | 0.698 | 145.6 ± 68.5 | 0.285 | 43.9 ± 36.3 | 0.753 |
| **Yes** | 37.1 ± 20.9 | | 35.2 ± 12.6 | | 131.8 ± 50.9 | | 41.8 ± 23.9 | |

Abbreviations: GCS = generalized convulsive seizure; ICA = ictal central apnea; PCCA = postconvulsive central apnea; PGES = postictal generalized EEG suppression; $Spo_2$ = capillary peripheral oxygen saturation; SRI = serotonin or serotonin-noradrenaline reuptake inhibitor.
Mean (x̄) and SD are provided with *p* values obtained from generalized estimating equations.
[a] Variables introduced in multivariate analysis because $p < 0.1$, including age and sex as force-in variables.

Ictal decerebration (Est 9.57%, 95% CI 3.83–15.32, $p = 0.001$), ictal decortication (Est 11.37%, 95% CI 4.32–18.42, $p = 0.002$), and ictal hemi-decerebration (Est 12.52%, 95% CI 4.19–20.84, $p = 0.003$) were also related to larger drops in $Spo_2$ compared to patients without tonic phase. Changes in $Spo_2$ were smaller in patients with respiratory comorbid conditions (Est −9.38%, 95% CI −15.26 to −3.50, $p = 0.002$, table 6).

Postictal posturing was associated with increased risk of PCCA (OR 6.06, 95% CI 1.76–20.89, $p = 0.004$). Other variables associated with PCCA were sex (male, relative risk 0.26, 95% CI 0.09–0.73, $p = 0.010$), epilepsy type (focal, relative risk 0.29, 95% CI 0.11–0.80, $p = 0.017$), and shorter duration of GCS (OR 0.95, 95% CI 0.91–0.99, $p = 0.017$). Postictal posturing was associated with prolonged hypoxemia duration (Est 47.87 seconds, 95% CI 24.47–71.27, $p < 0.001$). Hypoxemia duration was also longer in men (Est 40.14 seconds, 95% CI 16.61–63.67, $p < 0.001$), increased with GCS duration (Est 0.87 second, 95% CI 0.03–1.70, $p = 0.041$), and decreased with increasing age at study (Est −1.61 seconds, 95% CI −2.44 to −0.78, $p < 0.001$). Postictal posturing was also associated with longer $Spo_2$ recovery (Est 27.84 seconds, 95% CI 1.98–53.69, $p = 0.035$). Conversely, $Spo_2$ recovery was shorter with early administration of oxygen (Est −17.69 seconds, 95% CI −29.56 to −5.83, $p = 0.003$) and with increased duration of the GCS (Est −0.53 second, 95% CI −0.92 to −0.14, $p = 0.009$, table 6). Given the apparent paradoxical results regarding GCS duration and its association with PCCA and $Spo_2$ recovery, we sought to determine the ratio of tonic phase duration to clonic phase duration and its association with overall GCS duration. An increase in tonic/clonic duration ratio was associated with a decrease in total GCS duration (Est −19.29 seconds, 95% CI −29.52 to −9.07, $p < 0.001$).

## Discussion

Our findings suggest that peri-ictal semiology is related to markers of GCS seizure severity such as PGES and peri-ictal breathing dysfunction in the form of PCCA and oxygen desaturation. We found a clear gradation of semiologic severity such that the presence of ictal decerebration, decortication, and hemi-decerebration was associated with the most striking signs of compromise (presence of PGES and larger drops in $Spo_2$), with

**Table 3** Univariate Analysis for Continuous Variables With Independent Continuous Variables

| | PGES Duration, s | | | Change in $Spo_2$, % | | | Hypoxemia Duration, s | | | $Spo_2$ Recovery, s | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Est | SE | *p* Value | Est | SE | *p* Value | Est | SE | *p* Value | Est | SE | *p* Value |
| **Age at study, y** | 0.440 | 0.130 | 0.001[a] | −0.070 | 0.087 | 0.423[a] | −1.295 | 0.460 | 0.005[a] | −0.026 | 0.371 | 0.945 |
| **Age at epilepsy onset, y** | 0.304 | 0.131 | 0.020[a] | −0.058 | 0.084 | 0.493 | −0.506 | 0.330 | 0.126 | −0.054 | 0.220 | 0.808 |
| **Clinical GCS duration, s** | 0.001 | 0.129 | 0.992 | −0.093 | 0.084 | 0.267 | 0.730 | 0.423 | 0.084[a] | −0.752 | 0.221 | 0.010[a] |

Abbreviations: Est = β estimate; GCS = generalized convulsive seizure; SE = standard error; $Spo_2$ = capillary peripheral oxygen saturation.
Covariate coefficient estimates, standard error, and corresponding *p* values from generalized estimating equations method.
[a] Variables introduced in multivariate analysis because $p < 0.1$, including age and sex as force-in variables.

**Table 4** Univariate Analysis for Categorical Variables

| | PGES, n | | | PCCA, n | | |
|---|---|---|---|---|---|---|
| | No | Yes | *p* Value | No | Yes | *p* Value |
| **Sex, n (%)** | | | 0.188[a] | | | [a]0.001 |
| **Male** | 55 (37.7) | 91 (62.3) | | 132 (92.3) | 11 (7.7) | |
| **Female** | 41 (27.9) | 106 (72.1) | | 108 (76.1) | 34 (23.9) | |
| **Age at study, $\bar{x}$ ± SD, y** | 34.4 ± 13.7 | 37.2 ± 13.2 | 0.229[a] | 36.7 ± 13.3 | 34.4 ± 14.0 | [a]0.397 |
| **Age at epilepsy onset, $\bar{x}$ ± SD, y** | 16.1 ± 15.0 | 19.8 ± 15.4 | 0.137 | 18.8 ± 16.2 | 18.8 ± 11.2 | 0.983 |
| **State, n (%)** | | | 0.250 | | | 0.961 |
| **Awake** | 42 (28.6) | 105 (71.4) | | 120 (84.5) | 22 (15.5) | |
| **Asleep** | 51 (35.7) | 92 (64.3) | | 118 (84.3) | 22 (15.7) | |
| **Epilepsy type, n (%)** | | | 0.060[a] | | | [a]0.031 |
| **Focal** | 87 (35.4) | 159 (64.6) | | 212 (88.0) | 29 (12.0) | |
| **Generalized** | 7 (17.9) | 32 (82.1) | | 25 (67.6) | 12 (32.4) | |
| **Neuroimaging, n (%)** | | | 0.633 | | | 0.415 |
| **Negative** | 54 (33.3) | 108 (66.7) | | 134 (84.3) | 25 (15.7) | |
| **Positive** | 39 (37.1) | 66 (62.9) | | 89 (88.1) | 12 (11.9) | |
| **Tonic phase semiology, n (%)** | | | 0.000[a] | | | 0.547 |
| **No tonic phase** | 67 (69.1) | 30 (30.9) | | 80 (87.0) | 12 (13.0) | |
| **Decerebration** | 16 (13.2) | 105 (86.8) | | 98 (81.7) | 22 (18.3) | |
| **Decortication** | 11 (23.4) | 36 (76.6) | | 40 (88.9) | 5 (11.1) | |
| **Hemi-decerebration** | 2 (7.1) | 26 (92.9) | | 22 (78.6) | 6 (21.4) | |
| **Postictal posturing, n (%)** | | | 0.001[a] | | | [a]0.064 |
| **No** | 95 (34.5) | 180 (65.5) | | 230 (86.1) | 37 (13.9) | |
| **Yes** | 1 (5.6) | 17 (94.4) | | 10 (55.6) | 8 (44.4) | |
| **Clinical GCS duration, $\bar{x}$ ± SD, s** | 55.0 ± 22.7 | 51.0 ± 15.1 | 0.230 | 54.0 ± 17.6 | 44.2 ± 16.3 | [a]0.010 |
| **Early $O_2$ administration, n (%)** | | | 0.091[a] | | | 0.390 |
| **No** | 22 (25.0) | 66 (75.0) | | 68 (81.0) | 16 (19.0) | |
| **Yes** | 74 (36.1) | 131 (63.9) | | 172 (85.6) | 29 (14.4) | |
| **ICA, n (%)** | | | 0.302 | | | 0.972 |
| **No** | 38 (31.4) | 83 (68.6) | | 99 (82.5) | 21 (17.5) | |
| **Yes** | 19 (22.9) | 64 (77.1) | | 67 (82.7) | 14 (17.3) | |
| **PCCA, n (%)** | | | 0.064[a] | | | — |
| **No** | 81 (33.9) | 158 (66.1) | | — | — | |
| **Yes** | 9 (20.5) | 35 (79.5) | | — | — | |
| **Cardiac comorbid conditions, n (%)** | | | 0.625 | | | 0.240 |
| **No** | 92 (33.2) | 185 (66.8) | | 229 (84.8) | 41 (15.2) | |
| **Yes** | 2 (25.0) | 6 (75.0) | | 5 (62.5) | 3 (37.5) | |

Continued

**Table 4** Univariate Analysis for Categorical Variables *(continued)*

| | PGES, n | | | PCCA, n | | |
|---|---|---|---|---|---|---|
| | No | Yes | *p* Value | No | Yes | *p* Value |
| **Respiratory comorbid conditions, n (%)** | | | 0.885 | | | 0.741 |
| **No** | 84 (32.8) | 172 (67.2) | | 212 (84.5) | 39 (15.5) | |
| **Yes** | 10 (34.5) | 19 (65.5) | | 22 (81.5) | 5 (18.5) | |
| **GCS frequency, n (%)** | | | 0.606 | | | 0.302 |
| **0** | 15 (46.9) | 17 (53.1) | | 30 (93.8) | 2 (6.3) | |
| **1–2** | 19 (37.3) | 32 (62.7) | | 42 (85.7) | 7 (14.3) | |
| **3–12** | 23 (28.8) | 57 (71.3) | | 68 (87.2) | 10 (12.8) | |
| **>12** | 34 (34.7) | 64 (65.3) | | 77 (80.2) | 19 (19.8) | |
| **Long-term SRI treatment, n (%)** | | | 0.297 | | | 0.611 |
| **No** | 80 (34.33) | 153 (65.67) | | 191 (84.5) | 35 (15.49) | |
| **Yes** | 13 (24.07) | 41 (75.93) | | 43 (81.13) | 10 (18.87) | |

Abbreviations: GCS = generalized convulsive seizure; ICA = ictal central apnea; PCCA = postconvulsive central apnea; PGES = postictal generalized EEG suppression; $Spo_2$ = capillary peripheral oxygen saturation; SRI = serotonin or serotonin-noradrenaline reuptake inhibitor.
Frequency and percentage and mean ($\bar{x}$) and SD were provided for categorical and continuous variables, respectively, with *p* values obtained from the generalized estimating equations method.
[a] Variables introduced in the multivariate analysis because $p < 0.1$, including age and sex as force-in variables.

ictal decerebration being associated with prolonged PGES. Absence of GCS tonic phase was associated with less profound changes. We also made the novel observation that postictal brainstem-type posturing is related to a 6-fold increased risk for PCCA and to longer hypoxemia duration and $Spo_2$ recovery periods after GCS seizures. Because PCCA has been observed in SUDEP and near-SUDEP, postictal brainstem posturing may suggest a semiologic marker of seizure severity and reflect a brainstem mechanism for SUDEP and near-SUDEP phenomena.

Decerebration and decortication are release phenomena in animal brainstem transection and stimulation studies[23–25] and are used to grade severity of encephalopathy in the Glasgow Coma Scale.[26] Brainstem transection between the red nucleus and vestibular nuclei produces decerebration, resulting from loss of inhibitory cerebral and cerebellar input on tonic vestibular responses, and disruption of rubrospinal function, resulting in opisthotonic posturing.[27] Brainstem transection above the red nucleus effectively removes most cortical influences, leaving unrestrained intact cerebellar afferents to vestibular nuclei.[27,28] Human studies provide less precise anatomic correlates, although flexor (decorticate) responses likely reflect more rostral and less severe supratentorial involvement than extensor (decerebrate) responses.[26,29] Functional, reversible decerebrate and decorticate responses similar to those found in GCS occur in human hepatic and other nonstructural causes of coma.[30,31] Similar posturing can occur in the postictal state. Immediate postictal tonic contractions were described by Gastaut and Broughton[32] at times as being "as intense as that of the tonic phase of the tonic-clonic attack," with trismus, and limb and back extension, indicating what they described as a "functional decerebrate state" in the absence of scalp EEG discharges. However, these have not hitherto been associated with seizure severity or SUDEP risk.

Tonic posturing during and after GCS may indicate dysfunction in cortical and diencephalic influences on descending pathways exerted through brainstem and cerebellar nuclei, likely through disinhibitory processes. The various patterns of observed posturing may reflect extent of seizure spread, with most caudal bilateral spread causing the most severe tonic semiologies. Sensitive respiratory structures amenable to descending seizure influences include the periaqueductal gray (PAG) and parabrachial pons, putative pre-Botzinger area, raphe nuclei, solitary tract nucleus, and nucleus ambiguus.[33–36] The PAG integrates multiple cortical and subcortical afferent signals and influences several respiratory-regulatory nuclei such as the pre-Botzinger complex. Ventrolateral caudal PAG activation in the cat decreases spontaneous activity and responsiveness to surrounding stimuli and elicits irregular breathing, hypotension, and bradycardia.[35] The ventrolateral medulla shows serotoninergic neuronal loss in patients with SUDEP; seizure spread to such brainstem levels, as evidenced by characteristic posturing, may produce postictal respiratory compromise in high-risk patients.[37] At the same time, disruption of ascending pathways, which impinge on cortical, basal ganglia, and other rostral motor control structures, may prolong the comatose postictal state and impair the protective effect of arousal.[38] PGES may reflect both cortical descending dysfunction and disruption of ascending inputs.[22]

Another potential explanation for posturing during and after GCS is brainstem depolarization.[39] Brainstem seizures have not

**Table 5** Multivariate Analysis for PGES Incidence and Duration

| | PGES | | | PGES Duration, s | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *p* Value | Est | 95% CI | *p* Value |
| **Sex, male** | 0.75 | 0.31 to 1.82 | 0.519 | −2.54 | −10.49 to 5.41 | 0.531 |
| **Age at study** | 1.01 | 0.97 to 1.044 | 0.734 | 0.51 | 0.13 to 0.89 | 0.008[a] |
| **Age at epilepsy onset** | — | — | — | 0.13 | −0.26 to 0.51 | 0.516 |
| **State, asleep** | — | — | — | — | — | — |
| **Epilepsy type, focal** | 0.82 | 0.23 to 2.91 | 0.752 | — | — | — |
| **Neuroimaging, positive** | — | — | — | — | — | — |
| **Tonic phase semiology** | | | | | | |
| **Decerebration** | 14.79 | 6.18 to 35.39 | <0.001[a] | 20.45 | 4.74 to 36.15 | 0.011[a] |
| **Decortication** | 11.26 | 2.96 to 42.93 | <0.001[a] | 11.09 | −4.41 to 26.59 | 0.161 |
| **Hemi-decerebration** | 48.56 | 6.07 to 388.78 | <0.001[a] | 5.22 | −10.16 to 20.61 | 0.506 |
| **Postictal posturing** | 3.57 | 0.26 to 49.99 | 0.345 | — | — | — |
| **Clinical GCS duration** | — | — | — | — | — | — |
| **Early $O_2$ administration** | 0.57 | 0.23 to 1.41 | 0.221 | −0.67 | −6.85 to 5.51 | 0.832 |
| **ICA** | — | — | — | 4.09 | −3.06 to 11.23 | 0.262 |
| **PCCA** | 2.43 | 0.78 to 7.54 | 0.125 | — | — | — |
| **Cardiac comorbid conditions** | — | — | — | — | — | — |
| **Respiratory comorbid conditions** | — | — | — | — | — | — |
| **GCS frequency** | — | — | — | — | — | — |
| **1–2** | | | | | | |
| **3–12** | | | | | | |
| **>12** | | | | | | |

Abbreviations: CI = confidence interval; Est = β estimate; GCS = generalized convulsive seizure; ICA = ictal central apnea; OR = odds ratio; PCCA = post-convulsive central apnea; PGES = postictal generalized EEG suppression; $Spo_2$ = capillary peripheral oxygen saturation.
[a] Statistically significant, $p < 0.05$.

been elicited in humans but have been triggered in animals after stimulation of the mesencephalic reticular formation, pons, and medulla.[24,40] PAG hyperactivation occurs in audiogenic seizures.[41] In a rodent model of 4-aminopyridine–induced hippocampal seizures, only those rats receiving high doses of 4-aminopyridine with tonic-clonic seizures and longer hippocampal discharges exhibited brainstem discharges. Longer brainstem discharges (>30 seconds) were associated with a respiratory arrest and accompanying cortical and hippocampal EEG flattening. In this study, spreading depression in the brainstem was not noted before respiratory dysfunction.[17] Similarly, in Kv1.1 knockout and Scn1a mice, an animal model of SUDEP, postictal spreading depolarization in the dorsal medulla after seizures produced cardiorespiratory arrest, preceded by EEG suppression and apnea.[42] Spreading depolarization has also been reproduced recently in a homozygous Cacna1a mouse model, in this case coincidently with apnea.[43] Specific subcortical structures such as superior olivary complex, PAG, pontine and midbrain reticular formation, substantia nigra pars reticularis, and amygdala, as well as Kolliker-Fuse, facial nucleus, and rostroventrolateral medullar, were significantly activated in an MRI study of DBA/1 mice with audiogenic seizures and seizure-induced respiratory arrest.[44] These findings suggest widespread but unsuccessful activation of compensatory mechanisms needed to overcome respiratory arrest. PAG stimulation in DBA/1 mice and C57BL/6 mice (nonepileptic mice) produced significant intensity-related decreases in interbreathing interval in both strains.[45] However, the effects were significantly reduced in DBA/1 compared to C57BL/6 mice, suggesting that PAG-deficient responses would confer susceptibility to seizure-induced cardiorespiratory failure.[45] Lastly, in the same animal model of SUDEP, neural activity in PAG was enhanced when a selective serotonin reuptake inhibitor was administered, preventing seizure-induced SUDEP.[46] These results are broadly in line with human neuroimaging and neuropathologic studies

**Table 6** Multivariate Analysis for Respiratory Outcomes

| | Presence of PCCA | | | Change in $Spo_2$, % | | | Hypoxemia Duration, s | | | $Spo_2$ Recovery, s | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | *p* Value | Est | 95% CI | *p* Value | Est | 95% CI | *p* Value | Est | 95% CI | *p* Value |
| **Sex, male** | 0.26 | 0.09–0.73 | 0.010[a] | −3.47 | −8.95 to 2.01 | 0.214 | 40.14 | 16.61 to 63.67 | <0.001[a] | 5.44 | −7.38 to 18.26 | 0.406 |
| **Age at study** | 0.99 | 0.95, 1.03 | 0.622 | −0.06 | −0.26 to 0.31 | 0.526 | −1.61 | −2.44 to −0.78 | <0.001[a] | −0.06 | −0.62 to 0.50 | 0.834 |
| **Age at epilepsy onset** | — | — | — | — | — | — | — | — | — | — | — | — |
| **State, asleep** | — | — | — | — | — | — | 3.85 | −20.02 to 27.72 | 0.752 | −11.00 | −22.01 to 0.02 | 0.050 |
| **Epilepsy type, focal** | 0.29 | (0.11, 0.80) | 0.017[a] | −3.061 | −9.57 to 3.45 | 0.356 | — | — | — | — | — | — |
| **Neuroimaging, positive** | — | — | — | — | — | — | — | — | — | — | — | — |
| **Tonic phase semiology** | — | — | — | | | | | | | — | — | — |
| **Decerebration** | | | | 9.57 | 3.83 to 15.32 | 0.001[a] | 14.48 | −12.24 to 41.20 | 0.288 | | | |
| **Decortication** | | | | 11.37 | 4.32 to 18.42 | 0.002[a] | −11.86 | −41.45 to 17.73 | 0.432 | | | |
| **Hemi-decerebration** | | | | 12.52 | 4.19 to 20.84 | 0.003[a] | −5.40 | −32.45 to 21.64 | 0.695 | | | |
| **Postictal posturing** | 6.06 | 1.76–20.89 | 0.004[a] | — | — | — | 47.87 | 24.47 to 71.27 | <0.001[a] | 27.84 | 1.98 to 53.69 | 0.035[a] |
| **Clinical GCS duration** | 0.95 | 0.91–0.99 | 0.017[a] | — | — | — | 0.87 | 0.03 to 1.70 | 0.041[a] | −0.53 | −0.92 to −0.14 | 0.009[a] |
| **Early $O_2$ administration** | — | — | — | — | — | — | — | — | — | −17.69 | −29.56 to −5.83 | 0.003[a] |
| **ICA** | — | — | — | — | — | — | — | — | — | — | — | — |
| **PCCA** | — | — | — | — | — | — | — | — | — | — | — | — |
| **Cardiac comorbid conditions** | — | — | — | — | — | — | — | — | — | — | — | — |
| **Respiratory comorbid conditions** | — | — | — | −9.38 | −15.26 to −3.50 | 0.002[a] | — | — | — | — | — | — |
| **GCS frequency** | — | — | — | | | | — | — | — | — | — | — |
| **0** | | | | 2.49 | −4.24 to 9.22 | 0.469 | | | | | | |
| **1–2** | | | | −5.43 | −11.67 to 0.82 | 0.089 | | | | | | |
| **2–12** | | | | 3.67 | −3.11 to 10.44 | 0.289 | | | | | | |

Abbreviations: CI = confidence interval; Est = β estimate; GCS = generalized convulsive seizure; ICA = ictal central apnea; OR = odds ratio; PCCA = postconvulsive central apnea; $Spo_2$ = capillary peripheral oxygen saturation.
[a] Statistically significant, $p < 0.05$.

that show damage in brainstem structures responsible for breathing modulation.[37,47]

Lastly, hypoxemia has been reported to cause reversible decerebration and decortication in humans. This suggests that hypoxemia during GCS could functionally transect the cerebrum from caudal structures, which would be reflected as postictal posturing. Ictal decerebration is associated with PGES,[13,48] although none of the previous studies observed decortication, which occurred in 16% of seizures in our study. We found any ictal brainstem posturing to be associated with PGES compared to seizures without tonic phase. However, when decerebration occurred, PGES duration was significantly longer; this lengthening did not occur with other semiologies. We postulate that ictal decerebration may be a clinical manifestation of caudal brainstem seizure spread, which in turn causes more severe cortical deafferentation, reflected by longer PGES duration. Thus, ictal decerebration may be a potential clinical biomarker of SUDEP.

Our finding of a relationship between postictal brainstem posturing and PCCA is intriguing. The former is a known phenomenon[32] further described in 31 GCS in 16 patients, in whom 48% of seizures had postictal clinical motor manifestations, including focal dystonic posturing.[16] Although precise descriptions of such posturing were not provided by the authors, the very specific brainstem-type posturing described in our study was found in only a minority of our study seizures (6%). Such postictal phenomena may represent seizure discharges in unrecorded brain regions such as the brainstem.[16] Direct human recordings of brainstem-propagated seizures are lacking, although there is some animal evidence to this effect.[17] There appears to be no direct causal relationship between ictal and postictal brainstem posturing, although it is clear that ictal brainstem posturing is associated with larger changes in $Spo_2$ and that decerebration is particularly related to prolonged PGES. Thus, there is a setting for severe breathing compromise in patients with ictal decerebration, and the subsequent occurrence of postictal brainstem posturing and PCCA in such patients may prove fatal. The 6-fold elevation in PCCA risk with postictal brainstem posturing and the prolongation in $Spo_2$ recovery and hypoxemia duration are striking findings and encourage scrutiny of the postictal VEEG recording in patients with high-risk SUDEP phenotypes.

Our study is a multicenter, prospectively designed study with a large sample size and detailed cardiorespiratory polygraphy compared to previous studies.[13,48] However, several limitations should be considered. Regarding consideration of false positives, the results for our main findings remain significant ($p < 0.01$ or 0.001), even after adjustment for multiple testing on 6 primary outcomes; thus, our conclusions remain. Our definition of apnea differs from previous extended definitions (10-second duration) based on sleep studies. Our definition is pragmatic, reflecting stimulation studies for symptomatogenic zones underpinning ICA, which has a consistent minimum duration of 5 seconds, even with brief 2-second stimulation bursts.[49] Thus, our definition is more sensitive to transient disturbances of breathing but may overdetect apnea.[5,22] Information regarding hypoxemia was available in <43% of seizures due to absence of $Spo_2$ sensors or loss of signal during monitoring from tonic-clonic movements, which is a difficulty consistently reported in prior literature.[7] However, we confirmed earlier observations regarding the effect of oxygen administration on $Spo_2$ recovery after GCS, which validates the reliability of the results.[7,50] Paradoxically, in our study, we found that PCCA was associated with shorter duration of GCS and similarly that $Spo_2$ recovery decreased with longer GCS duration. However, shorter duration of the GCS was associated with a more prolonged tonic phase compared to clonic phase. Our hypothesis is that not the tonic phase duration itself but its duration in comparison to the clonic phase duration may explain the seemingly paradoxical results. There were only 45 seizures in 34 patients with PCCA and 16 seizures in 12 patients with postictal brainstem posturing, and validation is required in a larger dataset, which we hope to achieve at the conclusion of this multicenter study. Our analysis did not include SUDEP outcomes in our patients, and thus, extrapolation of our findings to the SUDEP and near-SUDEP settings is speculative. Nonetheless, we believe that ictal and postictal brainstem posturing is associated with biomarkers of GCS severity, determined by PGES presence and duration and breathing compromise in the form of oxygen desaturation and PCCA. Further prospective follow-up is required to validate this hypothesis and to elucidate the role of peri-ictal semiology and SUDEP risk.

## Study Funding

Samden Lhatoo is funded by the Center for SUDEP Research: NIH/National Institute for Neurological Disorders and Stroke (NINDS) U01-NS090405 and NIH/NINDS U01-NS090407. Orrin Devinsky is funded by the Center for SUDEP Research: NIH/NINDS U01-NS090407 and NS090415. He has equity interest in Empatica, Tilray, Receptor Life Sciences, Egg Rock, Rettco, Qstate Biosciences, Tevard, and Engage. George Richerson is funded by the Center for SUDEP Research: NIH/NINDS U01-NS090414.

## Disclosure

Laura Vilella, Nuria Lacuey, Johnson P. Hampson, Liang Zhu, M.R. Sandhya Rani, Shirin Omidi, Manuela Ochoa-Urrea, Shiqiang Tao, and Rup K. Sanju report no disclosures. Daniel Friedman receives salary support for consulting and clinical trial related activities performed on behalf of The Epilepsy Study Consortium, a nonprofit organization. Dr. Friedman receives no personal income for these activities. NYU receives a fixed amount from the Epilepsy Study Consortium toward Dr. Friedman's salary. Within the past year, The Epilepsy Study Consortium received payments for research services performed by Dr. Friedman from Adamas, Axcella, Biogen, Crossject, CuroNZ, Engage Pharmaceuticals, Eisai, GW Pharmaceuticals, Pfizer, SK Life Science, Takeda, Xenon, and Zynerba. He has also served as a paid consultant for Eisai and Penumbra. He has received honorarium from Neuropace, Inc. He has received travel support from Medtronics and the Epilepsy Foundation. He receives research support from the

Centers for Disease Control and Prevention, NINDS, Epilepsy Foundation, Empatica, Epitel, UCB, Inc, and Neuropace. He serves on the scientific advisory board for Receptor Life Sciences. He holds equity interests in Neuroview Technology and Receptor Life Sciences. Maromi Nei, Kingman Strohl, Catherine Scott, Brian K Gehlbach, Norma J. Hupp, Jaison Hampson, Nassim Shafiabadi, Xiuhe Zhao, Victoria Reick-Mitrisin, Stephan Schuele, Jennifer Ogren, Ronald M. Harper, Beate Diehl, Lisa M. Bateman reports no disclosures. Philippe Ryvlin reports no disclosures, and Guo-Qiang Zhang report no disclosures. Go to Neurology.org/N for full disclosures.

## Publication History

Received by *Neurology* August 18, 2019. Accepted in final form August 17, 2020.

## Appendix Authors

| Name | Location | Contribution |
|---|---|---|
| **Laura Vilella, MD** | NINDS Center for SUDEP Research and Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston; Departament de Medicina, Universitat Autonoma de Barcelona, Spain | Major role in the acquisition and analysis of data; designed and conceptualized study; interpreted the data; drafted the manuscript for intellectual content |
| **Nuria Lacuey, MD, PhD** | Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston | Design and conceptualized study; interpreted the data; revised the manuscript for intellectual content |
| **Johnson P. Hampson, MSBME** | Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston | Analysis of data; video editing |
| **Liang Zhu, PhD** | Biostatistics & Epidemiology Research Design Core, Division of Clinical and Translational Sciences, McGovern Medical School, University of Texas Health Science Center at Houston | Analysis of data; statistical analysis; reviewed the manuscript for intellectual content |
| **Shirin Omidi, MD** | NINDS Center for SUDEP Research and Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston | Data acquisition |
| **Manuela Ochoa-Urrea, MD** | NINDS Center for SUDEP Research and Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston | Data acquisition |
| **Shiqiang Tao, PhD** | NINDS Center for SUDEP Research and Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA | Analysis of data |
| **M.R. Sandhya Rani, PhD** | NINDS Center for SUDEP Research and Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA | Recruiter; revised the manuscript for intellectual content |
| **Rup K. Sanju, MBBS** | NINDS Center for SUDEP Research, McGovern Medical School, University of Texas Health Science Center at Houston; University of Iowa Carver College of Medicine, Iowa City | Data acquisition; interpreted the data |
| **Daniel Friedman, MD** | NINDS Center for SUDEP Research, McGovern Medical School, University of Texas Health Science Center at Houston; NYU Langone School of Medicine, New York | Revised the manuscript for intellectual content |
| **Maromi Nei, MD** | NINDS Center for SUDEP Research, McGovern Medical School, University of Texas Health Science Center at Houston; Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA | Revised the manuscript for intellectual content |
| **Kingman Strohl, MD** | Division of Pulmonary, Critical Care and Sleep Medicine, University Hospitals Medical Center, Cleveland, OH | Interpreted the data |
| **Catherine Scott, MPhil** | NINDS Center for SUDEP Research, McGovern Medical School, University of Texas Health Science Center at Houston; Institute of Neurology, University College London, UK | Data acquisition |
| **Luke Allen, PhD** | NINDS Center for SUDEP Research, McGovern Medical School, University of Texas Health Science Center at Houston; Institute of Neurology, University College London, UK | Data acquisition |
| **Brian K. Gehlbach, MD** | NINDS Center for SUDEP Research, McGovern Medical School, University of Texas Health Science Center at Houston; University of Iowa Carver College of Medicine, Iowa City | Data acquisition; interpreted the data |
| **Norma J. Hupp, REEGTCLTm** | Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston | Data acquisition |
| **Jaison S. Hampson, MD** | NINDS Center for SUDEP Research and Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston | Data acquisition |

Continued

## Appendix *(continued)*

| Name | Location | Contribution |
|---|---|---|
| **Nassim Shafiabadi, MD** | Department of Neurology, Case Western Reserve University, Cleveland, OH | Data acquisition |
| **Xihue Zhao, MD** | Epilepsy Center, University Hospitals Cleveland Medical Center, OH | Data acquisition |
| **Victoria Reick-Mitrisin, MS** | Epilepsy Center, University Hospitals Cleveland Medical Center, OH | Data acquisition |
| **Stephan Schuele, MD, MPH** | NINDS Center for SUDEP Research, McGovern Medical School, University of Texas Health Science Center at Houston; Feinberg School of Medicine, Northwestern University, Chicago, IL | Revised the manuscript for intellectual content |
| **Jennifer Ogren, PhD** | Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston; Department of Neurobiology and the Brain Research Institute, University of California, Los Angeles | Data acquisition |
| **Ronald M. Harper, PhD** | Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston; Department of Neurobiology and the Brain Research Institute, University of California, Los Angeles | Revised the manuscript for intellectual content |
| **Beate Diehl, MD, PhD, FRCP** | Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston; Institute of Neurology, University College London, UK | Revised the manuscript for intellectual content |
| **Lisa M. Bateman, MD** | Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston; Department of Neurology, Columbia University, New York, NY | Revised the manuscript for intellectual content |
| **Orrin Devinsky, MD** | Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston; NYU Langone School of Medicine, New York | Revised the manuscript for intellectual content |
| **George B. Richerson, MD, PhD** | Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston; University of Iowa Carver College of Medicine, Iowa City | Data acquisition; interpreted the data |
| **Philippe Ryvlin, MD, PhD** | Department of Clinical Neuroscience, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland | Conceptualized study; revised the manuscript for intellectual content |

## Appendix *(continued)*

| Name | Location | Contribution |
|---|---|---|
| **Guo-Qiang Zhang, MS PhD** | NINDS Center for SUDEP Research and Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA | Analysis of data |
| **Samden D. Lhatoo, MD, FRCP** | NINDS Center for SUDEP Research and Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston | Designed and conceptualized study; analysis and interpretation of data; revised the manuscript for intellectual content |

## References


1. Sveinsson O, Andersson T, Carlsson S, Tomson T. The incidence of SUDEP: a nationwide population-based cohort study. Neurology 2017;89:170–177.
2. Tomson T, Nashef L, Ryvlin P. Sudden unexpected death in epilepsy: current knowledge and future directions. Lancet Neurol 2008;7:1021–1031.
3. Hesdorffer DC, Tomson T, Benn E, et al. Combined analysis of risk factors for SUDEP. Epilepsia 2011;52:1150–1159.
4. Lacuey N, Zonjy B, Hampson JP, et al. The incidence and significance of periictal apnea in epileptic seizures. Epilepsia 2018;59:573–582.
5. Vilella L, Lacuey N, Hampson JP, et al. Postconvulsive central apnea as a biomarker for sudden unexpected death in epilepsy (SUDEP). Neurology 2019;92:e171–e182.
6. Lhatoo SD, Faulkner HJ, Dembny K, Trippick K, Johnson C, Bird JM. An electroclinical case-control study of sudden unexpected death in epilepsy. Ann Neurol 2010;68:787–796.
7. Rheims S, Alvarez BM, Alexandre V, et al. Hypoxemia following generalized convulsive seizures: risk factors and effect of oxygen therapy. Neurology 2019;92:e183–e193.
8. Nass RD, Motloch LJ, Paar V, et al. Blood markers of cardiac stress after generalized convulsive seizures. Epilepsia 2019;60:201–210.
9. Park KJ, Sharma G, Kennedy JD, Seyal M. Potentially high-risk cardiac arrhythmias with focal to bilateral tonic-clonic seizures and generalized tonic-clonic seizures are associated with the duration of periictal hypoxemia. Epilepsia 2017;58:2164–2171.
10. Ryvlin P, Nashef L, Lhatoo SD, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. Lancet Neurol 2013;12:966–977.
11. Kuo J, Zhao W, Li CS, Kennedy JD, Seyal M. Postictal immobility and generalized EEG suppression are associated with the severity of respiratory dysfunction. Epilepsia 2016;57:412–417.
12. Peng W, Danison JL, Seyal M. Postictal generalized EEG suppression and respiratory dysfunction following generalized tonic-clonic seizures in sleep and wakefulness. Epilepsia 2017;58:1409–1414.
13. Alexandre V, Mercedes B, Valton L, et al. Risk factors of postictal generalized EEG suppression in generalized convulsive seizures. Neurology 2015;85:1598–1603.
14. Marchi A, Giusiano B, King M, et al. Postictal electroencephalographic (EEG) suppression: a stereo-EEG study of 100 focal to bilateral tonic-clonic seizures. Epilepsia 2019;60:63–73.
15. Tao JX, Yung I, Lee A, Rose S, Jacobsen J, Ebersole JS. Tonic phase of a generalized convulsive seizure is an independent predictor of postictal generalized EEG suppression. Epilepsia 2013;54:858–865.
16. Bateman LM, Mendiratta A, Liou JY, et al. Postictal clinical and electroencephalographic activity following intracranially recorded bilateral tonic-clonic seizures. Epilepsia 2019;60:74–84.
17. Salam MT, Montandon G, Genov R, Devinsky O, Del Campo M, Carlen PL. Mortality with brainstem seizures from focal 4-aminopyridine-induced recurrent hippocampal seizures. Epilepsia 2017;58:1637–1644.
18. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;51:1069–1077.
19. Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58:522–530.
20. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58:512–521.
21. Theeranaew W, McDonald J, Zonjy B, et al. Automated detection of postictal generalized EEG suppression. IEEE Trans Biomed Eng 2018;65:371–377.
22. Vilella L, Lacuey N, Hampson JP, et al. Incidence, recurrence, and risk factors for periictal central apnea and sudden unexpected death in epilepsy. Front Neurol 2019;10:166.

23. Sherrington CS. Decerebrate rigidity, and reflex coordination of movements. J Physiol 1898;22:319–332.
24. Fromm GH, Faingold C, Browning RA, Burnham WM. Epilepsy and the Reticular Formation: The Role of the Reticular Core in Convulsive Seizures. New York: Wiley-Liss; 1987.
25. Feldman MH. The decerebrate state in the primate, I: studies in monkeys. Arch Neurol 1971;25:501–516.
26. Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. Lancet 1974;2:81–84.
27. Kandel ER, Schwartz JH, Jessell TM, Siegelbaum SA, Hudspeth AJ. Principles of Neural Science. New York: McGraw-Hill Cos; 2000.
28. Feldman MH. The decerebrate state in the primate, II: studies in man. Arch Neurol 1971;25:517–525.
29. Plum F, Posner J. The Diagnosis of Stupor and Coma. Philadelphia, PA: FA Davis Co; 1982.
30. Conomy JP, Swash M. Reversible decerebrate and decorticate postures in hepatic coma. N Engl J Med 1968;278:876–879.
31. Seibert DG. Reversible decerebrate posturing secondary to hypoglycemia. Am J Med 1985;78:1036–1037.
32. Gastaut H, Broughton RJ. Epileptic Seizures. Clinical and Electrographic Features, Diagnosis and Treatment. Springfield, IL: Charles C Thomas; 1972.
33. Subramanian HH, Balnave RJ, Holstege G. The midbrain periaqueductal gray control of respiration. J Neurosci 2008;28:12274–12283.
34. Subramanian HH. Descending control of the respiratory neuronal network by the midbrain periaqueductal grey in the rat in vivo. J Physiol 2013;591:109–122.
35. Carrive P. The periaqueductal gray and defensive behavior: functional representation and neuronal organization. Behav Brain Res 1993;58:27–47.
36. Benarroch EE. Periaqueductal gray: an interface for behavioral control. Neurology 2012;78:210–217.
37. Patodia S, Somani A, O'Hare M, et al. The ventrolateral medulla and medullary raphe in sudden unexpected death in epilepsy. Brain 2018;141:1719–1733.
38. Dlouhy BJ, Gehlbach BK, Richerson GB. Sudden unexpected death in epilepsy: basic mechanisms and clinical implications for prevention. J Neurol Neurosurg Psychiatry 2016;87:402–413.
39. Faingold CL. Locomotor behaviors in generalized convulsions are hierarchically driven from specific brain-stem nuclei in the network subserving audiogenic seizure. Ann NY Acad Sci 1998;860:566–569.
40. Noebels JLAM, Rogawski MA, Olsen RW, Delgado-Escueta AV. Jasper's Basic Mechanisms of the Epilepsies. Oxford: Oxford University Press; 2010.
41. N'Gouemo P, Faingold CL. Periaqueductal gray neurons exhibit increased responsiveness associated with audiogenic seizures in the genetically epilepsy-prone rat. Neuroscience 1998;84:619–625.
42. Aiba I, Noebels JL. Spreading depolarization in the brainstem mediates sudden cardiorespiratory arrest in mouse SUDEP models. Sci Transl Med 2015;7:282ra246.
43. Loonen ICM, Jansen NA, Cain SM, et al. Brainstem spreading depolarization and cortical dynamics during fatal seizures in Cacna1a S218L mice. Brain 2019;142:412–425.
44. Kommajosyula SP, Randall ME, Brozoski TJ, Odintsov BM, Faingold CL. Specific subcortical structures are activated during seizure-induced death in a model of sudden unexpected death in epilepsy (SUDEP): a manganese-enhanced magnetic resonance imaging study. Epilepsy Res 2017;135:87–94.
45. Kommajosyula SP, Tupal S, Faingold CL. Deficient post-ictal cardiorespiratory compensatory mechanisms mediated by the periaqueductal gray may lead to death in a mouse model of SUDEP. Epilepsy Res 2018;147:1–8.
46. Kommajosyula SP, Faingold CL. Neural activity in the periaqueductal gray and other specific subcortical structures is enhanced when a selective serotonin reuptake inhibitor selectively prevents seizure-induced sudden death in the DBA/1 mouse model of sudden unexpected death in epilepsy. Epilepsia 2019;60:1221–1233.
47. Wandschneider B, Koepp M, Scott C, et al. Structural imaging biomarkers of sudden unexpected death in epilepsy. Brain 2015;138:2907–2919.
48. Okanari K, Otsubo H, Kouzmitcheva E, et al. Ictal symmetric tonic extension posturing and postictal generalized EEG suppression arising from sleep in children with epilepsy. Pediatr Neurol 2017;76:54–59.
49. Lacuey N, Hampson JP, Harper RM, Miller JP, Lhatoo S. Limbic and paralimbic structures driving ictal central apnea. Neurology 2019;92:e655–e669.
50. Seyal M, Hardin KA, Bateman LM. Postictal generalized EEG suppression is linked to seizure-associated respiratory dysfunction but not postictal apnea. Epilepsia 2012;53:825–831.

## 4.2. Incidence and Types of Cardiac Arrhythmias in the Peri-Ictal Period in Patients Having a Generalized Convulsive Seizure

Laura Vilella, MD, Christina Y. Miyake, MD, Ganne Chaitanya, MD, PhD, Johnson P. Hampson, MSBME, Shirin Jamal Omidi, MD, Manuela Ochoa-Urrea, MD, Blanca Talavera, MD, Oscar Mancera, MD, Norma J. Hupp, AAS, Jaison S. Hampson, MBBS, M.R. Sandhya Rani, PhD, Nuria Lacuey, MD, PhD, Shiqiang Tao, PhD, Rup K. Sainju, MBBS, Daniel Friedman, MD, Maromi Nei, MD, Catherine A. Scott, MPhil, Brian Gehlbach, MD, Stephan U. Schuele, MD, MPH, Jennifer A. Ogren, PhD, Ronald M. Harper, PhD, Beate Diehl, MD, PhD, FRCP, Lisa M. Bateman, MD, Orrin Devinsky, MD, George B. Richerson, MD, Guo-Qiang Zhang, PhD, and Samden D. Lhatoo, MD, FRCP

Neurology. 2024 Jul 9;103(1):e209501 Epub 2024 Jun 13.

PMID: 38870452.

DOI: 10.1212/WNL.0000000000209501

DOI: 10.1212/WNL.0000000000209501

DOI: 10.1212/WNL.0000000000209501

DOI: 10.1212/WNL.0000000000209501

DOI: 10.1212/WNL.0000000000209501

DOI: 10.1212/WNL.0000000000209501

DOI: 10.1212/WNL.0000000000209501

DOI: 10.1212/WNL.0000000000209501

DOI: 10.1212/WNL.0000000000209501

DOI: 10.1212/WNL.0000000000209501

DOI: 10.1212/WNL.0000000000209501

DOI: 10.1212/WNL.0000000000209501

# 5. GLOBAL SUMMARY OF THE RESULTS

We first analyzed the association of peri-ictal brainstem semiology with PGES and breathing dysfunction parameters in 295 GCS in 180 patients (90 females).

**Description of semiological findings**

*Ictal brainstem semiology*

The *tonic phase occurred in 197/295 (67%) seizures, and the jittery phase* in 238/295 (80.7%) seizures. By definition, the *clonic phase* was present in all seizures. The mean duration of the respective phases was 7.9 ± 4 seconds (median 7; 1–22 seconds), 9.5 ± 7.3 seconds (7; 1–55 seconds), and 39.3 ± 17.7 seconds (36; 5–123 seconds). The total duration of GCS was 52.3 ± 17.9 seconds (51; 5–154 seconds).

*Ictal decerebration* was seen in 122/295 (41.4%) seizures; *ictal decortication* was observed in 47/295 (15.9%) seizures; and *ictal hemi-decerebration* occurred in 28/295 (9.5%) seizures.

*Postictal brainstem semiology*

*Postictal brainstem posturing* was observed in 18/295 (6.1%) seizures in 12 patients (6.6%). In 16/18 (88.8%), seizures in 10/12 patients (83.3%) consisted of tonic flexion of the upper extremities, as seen in ictal decortication. In the remaining 2/18 seizures (2/12 patients), there was a tonic extension of the upper extremities, resembling ictal decerebration. Electrographic burst discharges were seen with decortication in 2 seizures (2 patients) followed by PGES. In the remainder, postictal brainstem posturing occurred along with PGES. Posturing was noted 7 ± 7.9 seconds (4; 1–30 seconds) after the last clonic jerk.

**PGES and breathing dysfunction during GCS and their association with peri-ictal brainstem semiology**

*Postictal Generalized Electroencephalographic Suppression (PGES)*

It was noted in 197/293 (67%) GCS in 132 patients. PGES duration was 36.5 ± 21.4 seconds (35; 1–169 seconds); we could not assess PGES in 2 GCS because of electrode artifacts.

In multivariate analysis, PGES risk increased with *ictal decerebration* (OR 14.79, 95%, CI 6.18 to 35.39, p < 0.001), *ictal decortication* (OR 11.26, 95% CI 2.96 to 42.93, p < 0.001), or *ictal hemi-decerebration* (OR 48.56, 95% CI 6.07 to 388.78, p < 0.001) compared to the absence of tonic phase.

PGES duration was longer in the presence of *ictal decerebration* (Est 20.45 seconds, 95% CI 4.74 to 36.15, p = 0.011) compared to GCS with absent tonic phase. There were no differences in PGES duration between seizures exhibiting ictal decortication (Est 11.09, 95% CI −4.41 to 26.59, p = 0.161) or hemi-decerebration (Est 5.22, 95% CI −10.16 to 20.61, p = 0.506) and GCS without tonic phase.

*Postconvulsive central apnea*

ICA occurred in 83/205 (40.4%) seizures in 48 patients, with a mean duration of 14.7 ± 8.6 seconds (12; 5–39 seconds). PCCA was noted in 45/285 (15.8%) seizures in 34 patients (mean duration 11.2 ± 12 seconds [8; 5–85 seconds]). Because of movement artifacts or loss of belt signal, the incidence of ICA and PCCA could not be determined in 90 and 10 GCS, respectively.

PCCA risk increased with *postictal brainstem posturing* (OR 6.06, 95% CI 1.76 to 20.89, p = 0.004).

*Hypoxemia duration*

It was available in 127 seizures, 142.6 ± 65.5 seconds (124; 25–314 seconds). It was associated with *postictal brainstem posturing* (Est 47.87 seconds, 95% CI 24.47 to 71.27, p < 0.001).

*$SpO_2$ recovery*

$SpO_2$ recovery was available in 120 seizures, 43.2 ± 34.2 seconds (35.5; −27 to 179 seconds). It was longer in the presence of *postictal brainstem posturing* (Est 27.84 seconds, 95% CI 1.98 to 53.69, p = 0.035).

Change in $SpO_2$

It could be reliably determined in 119 seizures, 34.4 ± 14.5% (33%; 2–77%).

Changes in $SpO_2$ were more extensive in GCS with *ictal decerebration* (Est 9.57%, 95% CI

3.83 to 15.32, p = 0.001), *ictal decortication* (Est 11.37%, 95% CI 4.32 to 18.42, p = 0.002), and *ictal hemi-decerebration* (Est 12.52%, 95% CI 4.19 to 20.84, p = 0.003) compared to GCS without tonic phase.

Full details on multivariate analysis results are shown in **Table 1** and **Table 2**

| | PGES | | | PGES duration (s) | | |
|---|---|---|---|---|---|---|
| | **OR** | **CI 95%** | **P** | **Est** | **CI 95%** | **P** |
| **Sex, male** | 0.75 | 0.31 to 1.82 | 0.519 | -2.54 | -10.49 to 5.41 | 0.531 |
| **Age at study** | 1.01 | 0.97 to 1.044 | 0.734 | 0.51 | 0.13 to 0.89 | 0.008* |
| **Age at epilepsy onset** | - | - | - | 0.13 | -0.26 to 0.51 | 0.516 |
| **State, asleep** | - | - | - | - | - | - |
| **Epilepsy type, focal** | 0.82 | 0.23 to 2.91 | 0.752 | - | - | - |
| **Neuroimaging, positive** | - | - | - | - | - | - |
| **Tonic Phase semiology** | | | | | | |
| Decerebration | 14.79 | 6.18 to 35.39 | <0.001* | 20.45 | 4.74 to 36.15 | 0.011* |
| Decortication | 11.26 | 2.96 to 42.93 | <0.001* | 11.09 | -4.41 to 26.59 | 0.161 |
| Hemi-decerebration | 48.56 | 6.07 to 388.78 | <0.001* | 5.22 | -10.16 to 20.61 | 0.506 |
| **Postictal posturing** | 3.57 | 0.26 to 49.99 | 0.345 | - | - | - |
| **Clinical GCS duration** | - | - | - | - | - | - |
| **Early $O_2$ administration** | 0.57 | 0.23 to 1.41 | 0.221 | -0.67 | -6.85 to 5.51 | 0.832 |
| **ICA** | - | - | - | 4.09 | -3.06 to 11.23 | 0.262 |
| **PCCA** | 2.43 | 0.78 to 7.54 | 0.125 | - | - | - |
| **Cardiac comorbidities** | - | - | - | - | - | - |
| **Respiratory comorbidities** | - | - | - | - | - | - |
| **GCS frequency** | - | - | - | - | - | - |
| 1-2 | | | | | | |
| 3-12 | | | | | | |
| >12 | | | | | | |

**Table 1. Multivariate analysis for PGES incidence and duration.** CI: confidence interval; Est: beta estimate; GCS: generalized convulsive seizure; ICA: ictal central apnea; OR: odds ratio; $O_2$: oxygen; PCCA: postconvulsive central apnea; PGES: postictal generalized EEG suppression; *statistically significant, p<0.05

| | Presence of PCCA | | | Change in SpO2 (%) | | | Hypoxemia duration (s) | | | $SpO_2$ recovery (s) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **OR** | **CI 95%** | **P** | **Est** | **CI 95%** | **P** | **Est** | **CI 95%** | **P** | **Est** | **CI 95%** | **P** |
| **Sex, male** | 0.26 | 0.09 to 0.73 | 0.010* | -3.47 | -8.95 to 2.01 | 0.214 | 40.14 | 16.61 to 63.67 | <0.001* | 5.44 | -7.38 to 18.26 | 0.406 |
| **Age at study** | 0.99 | 0.95 to 1.03 | 0.622 | -0.06 | -0.26 to 0.31 | 0.526 | -1.61 | -2.44 to -0.78 | <0.001* | -0.06 | -0.62 to 0.50 | 0.834 |
| **Age at epilepsy onset** | - | - | - | - | - | - | - | - | - | - | - | - |
| **State, asleep** | - | - | - | - | - | - | 3.85 | -20.02 to 27.72 | 0.752 | -11.00 | -22.01 to 0.02 | 0.050 |
| **Epilepsy type, focal** | 0.29 | 0.11 to 0.80 | 0.017* | -3.061 | -9.57 to 3.45 | 0.356 | - | - | - | - | - | - |
| **Neuroimaging, positive** | - | - | - | - | - | - | - | - | - | - | - | - |
| **Tonic Phase semiology** | - | - | - | | | | | | | - | - | - |
| Decerebration | | | | 9.57 | 3.83 to 15.32 | 0.001* | 14.48 | -12.24 to 41.20 | 0.288 | | | |
| Decortication | | | | 11.37 | 4.32 to 18.42 | 0.002* | -11.86 | -41.45 to 17.73 | 0.432 | | | |
| Hemi-decerebration | | | | 12.52 | 4.19 to 20.84 | 0.003* | -5.40 | -32.45 to 21.64 | 0.695 | | | |
| **Postictal posturing** | 6.06 | 1.76 to 20.89 | 0.004* | - | - | - | 47.87 | 24.47 to 71.27 | <0.001* | 27.84 | 1.98 to 53.69 | 0.035* |
| **Clinical GCS duration** | 0.95 | 0.91 to 0.99 | 0.017* | - | - | - | 0.87 | 0.03 to 1.70 | 0.041* | -0.53 | -0.92 to -0.14 | 0.009* |
| **Early $O_2$ administration** | - | - | - | - | - | - | - | - | - | -17.69 | -29.56 to -5.83 | 0.003* |
| **ICA** | - | - | - | - | - | - | - | - | - | - | - | - |
| **PCCA** | - | - | - | - | - | - | - | - | - | - | - | - |
| **Cardiac comorbidities** | - | - | - | - | - | - | - | - | - | - | - | - |
| **Respiratory comorbidities** | - | - | - | -9.38 | -15.26 to -3.50 | 0.002* | - | - | - | - | - | - |
| **GCS frequency** | - | - | - | | | | - | - | - | - | - | - |
| 0 | | | | 2.49 | -4.24 to 9.22 | 0.469 | | | | | | |
| 1-2 | | | | -5.43 | -11.67 to 0.82 | 0.089 | | | | | | |
| 3-12 | | | | 3.67 | -3.11 to 10.44 | 0.289 | | | | | | |

**Table 2. Multivariate analysis for respiratory outcomes** CI: confidence interval; Est: beta estimate; GCS: generalized convulsive seizure; ICA: ictal central apnea; OR: odds ratio; $O_2$: oxygen; PCCA: postconvulsive central apnea; s: seconds; $SpO_2$: peripheral capillary oxygen saturation *statistically significant, p<0.05

## Incidence of cardiac arrhythmias during GCS

To analyze cardiac arrhythmias during GCS, we studied 455 GCS in 249 patients (137 females). Patients had a mean of 1.8 seizures (minimum 1—maximum 12). Seizure characteristics are shown in **Table 3.**

| | Seizures with available data (n=455) | Results |
|---|---|---|
| **State, n (%)**<br>Awake<br>Sleep | 451 | <br>235 (52.1%)<br>216 (47.9%) |
| **Tonic phase semiology, n (%)**<br>Decerebration<br>Decortication<br>Hemi-decerebration<br>No tonic phase | 455 | <br>179 (39.3%)<br>72 (15.8%)<br>56 (12.3%)<br>148 (32.5%) |
| **Tonic phase duration, s, $\overline{X}$±sd (median [IQR])** | 455 | 8±3.9 (6 [5-10]) |
| **GCS duration, s, $\overline{X}$±sd (median [IQR])** | 455 | 51.8±18.9 (50 [41-60]) |
| **Postictal posturing, n (%)** | 448 | 41 (9.2%) |
| **Postictal posturing duration, s, $\overline{X}$±sd (median [IQR])** | 447 | 14.6±1.3 (12.5 [8-19]) |
| **Presence of PGES, n (%)** | 442 | 304 (68.8%) |
| **PGES duration, s (median [IQR])** | 441 | 40.12±1.3 (38 [27-46]) |
| **Hypoxemia pre-GCS duration, s (median [IQR])** | 234 | 23±21 (18 [9-31]) |
| **$SpO_2$ at GCS onset (%)** | 239 | 92.5±6.5 (94 [91-96]) |
| **$SpO_2$ recovery, s, $\overline{X}$±sd (median [IQR])** | 182 | 39.49±36.83 (34 [21-53]) |
| **Change in $SpO_2$ (%)** | 168 | 31.7±15.6 (31.5 [22-42]) |
| **ICA, n (%)** | 263 | 123 (46.8%) |
| **ICA duration, s, $\overline{X}$±sd (median [IQR])** | 263 | 17.5±1.1 (14 [9-23]) |
| **PCCA, n (%)** | 434 | 61 (15.1%) |
| **PCCA duration, s, $\overline{X}$±sd (median [IQR])** | 434 | 11.7±1.4 (9 [6-13]) |
| **Early $O_2$ administration, n (%)** | 455 | 237 (52.1%) |
| **Early suction, n (%)** | 455 | 217 (47.7%) |

**Table 3. Seizure characteristics.** GCS: generalized convulsive seizure; ICA: ictal central apnea; IQR: interquartile range; n: number; $O_2$: oxygen; PCCA: postconvulsive central apnea; PGES: postictal generalized electroencephalographic suppression; s: seconds; sd: standard deviation; $SpO_2$: peripheral capillary oxygen saturation; $\overline{X}$: mean;

Of note, for variables with conditional missing values (tonic phase duration, postictal posturing duration, PGES duration, Hypoxemia pre-GCS duration, ICA duration and PCCA duration) descriptive values summarize only those seizures in which the variable of interest was present (duration different than 0).

Overall, ictal sinus tachycardia was observed in 352/431 (81.7%) seizures (204/262 [77.9%] patients), and postconvulsive sinus tachycardia in 422/428 (98.6%) seizures (238/244 [97.5%] patients).

Complete EKG data for the preictal, ictal, and periods was available for 397 seizures in 228 patients, to calculate the incidence of cardiac arrhythmias.

The most common seizure-induced cardiac arrhythmia was *exaggerated sinus arrhythmia (ESA)*. Its incidence was 137/382 (35.9%) seizures in 106/224 (47.3%) patients.

The incidence of overall *arrhythmias of interest* was 50/352 (14.2%) seizures in 41/204 (20.1%) patients. *Exaggerated sinus arrhythmia with bradycardia (ESAWB)* was the most frequent seizure-induced cardiac arrhythmia of interest, with an incidence of 22/394 (5.6%) seizures in 18/225 (8%) patients. *Supraventricular tachycardia (SVT)* was the second most common seizure-induced arrhythmia of interest, with an incidence of 18/397 seizures in 17/228 (7.5%) patients.

The incidence of *bradycardia* was 13/356 (3.6%) in 10/208 (4.8%) patients. *Asystole* incidence was 2/397 (0.5%) seizures in 2/228 (0.9%) patients. It was postconvulsive in both cases, which were monitored near-SUDEP cases reported in a previous publication.(51) Incidence of *atrioventricular block (AVB)* was 1/395 (0.3%) in 1/226 (0.9%) patient. There were 3/397 (0.8%) seizures in 3/228 (1.3%) patients with seizure-induced *non-sustained ventricular tachycardia (NSVT)*, and 1/397 (0.25%) seizure with seizure-induced *atrial fibrillation.* No cases of *ventricular fibrillation* were recorded.

The frequency and incidence of different cardiac arrhythmia types for the various periods are shown in **Table 4**.

| | Preictal Arr (szs) n= 436 | Preictal Arr (pts) n= 241 | Ictal Arr (szs) n= 424 | Ictal Arr (pts) n= 237 | Ictal de novo Arr (szs) n= 424 | Ictal de novo Arr (pts) n= 237 | Postcon-vulsive Arr (szs) n= 400 | Postcon-vulsive Arr (pts) n= 229 | Postconvul-sive de novo Arr (szs) n= 400 | Postcon-vulsive de novo Arr (pts) n= 229 | Incidence of Arr (szs) | Incidence of Arr (pts) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No Arr** | 360 (82.6 %) | 207 (85.9%) | 376 (88.7%) | 212 (89.5%) | - | - | 146 (36.5%) | 97 (42.4%) | - | - | - | - |
| **Asystole** | 0 | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) | 2 (0.9%) | 2 (0.5%) | 2 (0.9%) | 2/397 (0.5%) | 2/228 (0.9%) |
| **AVB** | 2 (0.5%) | 2 (0.8%) | 2 (0.5%) | 2 (0.8%) | 0 | 0 | 3 (0.8%) | 3 (1.3%) | 1 (0.3%) | 1 (0.4%) | 1/395 (0.3 %) | 1/226 (0.4%) |
| **Bradycardia** | ***45 (10.3%)*** | ***41 (17%)*** | 17 (4%) | ***16 (6.8%)*** | 6 (1.4%) | 6 (2.5%) | 12 (3%) | 9 (3.9%) | 7 (1.8%) | 4 (1.7 %) | 13/356 (3.6%) | 10/208 (4.8%) |
| **ESAWB** | 4 (0.9%) | 4 (1.7%) | 6 (1.4%) | 5 (2.1%) | 6 (1.4%) | 5 (2.1%) | **19 (4.8%)** | **16 (7%)** | 16 (4%) | 13 (5.9%) | **22/394 (5.6%)** | **18/225 (8%)** |
| **SVTs** | 0 | 0 | 2 (0.5%) | 2 (0.8%) | 2 (0.5%) | 2 (0.8%) | **18 (4.5%)** | **17 (7.4%)** | 16 (4%) | 15 (6.5 %) | 18/397 (4.5%) | 17/228 (7.5%) |
| **AFib** | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) | 1 (0.4%) | 1 (0.3%) | 1 (0.4%) | 1/397 (0.25%) | 1/228 (0.4%) |
| **NSVT** | 0 | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) | 3 (1.3%) | 3 (0.8%) | 3 (1.3%) | 3/397 (0.8%) | 3/228 (1.3%) |
| **VF** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **ESA** | 15 (3.4%) | 14 (5.8%) | 13 (3.1%) | 13 (5.5%) | 10 (2.4%) | 10 (4.2%) | *141 (35.3%)* | *107 (46.7%)* | 127 (31.8%) | 97 (42.4%) | *137/382 (35.9%)* | *106/224 (47.3%)* |
| **PAC- single** | 7 (1.6%) | 7 (2.9%) | 4 (0.9%) | 4 (1.7%) | 3 (0.7%) | 3 (1.3%) | 43 (10.8%) | 36 (15.7%) | 40 (10%) | 33 (14.4%) | 43/391 (11%) | 36/225 (16%) |
| **PAC- couplets, bigeminy, trigeminy** | 1 (0.2%) | 1 (0.4%) | 3 (0.7%) | 3 (1.3%) | 2 (0.5%) | 2 (0.8%) | 10 (2.5%) | 7 (3.1%) | 9 (2%) | 7 (2.6%) | 11/396 (2.7%) | 9/228 (3.9%) |
| **PVC- single** | 6 (1.4%) | 6 (2.5%) | 3 (0.7%) | 3 (1.3%) | 3 (0.7%) | 3 (1.3%) | 59 (14.8%) | 49 (21.4%) | 53 (13.3%) | 46 (20.1%) | 56/391 (14,3%) | 49/225 (21.2%) |
| **PVC- couplets, bigeminy, trigeminy** | 2 (0.46%) | 1 (0.4%) | 2 (0.5%) | 2 (0.8%) | 2 (0.5%) | 2 (0.8%) | 5 (1.3%) | 4 (1.7%) | 2 (0.5%) | 2 (0.9%) | 4/395 (1%) | 3/227 (1.3%) |

**Table 4. Frequency of different cardiac arrhythmia (Arr) types for the different periods and incidence.** In bold, the most frequent Arr of interest occurring during the preictal, ictal and postconvulsive periods respectively, as well as the most incident Arr of interest. In italics, the most frequent Arr type occurring during preictal, ictal and postconvulsive periods, as well as the most incident Arr . AFib: Atrial fibrillation; AVB: atrioventricular block; Arr: cardiac arrhythmia. ESA: exaggerated sinus arrhythmia; ESAWB: exaggerated sinus arrhythmia with bradycardia; NSVT: non-sustained ventricular tachycardia; PAC: premature auricular complexes; pts: patients; PVC: premature ventricular complexes; SVTs: supraventricular tachyarrhythmias; szs: seizures; VF: ventricular fibrillation. Of note, since different arrhythmia types could be seen in the same seizure in the same period, the addition of percentages may add up above 100%.

**Recurrence of cardiac arrhythmias of interest across repeated seizures**

In patients with multiple recorded seizures, *ictal ESAWB* recurred in 1/4 (25%), and *postconvulsive ESAWB* recurred in 2/9 patients (22.2%). Recurrence of *ictal SVT* could not be determined since patients only had one seizure each. Regarding recurrence of *postconvulsive SVT,* it was noted in 1/7 (14.3%) patients. *Ictal bradycardia* recurred in one out of two patients (50%) with multiple seizures, whereas *postconvulsive bradycardia* recurred in two out of three patients (signal was lost in the other one). Only one patient with *NSVT* had multiple seizures recorded, and it did not recur in any of them.

Recurrence for asystole, AVB, and Afib could not be determined since patients exhibiting these arrhythmias had only one seizure recorded with available information.

**Relationship between cardiac arrhythmias of interest and electroclinical variables**

After excluding seizures with arrhythmias of interest in the preictal period, 198 seizures in 115 patients had complete demographic and electroclinical data. None of these variables, including peri-ictal brainstem semiology and PGES, were associated with the incidence of arrhythmias of interest. Results are shown in **Table 5**.

| | OR | 95% CI | P |
|---|---|---|---|
| **Sex, male** | 3.06 | 0.84-11.12 | 0.090 |
| **Age** | 0.85 | 0.67-1.08 | 0.183 |
| **Age epilepsy onset** | 1.18 | 0.93-1.50 | 0.168 |
| **Epilepsy duration** | 1.13 | 0.90-1.42 | 0.291 |
| **BMI** | 1.02 | 0.94-1.10 | 0.668 |
| **GCS frequency** | | | |
| >12 | 0.20 | 0.04-1.12 | 0.068 |
| 3-12 | 0.91 | 0.21-3.98 | 0.900 |
| 1-2 | 0.60 | 0.10-3.49 | 0.571 |
| **Respiratory comorbidities** | 0.21 | 0.03-1.59 | 0.132 |
| **Epilepsy type, generalized** | 0.54 | 0.07-3.98 | 0.546 |
| **Neuroimaging, positive** | 0.82 | 0.31-2.17 | 0.696 |
| **ASM, polytherapy** | 0.55 | 0.12-2.58 | 0.450 |
| **Na channel blockers** | 2.04 | 0.48-8.60 | 0.331 |
| **State, asleep** | 0.90 | 0.30-2.70 | 0.853 |
| **Tonic phase semiology** | | | |
| Decerebration | 2.66 | 0.27-25.93 | 0.400 |
| Decortication | 2.24 | 0.17-29.26 | 0.539 |
| Hemi-decerebration | 1.12 | 0.09-14.48 | 0.931 |
| **Tonic phase duration** | 1.12 | 0.98-1.28 | 0.098 |
| **GCS duration** | 1.01 | 0.98-1.03 | 0.654 |
| **Postictal posturing, yes** | 72.42 | 0.01-700281.60 | 0.360 |
| **Posturing duration** | 0.78 | 0.45-1.36 | 0.381 |
| **Presence of PGES** | 0.64 | 0.11-3.77 | 0.623 |
| **PGES duration** | 1.02 | 1.00-1.05 | 0.060 |
| **Early $O_2$ administration** | 1.46 | 0.52-4.06 | 0.471 |
| **Early suction** | 1.04 | 0.33-3.26 | 0.951 |

**Table 5. Electroclinical variables and their association with seizure-induced arrhythmias of interest.** ASM: antiseizure medication; BMI: body mass index; CI: Confidence Interval; GCS: generalized convulsive seizure; Na: sodium; OR: odds ratio; $O_2$: oxygen; PGES: postictal generalized electroencephalographic suppression

When considering a subset of seizures with complete respiratory data (111 seizures in 73 patients), there was no association between the respiratory variables and the incidence of arrhythmias of interest, as shown in **Table 6**.

| | OR | 95% CI | P |
|---|---|---|---|
| **Hypoxemia pre-GCS duration** | 0.94 | 0.80-1.11 | 0.459 |
| **$SpO_2$ at GCS onset** | 1.05 | 0.89-1.25 | 0.559 |
| **$SpO_2$ recovery** | 1.01 | 0.99-1.03 | 0.537 |
| **Change in $SpO_2$** | 1.00 | 0.96-1.05 | 0.901 |
| **ICA** | 0.83 | 0.11-5.96 | 0.849 |
| **ICA duration** | 1.04 | 0.96-1.13 | 0.358 |
| **PCCA** | 1.28 | 0.16-10.31 | 0.818 |
| **PCCA duration** | 0.94 | 0.78-1.13 | 0.499 |

**Table 6. Respiratory variables and their association with seizure-induced arrhythmias of interest.** GCS: generalized convulsive seizure; CI: Confidence Interval; ICA: ictal central apnea; OR: odds ratio; PCCA: postconvulsive central apnea; $SpO_2$: oxygen saturation;

## Arrhythmias of interest in SUDEP patients

During a follow-up period of 48.36 ± 31.34 (43.97 [23.7–69.23]) months, eleven patients (who accounted for 18 seizures) were lost to follow-up.

There were 8 SUDEP cases (two female [two definite, five probable, 1 one possible]). One of them had bradycardia as an arrhythmia of interest in the preictal period. Three of the remaining patients (42%) had at least one seizure with a seizure-induced arrhythmia of interest. One patient had postconvulsive bradycardia in one seizure and postconvulsive ESAWB in another seizure. Another patient had postconvulsive ESAWB, and one patient had postconvulsive SVT. Seizures with ESAWB were proportionally higher amongst SUDEP cases (11%) than in the non-SUDEP cases (4.6%) ($z = -12.39$, $p < 0.01$). This was also true regarding the proportion of SUDEP patients with ESAWB (25%) was also higher compared to non-SUDEP patients (6.6%) ($z = -3.03$, $p < 0.01$). Postconvulsive bradycardia was proportionally more common in SUDEP patients (12.5%) when compared to non-SUDEP (3.8%) cases ($z = -16.66$, $p < 0.01$).

# 6. GLOBAL SUMMARY OF THE DISCUSSION

## 6.1. Discussion

In our first study, we provide descriptive information about brainstem semiological features during GCS, PGES, and variables of breathing dysfunction in a large cohort of patients. Specifically, a tonic phase is seen in over two-thirds of GCS, overlapping with PGES incidence (67%). Ictal central apnea is seen in 40% of the seizures, which is more than twice the incidence of PCCA (15%). The mean hypoxemia duration is 142 seconds, the mean $SpO_2$ recovery is 43 seconds, and $SpO_2$ decreases by one-third from the baseline. Moreover, we report the incidence of postictal brainstem posturing for the first time, which is seen in a small proportion of GCS (6%). In our second study, the descriptive results regarding GCS features are similar, given the overlap of two-thirds of the studied population, and we offer an in-depth analysis of cardiac arrhythmias occurring during GCS.

The results of our studies indicate that peri-ictal brainstem semiology is related to biomarkers of seizure severity in GCS, determined by PGES and peri-ictal breathing dysfunction. Contrarily, no association was found between semiology, PGES, or breathing dysfunction and the incidence of arrhythmias of interest.

Ictal decerebration, decortication, and hemi-decerebration were related to the presence of PGES and more significant drops in $SpO_2$ compared to patients without a tonic phase. Moreover, ictal decerebration was associated with a longer duration of PGES, whereas ictal decortication and hemi-decerebration were not. These findings suggest a semiologic scale of severity in which ictal decerebration, followed by decortication and hemi-decerebration, is associated with more profound arousal impairment after GCS.

Postictal brainstem posturing increased PCCA risk by sixfold and was also related to prolonged hypoxemia duration and $SpO_2$ recovery after GCS. Given that PCCA has been reported in SUDEP and near-SUDEP cases,(51) our finding confers postictal brainstem posturing a potential role as a biomarker of seizure severity and provides a potential SUDEP physiopathological mechanism through brainstem malfunction.

Decerebration and decortication have been described in animal studies as release phenomena.(16, 127, 128) Decerebration occurs when inhibitory cerebral and cerebellar input on

tonic vestibular responses is lost, and the rubrospinal tract is disrupted, such as during transections between the red nucleus and vestibular nuclei. This results in opisthotonos (decerebration).(129) Transections above the red nucleus preserve cerebellar inputs to vestibular nuclei, removing most of the cortical effect (decortication).(129, 130)

In humans, decerebration and decortication are used in the Glasgow Coma Scale to evaluate the extent of impaired awareness.(131) Similar posturing has been described in human cases of hepatic encephalopathy and other non-lesional etiologies of coma, as well as in the postictal phase.(132, 133) Gastaut and Broughton described the latter as tonic contractions in the immediate postictal period, similar to the tonic phase.(12) They called it a "functional decerebrate state," but no association was looked for with peri-ictal breathing dysfunction until the work presented in this thesis.

Peri-ictal brainstem posturing may be the clinical manifestation of GCS-induced cortical and diencephalic dysfunction on inhibitory descending pathways to the brainstem and cerebellar nuclei, resulting in a release phenomenon. Following the animal transection models, we hypothesize that the variety of peri-ictal brainstem posturing patterns is attributable to different degrees of brainstem involvement, with the most caudal bilateral involvement translating into decerebration.

The brainstem hosts fundamental structures for respiratory homeostasis, such as the periaqueductal gray (PAG), the parabrachial pons, the pre-Botzinger complex, the raphe nuclei, the nucleus ambiguous, and the solitary tract nucleus.(134-137) The PAG acts as an integrative center and influences other breathing regulatory nuclei. Stimulation of the caudal ventrolateral PAG in cats produces irregular breathing, bradycardia, hypotension, and decreased responsiveness.(136) It is important to note that serotonergic neurons in the dorsal raphe nuclei protect against hypercapnia by promoting arousal through ascending pathways and increasing respiratory drive by activating the pre-Botzinger complex.(113) Seizure-induced malfunction of the brainstem nuclei mentioned earlier could lead to breathing dysfunction and impair the protective effect of arousal, putting patients with GCS at SUDEP risk.

Apart from being a release phenomenon, peri-ictal brainstem posturing could also be due to brainstem depolarization.(17) Brainstem seizures have not been demonstrated in humans but have been elicited in animals.(16, 138) Injection of 4-aminopyridine in the hippocampus in a rat model of seizures led to brainstem discharges in those animals exhibiting tonic-clonic seizures with sustained hippocampal discharges. Brainstem discharges were accompanied by hippocampal and cortical EEG suppression and respiratory arrest. In this particular study, spreading depression in the brainstem was not noted preceding respiratory dysfunc-

tion. (139) On the other hand, spreading depression has been observed in animal models of SUDEP, such as Kv1.1 knockout mice, Scn1a mice, and Cacna1a mice.(111, 112) Spreading depolarization in these models resulted in EEG flattening and apnea. Similarly, audiogenic seizures in DBA/1 mice can result in breathing arrest.(140) In this animal model of SUDEP, a manganese-enhanced MRI performed immediately after seizure-induced respiratory arrest showed an activation of the PAG, superior olivary complex, midbrain and pontine reticular formation, pars reticularis in the substantia nigra, the Koller-Fuse nucleus, facial nucleus, and amygdala.(140) These findings go in line with the observation that people with epilepsy have greater brainstem BOLD activation and recruit more structures following a hypercapnic challenge compared to healthy controls. (141) We postulate that such larger activations are an attempt to overcome hypercapnia and respiratory arrest by an already deficient respiratory network. This is supported by the observation that stimulation of the PAG in the DBA/1 model results in smaller increases in respiratory rate when compared to controls. (142) Moreover, in patients with epilepsy, interictal response to hypercapnia has an inverse relationship with baseline end-tidal $CO_2$ and the magnitude and duration of transcutaneous $CO_2$ after a GCS.(118) Neuroimaging and autopsy studies in SUDEP patients demonstrate brainstem atrophy, a decrease in neuropeptides in the ventrolateral medulla, and a reduction of serotonergic neurons in the dorsal raphe nuclei.(121, 122) Interestingly, mice lacking serotoninergic neurons in the central nervous system ($Lmx^{1bf/f/p}$mice) exhibit a lower threshold for seizures and increased mortality induced by seizures, which is prevented by mechanical ventilation or pretreatment with a serotonin receptor agonist.(114) Seizure-induced death has also been prevented in DBA/1 mice after administering selective serotonin reuptake inhibitors.(143) In humans, selective serotonin reuptake inhibitors decrease the incidence of ICA and are associated with less profound desaturation in non-GCS seizures. (144, 145)

Another explanation for peri-ictal brainstem posturing could be through functional brainstem transection due to GCS-induced hypoxemia since more significant drops in $SpO_2$ were noted in patients with ictal brainstem posturing, and postictal brainstem posturing was associated with longer hypoxemia and $SpO_2$ recovery durations. Lastly, ictal decerebration had already been reported to be associated with the incidence of PGES, but in our study, we also found it was associated with longer PGES duration.(103) This was not observed with other tonic phase semiologies. We hypothesize that the most caudal brainstem seizure spread results in decerebrate posturing and cortical deafferentation, leading to prolonged PGES.

Based on the results of our study, scrutiny of the ictal and postictal semiology may be relevant to flag patients with more severe seizures in terms of breathing dysfunction and PGES, potentially posing them at increased SUDEP risk.

Regarding cardiac arrhythmias, the incidence of potentially fatal arrhythmias was rare, just fewer than 1% of patients. Interestingly, cardiac arrhythmias of interest were not associated with GCS semiology, PGES, metrics of breathing dysfunction, or any other electroclinical variables.

The physiopathology for seizure-induced arrhythmias is ill-defined but likely reflects combined mechanisms. Ictal activation of the central autonomic network (e.g., insular cortex, amygdala, anterior cingulate, and orbitofrontal) (88, 90, 146, 147) is unlikely, given that arrhythmias did not occur consistently in patients with repeated seizures. An exception to this may be ictal asystole, but we did not have any cases among our patients.(148) Nevertheless, only 17% of the patients in our study had three or more seizures with cardiac arrhythmias of interest. Therefore, conclusions about the nature of seizure-induced cardiac arrhythmias (a semiological finding vs a stochastic phenomenon) cannot be made. Hypoxemia duration has been linked to peri-ictal high-risk cardiac arrhythmias, but we found no association between respiratory variables and the incidence of cardiac arrhythmias of interest.(68) Another explanation for the occurrence of cardiac arrhythmias in patients with epilepsy is the ictal catecholamine surge.(69, 149) This could produce effects acutely and also cause myocardial damage and electrical dysfunction due to repeated exposure, predisposing to an "epileptic heart".(150) Autopsy studies of SUDEP and control epilepsy patients have shown myocardial fibrosis and cardiac hypertrophy in up to 20%, both of which may predispose to arrhythmias.(151) Chronic ASM use may have harmful long-term effects, particularly those inducing cytochrome P450 and those with potential pro-arrhythmic properties (e.g., sodium channel blockers).(43, 150, 152-154) However, despite their potential pro-arrhythmogenic properties, no individual ASM has been associated with an increased SUDEP risk.(44, 45) Consistent with this, we did not find an association between sodium channel blockers and the incidence of arrhythmias of interest. The lack of association of arrhythmias of interest with any of the electroclinical variables suggests that arrhythmias caused by seizures may be unrelated to cortical suppression or hypoxia and may be due to underlying cardiac occult (structural [e.g., myocardial fibrosis] or functional [e.g., channelopathy]) abnormalities.

In our cohort, 82.6% of the seizures did not have any arrhythmia in the preictal period, whereas ictal and postconvulsive arrhythmias were seen in more than two-thirds. These results confirm prior reports of arrhythmias occurrence during and after epileptic seizures. (63, 155)

Seizure-induced, irregular changes in the R-R interval, alternating acceleration, and deceleration, resembling an ESA, were the most frequent arrhythmia in our study, with an incidence of 36% seizures. This was first observed in temporal lobe seizure patients.(156) ESA

was the second most frequent cardiac arrhythmia in GCS (18.8%, following premature atrial contractions)(63) and the most common (42%) in another study of GCS and non-GCS.(157) Sinus arrhythmia may be a surrogate of vagal tone. Nevertheless, sinus arrhythmia is modulated by breathing changes, showing a direct correlation with tidal volume and an inverse correlation with breathing rate.(158) Sinus arrhythmia is a significant component of heart rate variability (HRV).(159, 160) Research focused on HRV analysis after GCS has yielded inconsistent results across studies, although some investigations described a decrease in low-frequency power (LFP) and other time domain parameters, suggesting decreased HRV and exacerbated sympathetic tone.(161-163) Moreover, patients who succumb to SUDEP have a decreased LFP during the awake state compared to controls. However, such a difference is not encountered after excluding patients on beta-blockers in both groups. (83) The high prevalence of ESA in our cohort may translate to a preserved HRV rather than a biomarker of seizure severity. However, in less than 6% of the seizures, ESA was associated with bradycardic beats (ESAWB). Its underlying mechanism is unknown, but it may reflect a parasympathetic overdrive. Compared to non-SUDEP cases, ESAWB was proportionally higher among SUDEP patients. This finding is promising, but caution is advised since larger case-control studies should be conducted to understand the real impact of this observation.

Sinus tachycardia was observed in the postconvulsive period in 98.6% of the seizures, similar to other studies.(164) Whereas bradycardia was present at baseline in 10.3% of the seizures (mainly sleep onset), it persisted postictally in only 0.8%. Thus, tachycardia is the physiologic response to a GCS, and conversely, the presence of bradyarrhythmias, particularly if *de novo*, in the postictal period, likely indicates a maladaptive, aberrant response and abnormal post-seizure homeostasis.

The incidence of arrhythmias of interest was comparable to results obtained from prior retrospective studies on seizure-induced cardiac arrhythmias, which validates the reproducibility of our results. In our study, the incidence of bradycardia was 3.6%, similar to the frequency of ictal/postconvulsive bradycardia (2.7%) described in another study.(68) The incidence of SVT in our cohort was 4.5%, comparable to previously reported 0.5-6.3%.(63, 68) Only one seizure (0.25%) in our study induced Afib, whereas other series have reported an incidence of 0-6.3%.(63, 68) We found the incidence of NSVT was 0.8%, ranging from 0-2.7% in previous literature.(63, 68) In accordance with prior studies, we did not see any cases of VF.(63, 68) Surprisingly, we did not record any cases of ictal asystole (only two cases ([0.5%] of postconvulsive asystole), which has been reported to occur in 2.2%-6.3% of GCS series,(63, 68) and with an overall incidence of 0.27% in epilepsy patients.(165) Our findings align with a study with implantable loop-recorders, which applied similar criteria for defining arrhythmias of interest. However, in this study, arrhythmias were reported altogether

regardless of the seizure type.(157) These results differ from those of another study in which long-term monitoring did not detect any clinically significant arrhythmias.(166) However, in this latter study, the definition of clinically significant arrhythmia was stricter than our definition of arrhythmias of interest. Moreover, it included fewer patients (n=49), and patients with suspected seizure-induced asystole were excluded.(166)

In our cohort, almost half of the patients who later died from SUDEP exhibited seizure-induced arrhythmias of interest. None of these were malignant ventricular tachyarrhythmias; most exhibited transient bradycardic beats. This finding is consistent with observations from the MORTEMUS study, where some cases had transient postictal bradycardia and asystole preceding or concurrently with the onset of breathing alteration.(48) Therefore, the significance of seizure-induced bradycardia and ESAWB in SUDEP physiopathology is worth investigating. However, given that respiratory arrest preceded cardiac arrest in all monitored SUDEP cases, it is unlikely that seizure-induced bradycardia or ESAWB is the ultimate cause of SUDEP, although these, combined with breathing dysfunction and impaired arousal, could set the perfect grounding for SUDEP to occur. Interestingly, there are at least two patients in the literature who died of probable SUDEP despite having a well-functioning pacemaker.(70, 71) Therefore, the benefit of cardiac pacemakers, besides preventing falls, remains elusive regarding SUDEP prevention. On the contrary, respiratory pacemakers, mechanical ventilation, and other techniques to restore breathing function have prevented SUDEP in animal models, whereas cardiac muscarinic blockade to treat bradycardia did not.(58, 61, 167)

## 6.2. Limitations

Our studies are prospective, multicentric, and include a large number of patients. However, they have several limitations.

The first one is derived from the inevitable artifacts in polygraphy during GCS, particularly in the convulsive phase. Breathing cannot be reliably assessed during this period, and arrhythmia evaluation is limited to the artifact-free portions of the recording. The presence of transient ictal arrhythmias may have been underestimated, although if persistent, these were detected in the postconvulsive period and, therefore, appropriately labeled as seizure-induced. Moreover, we only analyzed two minutes before the seizure onset. Consequently, we cannot rule out that some patients had indeed intermittent arrhythmias at baseline that were not seen in the three-minute preictal period and were incorrectly labeled as seizure-induced.

Another limitation comes from definitions. Regarding apnea (ICA and PCCA), we used a pragmatic definition (one missed breath with a minimum duration of 5 seconds) based on stimulation studies for ICA, which have consistently shown a duration of at least 5 seconds, even when brief two-second stimulation trains were applied.(49) Regarding cardiac arrhythmias, the definition we used for arrhythmias of interest was less stringent than those used in other studies. We included bradycardia and ESAWB as arrhythmias of interest because tachycardia prevails during and after GCS, whereas postictal bradycardia has been mainly recorded in (near) SUDEP cases.(64, 68) Given that SUDEP is a rare phenomenon, understanding its physiopathology is based on identifying the most consistent responses (presumably physiological) and recognizing deviations from the norm.

In the study about cardiac arrhythmias, arrhythmias of interest were analyzed as a group since some of the arrhythmia types were seen in <1% of the seizures. Since the incidence is low, larger studies will be needed to analyze the association between individual arrhythmia types, seizure severity biomarkers, and SUDEP risk. On a similar note, associations between cardiac comorbidities, VNS treatment, and the occurrence of arrhythmias of interest could not be assessed because of an insufficient number of cases for statistical analysis. Lastly, information about medications with potential effects on cardiac rhythm besides ASM was not available.

# 7. CONCLUSIONS

- Peri-ictal brainstem semiology is a biomarker of GCS severity defined by PGES and variables of respiratory dysfunction, but not of cardiac arrhythmias of interest (ESAWB, SVT, Afib, AVB, bradycardia, asystole, NSVT, VF).

- A tonic phase, either as ictal decerebration, decortication, or hemi-decerebration is seen in two-thirds of GCS, which overlaps with the incidence of PGES. The sole presence of tonic phase during GCS increases the risk of PGES and is associated with larger drops in $SpO_2$. Moreover, ictal decerebration is associated with longer PGES duration.

- Postictal brainstem semiology, seen in less than 10% of GCS, is associated with a sixfold increased risk of PCCA and longer hypoxemia and $SpO_2$ recovery after GCS.

- Potentially fatal cardiac arrhythmias such as NSVT, VF, bradycardia, asystole, AVB, AFib, and SVT are rare. Along with ESAWB, these are unrelated to peri-ictal brainstem semiology, PGES, and variables of respiratory dysfunction. This suggests that arrhythmias caused by GCS are unrelated to cortical suppression or hypoxia and may be due to underlying occult (structural or functional) cardiac abnormalities.

# 8. FUTURE DIRECTIONS

A better understanding of SUDEP physiopathology and identification of SUDEP biomarkers are required to transform SUDEP research into meaningful interventions to prevent it.

The results of our research studies set the ground for conducting SUDEP case-control studies analyzing the role of peri-ictal brainstem semiology, PGES, PCCA, hypoxemia, and post-convulsive bradycardia/ESAWB as potential SUDEP biomarkers.

Identifying SUDEP biomarkers will allow the design of cost-effective clinical trials that assess interventions aimed at restoring arousal and respiratory function after GCS in patients at high SUDEP risk. Potential interventions to test should include drugs, such as modulators of the serotonin or adenosine axis, amongst others. Another strategy is using diaphragmatic or central respiratory pacemakers, based on prior cortical electrical stimulation studies showing that cortical and thalamic stimulation can enhance breathing.(168, 169) Interventions such as delivery of tactile/acoustic stimuli or oxygen therapy may also be effective in shortening the postictal state and deserve further investigation. On another note, in the era of wearable devices, it would be worth investigating whether these can reliably predict impending SUDEP or alert in case SUDEP occurs so that immediate resuscitation is initiated. (170, 171)

Investigating the presence of blood biomarkers, such as serotonin, adenosine, orexin,(172) and other markers of cardiorespiratory distress among different SUDEP-risk profiles based on clinical biomarkers may allow us to quantify SUDEP risk and understand SUDEP physiopathology.

Lastly, analysis of peri-ictal brainstem semiology may identify patients with severe GCS features without needing inpatient VEEG monitoring.

# 9. BIBLIOGRAPHY


1. Patel P, Moshé SL. The evolution of the concepts of seizures and epilepsy: What's in a name? Epilepsia Open. 2020;5(1):22-35.
2. Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, Engel J, Jr. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia. 2005;46(4):470-2.
3. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014;55(4):475-82.
4. Sempere AP, Mola S, Medrano V, Esguevillas T, Costa C, Salazar V, et al. Epidemiología descriptiva de la asistencia neurológica ambulatoria en el Área Vega Baja (Alicante). RevNeurol.35(09):0822-826.
5. Fiest KM, Sauro KM, Wiebe S, Patten SB, Kwon CS, Dykeman J, et al. Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies. Neurology. 2017;88(3):296-303.
6. García-Ramos R, García Pastor A, Masjuan J, Sánchez C, Gil A. [Feen report on epilepsy in Spain]. Neurologia (Barcelona, Spain). 2011;26(9):548-55.
7. Zack M, Kobau R. National and State Estimates of the Numbers of Adults and Children with Active Epilepsy — United States, 2015. MMWR Morb Mortal Wkly Rep. 2017:821-5.
8. Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. Epilepsia. 1993;34(3):453-68.
9. Gastaut H, Caveness WF, Landolt H, Lorenzt de Haas AM, McNaughton FL, Magnus O, et al. A proposed international classification of epileptic seizures. Epilepsia. 1964;5:297-306.
10. Gastaut H. Clinical and electroencephalographical classification of epileptic seizures. Epilepsia. 1969;10:Suppl:2-13.
11. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):522-30.
12. Gastaut H, Broughton R. Epileptic Seizures. Clinical and electrographic features, diagnosis and treatment. Springfield, Illinois, USA: Charles C Thomas; 1972.

13. Lhatoo S, Luders H. The semiology and pathophysiology of the secondary generalized tonic-clonic seizures. In: Hirsch E, Andermann E, Chauvel P, Engel J, F. LdS, Luders H, editors. Generalized Seizures: From clinical phenomenology to underlying systems and networks. France: Éditions John Libbey Eurotext; 2006. p. 229-45.
14. Chauvel P. What is a generalized seizure? In: Hirsch E, Andermann E, Chauvel P, Engel J, Lopez da Silva F, Luders H, editors. Generalized seizures: from clinical phenomenology to underlying systems and networks. France: Éditions John Libbey Eurotext; 2006. p. 3-22.
15. Faingold CL, Evans MS. Pathophysiology of Generalized Tonic-Clonic Seizures. In: Panayiotopoulos CP, editor. Atlas of Epilepsies. London: Springer London; 2010. p. 243-6.
16. Fromm GH FC, Browning RA, Burnham WM. Epilepsy and the Reticular Formation: The Role of the Reticular Core in Convulsive Seizures: Wiley-Liss; 1987.
17. Faingold CL. Locomotor behaviors in generalized convulsions are hierarchically driven from specific brain-stem nuclei in the network subserving audiogenic seizure. Ann N Y Acad Sci. 1998;860:566-9.
18. Lam A, Whelan N, Corcoran ME. Susceptibility of brainstem to kindling and transfer to the forebrain. Epilepsia. 2010;51(9):1736-44.
19. Steriade M, Contreras D. Spike-wave complexes and fast components of cortically generated seizures. I. Role of neocortex and thalamus. J Neurophysiol. 1998;80(3):1439-55.
20. Steriade M, Amzica F, Neckelmann D, Timofeev I. Spike-wave complexes and fast components of cortically generated seizures. II. Extra- and intracellular patterns. J Neurophysiol. 1998;80(3):1456-79.
21. Neckelmann D, Amzica F, Steriade M. Spike-wave complexes and fast components of cortically generated seizures. III. Synchronizing mechanisms. J Neurophysiol. 1998;80(3):1480-94.
22. Timofeev I, Grenier F, Steriade M. Spike-wave complexes and fast components of cortically generated seizures. IV. Paroxysmal fast runs in cortical and thalamic neurons. J Neurophysiol. 1998;80(3):1495-513.
23. Avoli M, Rogawski MA, Avanzini G. Generalized epileptic disorders: an update. Epilepsia. 2001;42(4):445-57.
24. Munson J. Deaths in Epilepsy. Medical Records. 1910;77:58-62.
25. Annegers JF. United States perspective on definitions and classifications. Epilepsia. 1997;38(11 Suppl):S9-12.
26. Nashef L. Sudden unexpected death in epilepsy: terminology and definitions. Epilepsia. 1997;38(11 Suppl):S6-8.
27. Nashef L, So EL, Ryvlin P, Tomson T. Unifying the definitions of sudden unexpected death in epilepsy. Epilepsia. 2012;53(2):227-33.

28. Watila MM, Balarabe SA, Ojo O, Keezer MR, Sander JW. Overall and cause-specific premature mortality in epilepsy: A systematic review. Epilepsy Behav. 2018;87:213-25.
29. Holst AG, Winkel BG, Risgaard B, Nielsen JB, Rasmussen PV, Haunso S, et al. Epilepsy and risk of death and sudden unexpected death in the young: a nationwide study. Epilepsia. 2013;54(9):1613-20.
30. Gorton HC, Webb RT, Carr MJ, DelPozo-Banos M, John A, Ashcroft DM. Risk of Unnatural Mortality in People With Epilepsy. JAMA Neurol. 2018;75(8):929-38.
31. Klovgaard M, Lynge TH, Tsiropoulos I, Uldall PV, Banner J, Winkel BG, et al. Epilepsy-Related Mortality in Children and Young Adults in Denmark: A Nationwide Cohort Study. Neurology. 2022;98(3):e213-e24.
32. Devinsky O, Spruill T, Thurman D, Friedman D. Recognizing and preventing epilepsy-related mortality: A call for action. Neurology. 2016;86(8):779-86.
33. Sveinsson O, Andersson T, Carlsson S, Tomson T. The incidence of SUDEP: A nationwide population-based cohort study. Neurology. 2017;89(2):170-7.
34. Harden C, Tomson T, Gloss D, Buchhalter J, Cross JH, Donner E, et al. Practice guideline summary: Sudden unexpected death in epilepsy incidence rates and risk factors: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2017;88(17):1674-80.
35. Devinsky O, Hesdorffer DC, Thurman DJ, Lhatoo S, Richerson G. Sudden unexpected death in epilepsy: epidemiology, mechanisms, and prevention. Lancet Neurol. 2016;15(10):1075-88.
36. Thurman DJ, Hesdorffer DC, French JA. Sudden unexpected death in epilepsy: assessing the public health burden. Epilepsia. 2014;55(10):1479-85.
37. Walczak TS, Leppik IE, D'Amelio M, Rarick J, So E, Ahman P, et al. Incidence and risk factors in sudden unexpected death in epilepsy: a prospective cohort study. Neurology. 2001;56(4):519-25.
38. Hesdorffer DC, Tomson T, Benn E, Sander JW, Nilsson L, Langan Y, et al. Combined analysis of risk factors for SUDEP. Epilepsia. 2011;52(6):1150-9.
39. Sveinsson O, Andersson T, Mattsson P, Carlsson S, Tomson T. Clinical risk factors in SUDEP: A nationwide population-based case-control study. Neurology. 2020;94(4):e419-e29.
40. Sveinsson O, Andersson T, Carlsson S, Tomson T. Type, Etiology, and Duration of Epilepsy as Risk Factors for SUDEP: Further Analyses of a Population-Based Case-Control Study. Neurology. 2023;101(22):e2257-e65.
41. Hesdorffer DC, Tomson T, Benn E, Sander JW, Nilsson L, Langan Y, et al. Do antiepileptic drugs or generalized tonic-clonic seizure frequency increase SUDEP risk? A combined analysis. Epilepsia. 2012;53(2):249-52.

42. Ryvlin P, Cucherat M, Rheims S. Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta-analysis of placebo-controlled randomised trials. Lancet Neurol. 2011;10(11):961-8.
43. French JA, Perucca E, Sander JW, Bergfeldt L, Baulac M, Auerbach DS, et al. FDA safety warning on the cardiac effects of lamotrigine: An advisory from the Ad Hoc ILAE/AES Task Force. Epilepsia Open. 2021;6(1):45-8.
44. Bunschoten JW, Husein N, Devinsky O, French JA, Sander JW, Thijs RD, Keezer MR. Sudden Death and Cardiac Arrythmia With Lamotrigine: A Rapid Systematic Review. Neurology. 2022.
45. Nightscales R, Barnard S, Laze J, Chen Z, Tao G, Auvrez C, et al. Risk of sudden unexpected death in epilepsy (SUDEP) with lamotrigine and other sodium channel-modulating antiseizure medications. Epilepsia Open. 2023;8(2):334-45.
46. Casadei CH, Carson KW, Mendiratta A, Bazil CW, Pack AM, Choi H, et al. All-cause mortality and SUDEP in a surgical epilepsy population. Epilepsy Behav. 2020;108:107093.
47. Sperling MR, Harris A, Nei M, Liporace JD, O'Connor MJ. Mortality after epilepsy surgery. Epilepsia. 2005;46 Suppl 11:49-53.
48. Ryvlin P, Nashef L, Lhatoo SD, Bateman LM, Bird J, Bleasel A, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. Lancet Neurol. 2013;12(10):966-77.
49. Lacuey N, Hampson JP, Harper RM, Miller JP, Lhatoo S. Limbic and paralimbic structures driving ictal central apnea. Neurology. 2019;92(7):e655-e69.
50. Lacuey N, Zonjy B, Hampson JP, Rani MRS, Zaremba A, Sainju RK, et al. The incidence and significance of periictal apnea in epileptic seizures. Epilepsia. 2018;59(3):573-82.
51. Vilella L, Lacuey N, Hampson JP, Rani MRS, Sainju RK, Friedman D, et al. Postconvulsive central apnea as a biomarker for sudden unexpected death in epilepsy (SUDEP). Neurology. 2019;92(3):e171-e82.
52. Vilella L, Lacuey N, Hampson JP, Rani MRS, Loparo K, Sainju RK, et al. Incidence, Recurrence, and Risk Factors for Peri-ictal Central Apnea and Sudden Unexpected Death in Epilepsy. Front Neurol. 2019;10:166.
53. Lacuey N, Hampson JP, Harper RM, Miller JP, Lhatoo S. Limbic and paralimbic structures driving ictal central apnea. Neurology. 2019.
54. Lacuey N, Zonjy B, Londono L, Lhatoo SD. Amygdala and hippocampus are symptomatogenic zones for central apneic seizures. Neurology. 2017;88(7):701-5.
55. Murugesan A, Rani MRS, Vilella L, Lacuey N, Hampson JP, Faingold CL, et al. Postictal serotonin levels are associated with peri-ictal apnea. Neurology. 2019.
56. Lacuey N, Vilella L, Hampson JP, Sahadevan J, Lhatoo SD. Ictal laryngospasm monitored by video-EEG and polygraphy: a potential SUDEP mechanism. Epileptic Disord. 2018.

**57.** Amir J, Ashkenazi S, Schonfeld T, Weitz R, Nitzan M. Laryngospasm as a single manifestation of epilepsy. Arch Dis Child. 1983;58(2):151-3.

**58.** Stewart M, Kollmar R, Nakase K, Silverman J, Sundaram K, Orman R, Lazar J. Obstructive apnea due to laryngospasm links ictal to postictal events in SUDEP cases and offers practical biomarkers for review of past cases and prevention of new ones. Epilepsia. 2017;58(6):e87-e90.

**59.** Nakase K, Kollmar R, Lazar J, Arjomandi H, Sundaram K, Silverman J, et al. Laryngospasm, central and obstructive apnea during seizures: Defining pathophysiology for sudden death in a rat model. Epilepsy Res. 2016;128:126-39.

**60.** Irizarry R, Sukato D, Kollmar R, Schild S, Silverman J, Sundaram K, et al. Seizures induce obstructive apnea in DBA/2J audiogenic seizure-prone mice: Lifesaving impact of tracheal implants. Epilepsia. 2020;61(2):e13-e6.

**61.** Purnell BS, Braun A, Fedele D, Murugan M, Boison D. Diaphragmatic pacing for the prevention of sudden unexpected death in epilepsy. Brain communications. 2022;4(5):fcac232.

**62.** Keilson MJ, Hauser WA, Magrill JP. Electrocardiographic changes during electrographic seizures. Arch Neurol. 1989;46(11):1169-70.

**63.** Nei M, Ho RT, Sperling MR. EKG abnormalities during partial seizures in refractory epilepsy. Epilepsia. 2000;41(5):542-8.

**64.** van der Lende M, Surges R, Sander JW, Thijs RD. Cardiac arrhythmias during or after epileptic seizures. J Neurol Neurosurg Psychiatry. 2016;87(1):69-74.

**65.** Tinuper P, Bisulli F, Cerullo A, Carcangiu R, Marini C, Pierangeli G, Cortelli P. Ictal bradycardia in partial epileptic seizures: Autonomic investigation in three cases and literature review. Brain. 2001;124(Pt 12):2361-71.

**66.** Strzelczyk A, Cenusa M, Bauer S, Hamer HM, Mothersill IW, Grunwald T, et al. Management and long-term outcome in patients presenting with ictal asystole or bradycardia. Epilepsia. 2011;52(6):1160-7.

**67.** Britton JW, Ghearing GR, Benarroch EE, Cascino GD. The ictal bradycardia syndrome: localization and lateralization. Epilepsia. 2006;47(4):737-44.

**68.** Park KJ, Sharma G, Kennedy JD, Seyal M. Potentially high-risk cardiac arrhythmias with focal to bilateral tonic-clonic seizures and generalized tonic-clonic seizures are associated with the duration of periictal hypoxemia. Epilepsia. 2017;58(12):2164-71.

**69.** Nass RD, Motloch LJ, Paar V, Lichtenauer M, Baumann J, Zur B, et al. Blood markers of cardiac stress after generalized convulsive seizures. Epilepsia. 2019;60(2):201-10.

**70.** Surges R, Adjei P, Kallis C, Erhuero J, Scott CA, Bell GS, et al. Pathologic cardiac repolarization in pharmacoresistant epilepsy and its potential role in sudden unexpected death in epilepsy: a case-control study. Epilepsia. 2010;51(2):233-42.

71. Bank AM, Dworetzky BA, Lee JW. Sudden unexpected death in epilepsy in a patient with a cardiac pacemaker. Seizure. 2018;61:38-40.
72. Katona PG, Jih F. Respiratory sinus arrhythmia: noninvasive measure of parasympathetic cardiac control. J Appl Physiol. 1975;39(5):801-5.
73. Myers KA, Sivathamboo S, Perucca P. Heart rate variability measurement in epilepsy: How can we move from research to clinical practice? Epilepsia. 2018;59(12):2169-78.
74. Fang SC, Wu YL, Tsai PS. Heart Rate Variability and Risk of All-Cause Death and Cardiovascular Events in Patients With Cardiovascular Disease: A Meta-Analysis of Cohort Studies. Biological research for nursing. 2020;22(1):45-56.
75. Billman GE. Heart rate variability - a historical perspective. Front Physiol. 2011;2:86.
76. Delogu AB, Spinelli A, Battaglia D, Dravet C, De Nisco A, Saracino A, et al. Electrical and autonomic cardiac function in patients with Dravet syndrome. Epilepsia. 2011;52 Suppl 2:55-8.
77. Ponnusamy A, Marques JL, Reuber M. Heart rate variability measures as biomarkers in patients with psychogenic nonepileptic seizures: potential and limitations. Epilepsy Behav. 2011;22(4):685-91.
78. Drake ME, Jr., Andrews JM, Castleberry CM. Electrophysiologic assessment of autonomic function in epilepsy. Seizure. 1998;7(2):91-6.
79. DeGiorgio CM, Miller P, Meymandi S, Chin A, Epps J, Gordon S, et al. RMSSD, a measure of vagus-mediated heart rate variability, is associated with risk factors for SUDEP: the SUDEP-7 Inventory. Epilepsy Behav. 2010;19(1):78-81.
80. Poh MZ, Loddenkemper T, Reinsberger C, Swenson NC, Goyal S, Madsen JR, Picard RW. Autonomic changes with seizures correlate with postictal EEG suppression. Neurology. 2012;78(23):1868-76.
81. Baysal-Kirac L, Serbest NG, Şahin E, Dede H, Gürses C, Gökyiğit A, et al. Analysis of heart rate variability and risk factors for SUDEP in patients with drug-resistant epilepsy. Epilepsy Behav. 2017;71(Pt A):60-4.
82. Lamberts RJ, Laranjo S, Kalitzin SN, Velis DN, Rocha I, Sander JW, Thijs RD. Postictal generalized EEG suppression is not associated with periictal cardiac autonomic instability in people with convulsive seizures. Epilepsia. 2013;54(3):523-9.
83. Sivathamboo S, Friedman D, Laze J, Nightscales R, Chen Z, Kuhlmann L, et al. Association of Short-term Heart Rate Variability and Sudden Unexpected Death in Epilepsy. Neurology. 2021;97(24):e2357-e67.
84. Hampel KG, Jahanbekam A, Elger CE, Surges R. Seizure-related modulation of systemic arterial blood pressure in focal epilepsy. Epilepsia. 2016;57(10):1709-18.
85. Esmaeili B, Kaffashi F, Theeranaew W, Dabir A, Lhatoo SD, Loparo KA. Post-ictal Modulation of Baroreflex Sensitivity in Patients With Intractable Epilepsy. Front Neurol. 2018;9:793.

**86.** Jaychandran R, Chaitanya G, Satishchandra P, Bharath RD, Thennarasu K, Sinha S. Monitoring peri-ictal changes in heart rate variability, oxygen saturation and blood pressure in epilepsy monitoring unit. Epilepsy Res. 2016;125:10-8.

**87.** Bozorgi A, Chung S, Kaffashi F, Loparo KA, Sahoo S, Zhang GQ, et al. Significant postictal hypotension: expanding the spectrum of seizure-induced autonomic dysregulation. Epilepsia. 2013;54(9):e127-30.

**88.** Lacuey N, Hampson JP, Theeranaew W, Zonjy B, Vithala A, Hupp NJ, et al. Cortical Structures Associated With Human Blood Pressure Control. JAMA Neurol. 2018;75(2):194-202.

**89.** Sanchez-Larsen A, Principe A, Ley M, Navarro-Cuartero J, Rocamora R. Characterization of the Insular Role in Cardiac Function through Intracranial Electrical Stimulation of the Human Insula. Ann Neurol. 2021;89(6):1172-80.

**90.** Benarroch EE. The central autonomic network: functional organization, dysfunction, and perspective. Mayo Clin Proc. 1993;68(10):988-1001.

**91.** Nass RD, Hampel KG, Elger CE, Surges R. Blood Pressure in Seizures and Epilepsy. Front Neurol. 2019;10:501.

**92.** Lhatoo SD, Faulkner HJ, Dembny K, Trippick K, Johnson C, Bird JM. An electroclinical case-control study of sudden unexpected death in epilepsy. Ann Neurol. 2010;68(6):787-96.

**93.** Yang X, Yang X, Liu B, Sun A, Zhao X. Risk factors for postictal generalized EEG suppression in generalized convulsive seizure: A systematic review and meta-analysis. Seizure. 2022;98:19-26.

**94.** Kang JY, Rabiei AH, Myint L, Nei M. Equivocal significance of post-ictal generalized EEG suppression as a marker of SUDEP risk. Seizure. 2017;48:28-32.

**95.** Lamberts RJ, Gaitatzis A, Sander JW, Elger CE, Surges R, Thijs RD. Postictal generalized EEG suppression: an inconsistent finding in people with multiple seizures. Neurology. 2013;81(14):1252-6.

**96.** Surges R, Strzelczyk A, Scott CA, Walker MC, Sander JW. Postictal generalized electroencephalographic suppression is associated with generalized seizures. Epilepsy Behav. 2011;21(3):271-4.

**97.** Johnson M, Samudra N, Gallagher MJ, Abou-Khalil B, Nobis WP. Near SUDEP during bilateral stereo-EEG monitoring characterized by diffuse postictal EEG suppression. Epilepsia. 2021;62(4):e60-e4.

**98.** Peng W, Danison JL, Seyal M. Postictal generalized EEG suppression and respiratory dysfunction following generalized tonic-clonic seizures in sleep and wakefulness. Epilepsia. 2017;58(8):1409-14.

**99.** Kuo J, Zhao W, Li CS, Kennedy JD, Seyal M. Postictal immobility and generalized EEG suppression are associated with the severity of respiratory dysfunction. Epilepsia. 2016;57(3):412-7.

**100.** Seyal M, Bateman LM, Li CS. Impact of periictal interventions on respiratory dysfunction, postictal EEG suppression, and postictal immobility. Epilepsia. 2013;54(2):377-82.

**101.** Rheims S, Alvarez BM, Alexandre V, Curot J, Maillard L, Bartolomei F, et al. Hypoxemia following generalized convulsive seizures: Risk factors and effect of oxygen therapy. Neurology. 2019;92(3):e183-e93.

**102.** Latreille V, Abdennadher M, Dworetzky BA, Ramel J, White D, Katz E, et al. Nocturnal seizures are associated with more severe hypoxemia and increased risk of postictal generalized EEG suppression. Epilepsia. 2017;58(9):e127-e31.

**103.** Alexandre V, Mercedes B, Valton L, Maillard L, Bartolomei F, Szurhaj W, et al. Risk factors of postictal generalized EEG suppression in generalized convulsive seizures. Neurology. 2015;85(18):1598-603.

**104.** Tao JX, Yung I, Lee A, Rose S, Jacobsen J, Ebersole JS. Tonic phase of a generalized convulsive seizure is an independent predictor of postictal generalized EEG suppression. Epilepsia. 2013;54(5):858-65.

**105.** Zhao X, Vilella L, Zhu L, Rani MRS, Hampson JP, Hampson J, et al. Automated Analysis of Risk Factors for Postictal Generalized EEG Suppression. Front Neurol. 2021;12:669517.

**106.** El Atrache R, Tamilia E, Amengual-Gual M, Mohammadpour Touserkani F, Yang Y, Wang X, et al. Association between semiologic, autonomic, and electrographic seizure characteristics in children with generalized tonic-clonic seizures. Epilepsy Behav. 2021;122:108228.

**107.** Theeranaew W, McDonald J, Zonjy B, Kaffashi F, Moseley BD, Friedman D, et al. Automated Detection of Postictal Generalized EEG Suppression. IEEE Trans Biomed Eng. 2018;65(2):371-7.

**108.** Altenmuller DM, Schulze-Bonhage A, Elger CE, Surges R. Local brain activity persists during apparently generalized postictal EEG suppression. Epilepsy Behav. 2016;62:218-24.

**109.** Bateman LM, Mendiratta A, Liou JY, Smith EJ, Bazil CW, Choi H, et al. Postictal clinical and electroencephalographic activity following intracranially recorded bilateral tonic-clonic seizures. Epilepsia. 2019;60(1):74-84.

**110.** Marchi A, Giusiano B, King M, Lagarde S, Trebuchon-Dafonseca A, Bernard C, et al. Postictal electroencephalographic (EEG) suppression: A stereo-EEG study of 100 focal to bilateral tonic-clonic seizures. Epilepsia. 2019;60(1):63-73.

**111.** Aiba I, Noebels JL. Spreading depolarization in the brainstem mediates sudden cardiorespiratory arrest in mouse SUDEP models. Sci Transl Med. 2015;7(282):282ra46.

**112.** Loonen ICM, Jansen NA, Cain SM, Schenke M, Voskuyl RA, Yung AC, et al. Brainstem spreading depolarization and cortical dynamics during fatal seizures in Cacna1a S218L mice. Brain. 2019;142(2):412-25.

**113.** Richerson GB, Buchanan GF. The serotonin axis: Shared mechanisms in seizures, depression, and SUDEP. Epilepsia. 2011;52 Suppl 1:28-38.

**114.** Buchanan GF, Murray NM, Hajek MA, Richerson GB. Serotonin neurones have anti-convulsant effects and reduce seizure-induced mortality. J Physiol. 2014;592(19):4395-410.

**115.** Uteshev VV, Tupal S, Mhaskar Y, Faingold CL. Abnormal serotonin receptor expression in DBA/2 mice associated with susceptibility to sudden death due to respiratory arrest. Epilepsy Res. 2010;88(2-3):183-8.

**116.** Faingold CL, Randall M, Tupal S. DBA/1 mice exhibit chronic susceptibility to audiogenic seizures followed by sudden death associated with respiratory arrest. Epilepsy Behav. 2010;17(4):436-40.

**117.** Tupal S, Faingold CL. Evidence supporting a role of serotonin in modulation of sudden death induced by seizures in DBA/2 mice. Epilepsia. 2006;47(1):21-6.

**118.** Sainju RK, Dragon DN, Winnike HB, Nashelsky MB, Granner MA, Gehlbach BK, Richerson GB. Ventilatory response to CO2 in patients with epilepsy. Epilepsia. 2019;60(3):508-17.

**119.** Purnell B, Murugan M, Jani R, Boison D. The Good, the Bad, and the Deadly: Adenosinergic Mechanisms Underlying Sudden Unexpected Death in Epilepsy. Front Neurosci. 2021;15:708304.

**120.** Faingold CL, Feng HJ. A unified hypothesis of SUDEP: Seizure-induced respiratory depression induced by adenosine may lead to SUDEP but can be prevented by autoresuscitation and other restorative respiratory response mechanisms mediated by the action of serotonin on the periaqueductal gray. Epilepsia. 2023;64(4):779-96.

**121.** Patodia S, Somani A, O'Hare M, Venkateswaran R, Liu J, Michalak Z, et al. The ventrolateral medulla and medullary raphe in sudden unexpected death in epilepsy. Brain. 2018.

**122.** Mueller SG, Nei M, Bateman LM, Knowlton R, Laxer KD, Friedman D, et al. Brainstem network disruption: A pathway to sudden unexplained death in epilepsy? Hum Brain Mapp. 2018.

**123.** Coll M, Oliva A, Grassi S, Brugada R, Campuzano O. Update on the Genetic Basis of Sudden Unexpected Death in Epilepsy. Int J Mol Sci. 2019;20(8).

**124.** Costagliola G, Orsini A, Coll M, Brugada R, Parisi P, Striano P. The brain-heart interaction in epilepsy: implications for diagnosis, therapy, and SUDEP prevention. Ann Clin Transl Neurol. 2021;8(7):1557-68.

**125.** Donnan AM, Schneider AL, Russ-Hall S, Churilov L, Scheffer IE. Rates of Status Epilepticus and Sudden Unexplained Death in Epilepsy in People With Genetic Developmental and Epileptic Encephalopathies. Neurology. 2023;100(16):e1712-e22.

**126.** Smith J, Richerson G, Kouchi H, Duprat F, Mantegazza M, Bezin L, Rheims S. Are we there yet? A critical evaluation of sudden and unexpected death in epilepsy models. Epilepsia. 2024;65(1):9-25.

**127.** Sherrington CS. Decerebrate Rigidity, and Reflex Coordination of Movements. J Physiol. 1898;22(4):319-32.

**128.** Feldman MH. The decerebrate state in the primate. I. Studies in monkeys. Arch Neurol. 1971;25(6):501-16.

**129.** Kandel E.R. SJH, Jessell T.M., Siegelbaum S.A., Hudspeth A.J. Principles of Neural Science: McGraw-Hill Companies; 2000.

**130.** Feldman MH. The decerebrate state in the primate. II. Studies in man. Arch Neurol. 1971;25(6):517-25.

**131.** Plum F PJ. The diagnosis of stupor and coma. Philadelphia, PA: F.A Davis Company; 1982.

**132.** Conomy JP, Swash M. Reversible decerebrate and decorticate postures in hepatic coma. N Engl J Med. 1968;278(16):876-9.

**133.** Seibert DG. Reversible decerebrate posturing secondary to hypoglycemia. Am J Med. 1985;78(6 Pt 1):1036-7.

**134.** Subramanian HH, Balnave RJ, Holstege G. The midbrain periaqueductal gray control of respiration. J Neurosci. 2008;28(47):12274-83.

**135.** Subramanian HH. Descending control of the respiratory neuronal network by the midbrain periaqueductal grey in the rat in vivo. J Physiol. 2013;591(1):109-22.

**136.** Carrive P. The periaqueductal gray and defensive behavior: functional representation and neuronal organization. Behav Brain Res. 1993;58(1-2):27-47.

**137.** Benarroch EE. Periaqueductal gray: an interface for behavioral control. Neurology. 2012;78(3):210-7.

**138.** Noebels JL AM, Rogawski MA, Olsen RW, Delgado-Escueta AV. Jasper's Basic Mechanisms of the Epilepsies: Oxford University Press; 2010.

**139.** Salam MT, Montandon G, Genov R, Devinsky O, Del Campo M, Carlen PL. Mortality with brainstem seizures from focal 4-aminopyridine-induced recurrent hippocampal seizures. Epilepsia. 2017;58(9):1637-44.

**140.** Kommajosyula SP, Randall ME, Brozoski TJ, Odintsov BM, Faingold CL. Specific subcortical structures are activated during seizure-induced death in a model of sudden unexpected death in epilepsy (SUDEP): A manganese-enhanced magnetic resonance imaging study. Epilepsy Res. 2017;135:87-94.

**141.** Hampson JP, Lacuey N, Rani MS, Hampson JS, Simeone KA, Simeone TA, et al. Functional MRI Correlates of Carbon Dioxide Chemosensing in Persons With Epilepsy. Front Neurol. 2022;13:896204.

**142.** Kommajosyula SP, Tupal S, Faingold CL. Deficient post-ictal cardiorespiratory compensatory mechanisms mediated by the periaqueductal gray may lead to death in a mouse model of SUDEP. Epilepsy Res. 2018;147:1-8.

**143.** Kommajosyula SP, Faingold CL. Neural activity in the periaqueductal gray and other specific subcortical structures is enhanced when a selective serotonin reuptake inhibitor selectively prevents seizure-induced sudden death in the DBA/1 mouse model of sudden unexpected death in epilepsy. Epilepsia. 2019.

**144.** Lacuey N, Martins R, Vilella L, Hampson JP, Rani MRS, Strohl K, et al. The association of serotonin reuptake inhibitors and benzodiazepines with ictal central apnea. Epilepsy Behav. 2019;98(Pt A):73-9.

**145.** Bateman LM, Li CS, Lin TC, Seyal M. Serotonin reuptake inhibitors are associated with reduced severity of ictal hypoxemia in medically refractory partial epilepsy. Epilepsia. 2010;51(10):2211-4.

**146.** Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. Neurology. 1992;42(9):1727-32.

**147.** Altenmuller DM, Zehender M, Schulze-Bonhage A. High-grade atrioventricular block triggered by spontaneous and stimulation-induced epileptic activity in the left temporal lobe. Epilepsia. 2004;45(12):1640-4.

**148.** Hampel KG, Thijs RD, Elger CE, Surges R. Recurrence risk of ictal asystole in epilepsy. Neurology. 2017;89(8):785-91.

**149.** Bhagat BD, Rao PS, Dhalla NS. Role of catecholamines in the genesis of arrhythmias. Adv Myocardiol. 1980;2:117-32.

**150.** Verrier RL, Pang TD, Nearing BD, Schachter SC. Epileptic heart: A clinical syndromic approach. Epilepsia. 2021;62(8):1780-9.

**151.** Liu Z, Thergarajan P, Antonic-Baker A, Chen Z, Sparks PB, Lannin NA, et al. Cardiac structural and functional abnormalities in epilepsy: A systematic review and meta-analysis. Epilepsia Open. 2023.

**152.** Josephson CB, Wiebe S, Delgado-Garcia G, Gonzalez-Izquierdo A, Denaxas S, Sajobi TT, et al. Association of Enzyme-Inducing Antiseizure Drug Use With Long-term Cardiovascular Disease. JAMA Neurol. 2021;78(11):1367-74.

**153.** Minomo S, Amino T, Hara N, Ichijo M, Miyake T, Yasuura A, Kamata T. Lacosamide-induced symptomatic sinus node dysfunction. Epileptic Disord. 2021;23(5):772-4.

**154.** Thimmisetty RK, Gorthi JR, Abu Hazeem M. Oral Phenytoin Toxicity Causing Sinus Arrest: A Case Report. Case Reports in Cardiology. 2014;2014:851767.

**155.** Keilson MJ, Hauser WA, Magrill JP, Goldman M. ECG abnormalities in patients with epilepsy. Neurology. 1987;37(10):1624-6.

**156.** Blumhardt LD, Smith PE, Owen L. Electrocardiographic accompaniments of temporal lobe epileptic seizures. Lancet. 1986;1(8489):1051-6.

**157.** Serdyuk S, Davtyan K, Burd S, Drapkina O, Boytsov S, Gusev E, Topchyan A. Cardiac arrhythmias and sudden unexpected death in epilepsy: Results of long-term monitoring. Heart Rhythm. 2021;18(2):221-8.

**158.** Grossman P, Taylor EW. Toward understanding respiratory sinus arrhythmia: relations to cardiac vagal tone, evolution and biobehavioral functions. Biol Psychol. 2007;74(2):263-85.

**159.** Cysarz D, Zerm R, Bettermann H, Fruhwirth M, Moser M, Kroz M. Comparison of respiratory rates derived from heart rate variability, ECG amplitude, and nasal/oral airflow. Ann Biomed Eng. 2008;36(12):2085-94.

**160.** Yeh CH, Juan CH, Yeh HM, Wang CY, Young HV, Lin JL, et al. The critical role of respiratory sinus arrhythmia on temporal cardiac dynamics. J Appl Physiol (1985). 2019;127(6):1733-41.

**161.** Sivathamboo S, Constantino TN, Chen Z, Sparks PB, Goldin J, Velakoulis D, et al. Cardiorespiratory and autonomic function in epileptic seizures: A video-EEG monitoring study. Epilepsy Behav. 2020;111:107271.

**162.** Faria MT, Rodrigues S, Campelo M, Dias D, Rego R, Rocha H, et al. Does the type of seizure influence heart rate variability changes? Epilepsy Behav. 2022;126:108453.

**163.** Toth V, Hejjel L, Fogarasi A, Gyimesi C, Orsi G, Szucs A, et al. Periictal heart rate variability analysis suggests long-term postictal autonomic disturbance in epilepsy. Eur J Neurol. 2010;17(6):780-7.

**164.** Eggleston KS, Olin BD, Fisher RS. Ictal tachycardia: the head-heart connection. Seizure. 2014;23(7):496-505.

**165.** Schuele SU, Bermeo AC, Alexopoulos AV, Locatelli ER, Burgess RC, Dinner DS, Foldvary-Schaefer N. Video-electrographic and clinical features in patients with ictal asystole. Neurology. 2007;69(5):434-41.

**166.** van der Lende M, Arends JB, Lamberts RJ, Tan HL, de Lange FJ, Sander JW, et al. The yield of long-term electrocardiographic recordings in refractory focal epilepsy. Epilepsia. 2019;60(11):2215-23.

**167.** Kim Y, Bravo E, Thirnbeck CK, Smith-Mellecker LA, Kim SH, Gehlbach BK, et al. Severe peri-ictal respiratory dysfunction is common in Dravet syndrome. J Clin Invest. 2018;128(3):1141-53.

**168.** Chaitanya G, Hampson JP, Toth E, Hupp NJ, Hampson JS, Mosher JC, et al. Limbic and paralimbic respiratory modulation: From inhibition to enhancement. Epilepsia. 2022;63(7):1799-811.

**169.** Talavera B, Chaitanya G, Hupp N, Pati S, Hampson JP, Luo X, et al. Stimulation-induced respiratory enhancement in corticothalamic regions. Epilepsia. 2023;64(7):1925-38.

**170.** Beniczky S, Wiebe S, Jeppesen J, Tatum WO, Brazdil M, Wang Y, et al. Automated seizure detection using wearable devices: A clinical practice guideline of the International League Against Epilepsy and the International Federation of Clinical Neurophysiology. Clin Neurophysiol. 2021;132(5):1173-84.

**171.** Beniczky S, Wiebe S, Jeppesen J, Tatum WO, Brazdil M, Wang Y, et al. Automated seizure detection using wearable devices: A clinical practice guideline of the International League Against Epilepsy and the International Federation of Clinical Neurophysiology. Epilepsia. 2021;62(3):632-46.

**172.** Iyer S, Hinman JE, Warren T, Matthews SA, Simeone TA, Simeone KA. Altered ventilatory responses to hypercapnia-hypoxia challenges in a preclinical SUDEP model involve orexin neurons. Neurobiol Dis. 2024:106592.

# 10. APPENDIX

## 10.1. Postconvulsive central apnea as a biomarker for sudden unexpected death in epilepsy (SUDEP).

Neurology. 2019 Jan 15;92(3):e171-e182. Epub 2018 Dec 19.
PMID: 30568003.
DOI: 10.1212/WNL.0000000000006785

ARTICLE

# Postconvulsive central apnea as a biomarker for sudden unexpected death in epilepsy (SUDEP)

Laura Vilella, MD, Nuria Lacuey, MD, Johnson P. Hampson, MSBME, M.R. Sandhya Rani, PhD, Rup K. Sainju, MBBS, Daniel Friedman, MD, Maromi Nei, MD, Kingman Strohl, MD, Catherine Scott, MPHil, Brian K. Gehlbach, MD, Bilal Zonjy, MD, Norma J. Hupp, Anita Zaremba, BA, Nassim Shafiabadi, MD, Xiuhe Zhao, MD, Victoria Reick-Mitrisin, MS, Stephan Schuele, MD, MPH, Jennifer Ogren, PhD, Ronald M. Harper, PhD, Beate Diehl, MD, PhD, FRCP, Lisa Bateman, MD, Orrin Devinsky, MD, George B. Richerson, MD, PhD, Philippe Ryvlin, MD, PhD, and Samden D. Lhatoo, MD, FRCP

**Correspondence**
Dr. Vilella
Lvilellabertran@gmail.com

*Neurology*® 2019;92:e171-e182. doi:10.1212/WNL.0000000000006785

## Abstract

### Objective
To characterize peri-ictal apnea and postictal asystole in generalized convulsive seizures (GCS) of intractable epilepsy.

### Methods
This was a prospective, multicenter epilepsy monitoring study of autonomic and breathing biomarkers of sudden unexpected death in epilepsy (SUDEP) in patients ≥18 years old with intractable epilepsy and monitored GCS. Video-EEG, thoracoabdominal excursions, nasal airflow, capillary oxygen saturation, and ECG were analyzed.

### Results
We studied 148 GCS in 87 patients. Nineteen patients had generalized epilepsy; 65 had focal epilepsy; 1 had both; and the epileptogenic zone was unknown in 2. Ictal central apnea (ICA) preceded GCS in 49 of 121 (40.4%) seizures in 23 patients, all with focal epilepsy. Postconvulsive central apnea (PCCA) occurred in 31 of 140 (22.1%) seizures in 22 patients, with generalized, focal, or unknown epileptogenic zones. In 2 patients, PCCA occurred concurrently with asystole (near-SUDEP), with an incidence rate of 10.2 per 1,000 patient-years. One patient with PCCA died of probable SUDEP during follow-up, suggesting a SUDEP incidence rate 5.1 per 1,000 patient-years. No cases of laryngospasm were detected. Rhythmic muscle artifact synchronous with breathing was present in 75 of 147 seizures and related to stertorous breathing (odds ratio 3.856, 95% confidence interval 1.395–10.663, $p = 0.009$).

### Conclusions
PCCA occurred in both focal and generalized epilepsies, suggesting a different pathophysiology from ICA, which occurred only in focal epilepsy. PCCA was seen in 2 near-SUDEP cases and 1 probable SUDEP case, suggesting that this phenomenon may serve as a clinical biomarker of SUDEP. Larger studies are needed to validate this observation. Rhythmic postictal muscle artifact is suggestive of post-GCS breathing effort rather than a specific biomarker of laryngospasm.

RELATED ARTICLE

**Editorial**
Postconvulsive central apnea and asystole: A risk marker for sudden unexpected death in epilepsy (SUDEP)?
Page 115

MORE ONLINE

**Videos**

From the NINDS Center for SUDEP Research (L.V., M.R.S.R., R.K.S., D.F., M.N., C.S., B.K.G., B.Z., A.Z., S.S., J.O., R.M.H., B.D., L.B., O.D., G.B.R., P.R., S.D.L.); Epilepsy Center (L.V., N.L., J.P.H., N.J.H., N.S., X.Z., V.R.-M., S.D.L.) and Division of Pulmonary, Critical Care and Sleep Medicine (K.S.), University Hospitals Cleveland Medical Center, OH; University of Iowa School of Medicine (R.K.S., B.K.G., G.B.R.), Iowa City; NYU Langone School of Medicine (D.F., O.D.), New York; Sidney Kimmel Medical College (M.N.), Thomas Jefferson University, Philadelphia, PA; Institute of Neurology (C.S., B.D.), University College London, UK; Feinberg School of Medicine (S.S.), Northwestern University, Chicago, IL; Department of Neurobiology and Brain Research Institute (J.O., R.M.H.), University of California, Los Angeles (UCLA); Department of Neurology (L.B.), Columbia University, New York, NY; and Department of Clinical Neuroscience (P.R.), Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

## Glossary

**CI** = confidence interval; **CPR** = cardiopulmonary resuscitation; **GCS** = generalized convulsive seizures; **ICA** = ictal central apnea; **MORTEMUS** = Mortality in Epilepsy Monitoring Units Study; **NINDS** = National Institute of Neurological Disorders and Stroke; **OR** = odds ratio; **PAG** = periaqueductal gray; **PCCA** = postconvulsive central apnea; **PGES** = postictal generalized EEG suppression; **PRISM** = Prevention and Risk Identification of SUDEP Mortality; **$Spo_2$** = peripheral capillary oxygen saturation; **SUDEP** = sudden unexpected death in epilepsy; **$tcCO_2$** = transcutaneous $CO_2$; **VEEG** = video-EEG.

The landmark Mortality in Epilepsy Monitoring Units Study (MORTEMUS) study[1] found sudden unexpected death in epilepsy (SUDEP) and near-SUDEP incidences to be 7.5 per 1,000 and 2.2 per 1,000 patient-years, respectively, in the intractable epilepsy population undergoing epilepsy monitoring unit evaluation. Profound postictal cardiorespiratory dysfunction was found in all monitored SUDEP cases, with terminal central apnea preceding terminal asystole in all cases. Six of 25 cases with SUDEP and near-SUDEP had previously noted postictal central apnea, postictal cardiorespiratory arrest, or ictal asystole,[1] suggesting that these features may be implicated in SUDEP pathophysiology. Ictal respiratory dysfunction during epileptic seizures is well described.[2–6] Less is known about postictal breathing, particularly after generalized convulsive seizures (GCS). Apnea is a particular concern; ictal central apnea (ICA) is usually transient and benign in partial seizures but poses danger in a minority when prolonged and associated with profound hypoxemia. In particular, postictal apnea, whether obstructive[7] or central,[1,2,4,6,8] may be associated with SUDEP.[8] Obstructive breathing dysfunction from laryngospasm is rarely reported[7] but may be more frequent.[9] Recent studies have re-examined muscle artifact from terminal breathing effort in the MORTEMUS study, as well as in an animal model of laryngospasm, leading to speculation about its potential as a SUDEP biomarker,[10] although immediately after GCS, there is increased muscle tone that may account for this.[11] There is general consensus that ictal asystole is likely benign,[12] although postictal asystole may not be.[13] We set out to characterize both central and obstructive breathing dysfunction and the occurrence of postictal asystole in GCS, the seizure type most associated with SUDEP.[14]

## Methods

### Patient selection

All patients were prospectively consented participants in the National Institute of Neurological Disorders and Stroke (NINDS) Center for SUDEP Research's Autonomic and Imaging Biomarkers of SUDEP multicenter project (U01-NS090407) and its preliminary phase, the Prevention and Risk Identification of SUDEP Mortality (PRISM) project (P20NS076965). Patients with intractable epilepsy (failure of adequate trials of ≥2 antiepileptic medications)[15] who were ≥18 years of age and were undergoing video-EEG (VEEG) evaluation in the adult epilepsy monitoring units of participating centers from September 2011 until December 2017 were studied. Follow-up was conducted until April 30, 2018, with 6-month telephone calls or clinic visits. We included patients with recorded GCS, including generalized tonic-clonic seizures, focal to bilateral tonic-clonic seizures, and focal-onset motor bilateral clonic seizures.[16] Exclusion criteria were status epilepticus and obscured or unavailable video. Demographic and clinical data were collected, including phenotypic epilepsy characteristics, epilepsy duration, seizure type and frequency, semiologic seizure features, awake or asleep states, and presence of major cardiac or respiratory disease. Epileptogenic zone was classified as generalized (genetic generalized epilepsy in all cases), focal, both, or unknown.[17] GCS duration was defined as time from onset of bilateral motor signs of tonicity or clonicity to clinical seizure end. Early nursing intervention was defined as oxygen administration or suction applied during the seizure or within 5 seconds of seizure termination.[18]

### Data collection

#### Cardiorespiratory monitoring and VEEG monitoring

All patients underwent prolonged surface VEEG monitoring with the 10–20 international electrode system. EEG and ECG were acquired with Nihon Kohden (Tokyo, Japan). Peripheral capillary oxygen saturation ($Spo_2$) and heart rate were monitored with pulse oximetry and plethysmography (Nellcor OxiMax N-600x, Covidien, MN). Chest wall and abdominal excursions were recorded with inductance plethysmography (Ambu, Ballerup, Denmark; and Sleepmate or Perfect Fit 2, Dymedix, St. Paul, MN). In a subset of 21 seizures (14 patients), oral and nasal airflow was also recorded with a nasal pressure transducer (BiNAPS, Salter Labs, Lake Forest, IL) and an oral/nasal thermistor (ThermiSense, Salter Labs), with simultaneous transcutaneous $CO_2$ ($tcCO_2$) recordings with the Sen TecDigital Monitoring System (SenTec AG, Therwil, Switzerland).

A board certified pulmonologist (K.S.) oversaw breathing analysis. Breathing assessments (breathing rate, $O_2$ saturation, $tcCO_2$) were made 2 minutes pre-ictally and 3 minutes after clinical seizure end[1] through careful composite analysis of inductance plethysmography, EEG breathing artifact, visually inspected thoracoabdominal excursions and synchrony with airflow, auditory breathing information, and nasal pressure signal when available. Postictal $tcCO_2$ was analyzed up to 5 minutes. Baseline interictal $Spo_2$ was defined as mean $Spo_2$ over a 15-second nonapneic, artifact-free epoch. Hypoxemia was defined as $Spo_2$<95% (mild [$Spo_2$ 90%–94%], moderate [$Spo_2$ 75%–89%], or severe [$Spo_2$ <75%]). When baseline

$Spo_2$ was already <95% (38 of 135 seizures), a >1% drop was considered significant.

Postconvulsive breathing rate was measured and averaged in 15-second epochs. Because breathing rate after GCS is usually significantly increased compared to baseline,[5] we classified abnormal postconvulsive breathing rate according to deviations from the mean in our cohort. Thus, seizures were divided into 3 groups: postconvulsive bradypnea (breathing rate 2 SD below the mean in any epoch), postconvulsive tachypnea (breathing rate 2 SD above the mean in any epoch), and eupnea (postconvulsive breathing rate within 2 SD of the mean). Postconvulsive breathing was classified as stertorous (audible, deep, snoring-like or snuffling-like sound in active inspiration or active expiration) or quiet.[19] Inspiratory stridor for laryngospasm was stringently analyzed with auditory analysis, tracheal/neck movements, and nasal airflow when available.

Central apnea was defined as ≥1 missed breaths without any other explanation (i.e., speech, movement, or intervention). ICA referred to apnea that occurred before GCS. Postconvulsive central apnea (PCCA) was considered immediate, if no breath was taken for at least 5 seconds after seizure end, or delayed, when apnea occurred after at least 1 breath was detected after GCS end. Asystole was defined as an R-R interval of >3 seconds. We defined near-SUDEP as simultaneous cardiac (asystole) and breathing (central apnea) cessation, with or without cardiopulmonary resuscitation (CPR).

Presence and duration of postictal generalized EEG suppression (PGES)[20] were determined by a validated automated EEG suppression detection tool[21] and supplemented by visual analysis by 2 epilepsy neurophysiologists when the tool gave no solution. Presence and duration of postictal EEG burst suppression were also determined. Combined PGES and burst suppression made up the EEG recovery duration. Finally, we analyzed the presence of postictal EEG muscle artifact in a 3-minute postictal period using previously described methodology[10] (time constant 0.03–0.001) in 60-second epochs.

### Statistical analysis

Statistical analysis was performed with SPSS (version 24, IBM Corp, Armonk, NY). Summary statistics were reported as mean ± SD (median, range). Statistical significance for intergroup differences was assessed with Pearson $\chi^2$ test and Fisher exact tests for dichotomous or nominal variables. The Mann-Whitney *U* test was used for continuous variables because they did not follow a normal distribution (Kolmogorov-Smirnov test). Binary logistic regressions were used to assess associations between dichotomous variables and other variables and combinations. The Kruskal-Wallis H test was used to determine differences in continuous variables. The Spearman correlation was used to determine correlation between continuous variables. The level of significance was set at $p < 0.05$. Central tendency and dispersion measures of breathing rate were obtained in each 15-second interval after clinical seizure end. Outliers for breathing rate were identified when values were above or below 2 SD of the mean.

### Data availability

The datasets used and analyzed during the current study are available from the corresponding author on request.

## Results

One hundred sixty-four GCS were identified in 94 patients. Reliable VEEG recordings that met study criteria were available in 148 seizures in 87 patients (47 female). Of the148, 108 were tonic-clonic GCS; the remainder were clonic GCS. Mean follow-up time was 27.7 ± 15.2 months (26.1; 5.1–84.9 months); total cohort follow-up was 195 person-years. Mean age was 37.9 ± 13.7 years (36; 18–77 years). Mean body mass index was 28.7 ± 6.6 kg/$m^2$ (28.1; 15.1–45.8 kg/$m^2$). Mean age at epilepsy onset was 21.4 ± 16.8 years (17; 1–67 years), and mean epilepsy duration was 16.4 ± 12.7 years (12 years; 1 month–45 years). Seventy-two seizures occurred during wakefulness, 73 during sleep, and 3 (1 patient) during postictal stupor due to a seizure cluster. PGES was present in 106 of 148 seizures (71.6%). Epilepsy phenotypic details are shown in table 1, and seizure characteristics are given in table 2.

### Peri-ictal apnea

In 27 of 148 seizures in 16 of 87 patients (3 with focal epilepsy, 13 with generalized epilepsy), movement or acquisition artifact prevented accurate analysis of ictal apnea. In the remaining 121 seizures, ICA was detected in 49 of 121 (40.4%) seizures in 23 of 71 (32.4%) patients. All patients with ICA had focal epilepsy (temporal 12 [23 seizures], frontal 4 [7 seizures], lateralized 4 [14 seizures], multifocal 3 [5 seizures]).

In 8 of 148 seizures in 6 patients (3 generalized epilepsy, 3 focal epilepsy), artifact contaminated the immediate postictal period. PCCA (figure 1) was found in 31 of 140 (22.1%) seizures in 22 of 81 (27.1%) patients and observed in generalized (5 of 16 patients [6 seizures], 31.2%) and focal (15 of 62 patients [22 seizures], 24.2%) epilepsies (frontal 6 [7 seizures], multifocal 4 [6 seizures], temporal 4 [6 seizures], lateralized left hemisphere 1 [3 seizures]) and in unknown (2 [3 seizures]). PCCA duration was 12.0 ± 14.3 seconds (8; 5–85 seconds), longer in male patients (14.4 ± 4.8 vs 11.4 ± 16 seconds, $p = 0.005$) and in focal epilepsy (13.7 ± 16.5 vs 6.5 ± 1.4 seconds, $p = 0.020$).

PCCA was immediate in 10 of 140 (7.1%) seizures in 8 of 81 (9.8%) patients and delayed in 18 of 140 (12.8%) seizures in 14 of 81 (17.2%) patients. In 3 of 140 seizures in 3 patients, both types were found. Two of these 3 patients had subsequent seizures, 1 with only delayed PCCA and the other patient with immediate and delayed PCCA separately. In 11 of 31 (35.4%) PCCA seizures (9 of 22 [40.9%] patients), PCCA was accompanied by an ongoing postconvulsive electrographic seizure discharge. Of the 10 seizures with immediate PCCA, 9 had continuation of EEG seizure compared to 2 of 18 seizures with

**Table 1** Epilepsy phenotypic and MRI neuroimaging details

| Variable | Patients, n | Seizures, n |
|---|---|---|
| **Seizure frequency** | | |
| **<3 GCS in the last year** | 26 | |
| **≥3 GCS in the last year** | 52 | |
| **Unknown frequency** | 9 | |
| **Respiratory comorbid conditions** | 7 | 9 |
| **Cardiac comorbid conditions** | 4 | 4 |
| **Epileptogenic zone** | | |
| **Generalized** | 19 | 27 |
| **Focal** | 65 | 116 |
| **Temporal** | 30 | 49 |
| **Frontal** | 15 | 23 |
| **Parietal** | 1 | 1 |
| **Multifocal** | 12 | 23 |
| **Lateralized** | 7 | 20 |
| **Both generalized and focal** | 1 | 2 |
| **Unknown** | 2 | 3 |
| **Lateralization of epilepsy** | | |
| **Left** | 22 | 48 |
| **Right** | 25 | 33 |
| **Generalized** | 19 | 27 |
| **Bilateral** | 8 | 35 |
| **Both generalized and focal** | 1 | 2 |
| **Unknown** | 2 | 3 |
| **Neuroimaging findings on MRI** | | |
| **Negative** | 50 | 90 |
| **Positive** | 27 | 40 |
| **Tumor** | 17 | 10 |
| **Encephalomalacia** | 7 | 8 |
| **Hippocampal asymmetry** | 4 | 6 |
| **Vascular malformation** | 3 | 4 |
| **Malformation of cortical development** | 3 | 6 |
| **Temporal horn asymmetry** | 2 | 4 |
| **Mesial temporal sclerosis** | 1 | 2 |
| **Unavailable** | 10 | 18 |

Abbreviation: GCS = generalized convulsive seizures.

delayed PCCA ($p$ = 0.001). PGES duration was longer in delayed PCCA (40.7 ± 15.1 seconds) than in immediate PCCA (27.22 ± 15.3, $p$ = 0.045). In 5 delayed PCCA seizures (5 patients), apnea was recurrent in the same seizure. In the 22 patients with PCCA, 13 patients had 43 subsequent seizures, 22 of them with PCCA. Five patients had PCCA in all their seizures.

In the subset of 21 seizures with available $tcCO_2$ recordings, complete data were available in 10 seizures in 8 patients. In 9 of 10 seizures, there was an increase in $tcCO_2$, with the peak occurring after clinical seizure end. Four seizures had PCCA (2 immediate and 2 delayed), with a mean change of $tcCO_2$ of 15.5 ± 3.87 mm Hg (16.5, 10–19 mm Hg) compared to 9.6 ± 7.2 mm Hg (7; 2–20 mm Hg) in patients without PCCA, although those $CO_2$ values did not reach statistical significance ($p$ = 0.238). Obstructive apnea/hypopnea was not found in the small subset of patients who underwent airflow monitoring.

ICA presence did not predict PCCA ($p$ = 0.356). PCCA was more common in female patients ($p$ = 0.003), in shorter seizure duration ($p$ = 0.033), when PGES was present (87% in patients with PCCA vs 67.8% in patients without PCCA, $p$ = 0.041), and with nadir $Spo_2$ in the postictal (rather than ictal) phase ($p$ = 0.031). Respiratory comorbid conditions were present in 3 patients (3 seizures) with PCCA (all with uncomplicated obstructive sleep apnea) and in 3 patients (5 seizures) without PCCA (asthma 1, chronic sinusitis 1, obstructive sleep apnea 1). PCCA was not associated with GCS frequency, epilepsy age at onset, or epilepsy duration data (table e-1 available from Dryad, doi.org/10.5061/dryad.1k7d35q). After binomial regression analysis, female sex remained an independent predictor for PCCA ($p$ = 0.007, odds ratio [OR] 7.8, 95% confidence interval [CI] 1.7–34.8).

## Patients with near-SUDEP and SUDEP

Two patients with PCCA each had a monitored near-SUDEP seizure (incidence rate 10.2 per 1,000 patient-years), and another with immediate PCCA had an out-of-hospital probable SUDEP (incidence rate 5.1 per 1,000 patient-years).

Patient 1 (video 1 and figure 2) was a 58-year-old right-handed woman with 3 years of intractable right mesial frontal lobe epilepsy and 3 to 4 GCS per year due to a meningioma. Two GCS arising were recorded; the first arose from wakefulness and lasted 47 seconds, ending with PCCA and asystole. After clinical seizure end, the EEG seizure continued for 14 seconds. During this postconvulsive period, immediate PCCA occurred for 10 seconds, followed by 1 breath and 3 delayed PCCA periods of 12, 32, and 31 seconds (total PCCA 85 seconds). Concurrent with immediate PCCA, she had bradytachycardia preceding an initial asystole of 40-second duration, followed by 2 more asystole periods of 12 and 7 seconds (total asystole period 59 seconds). Oxygen administration, alerting stimuli, and repositioning of the patient were performed. PGES lasted 169 seconds, and EEG recovery duration was 1,091 seconds

**Table 2** Electroclinical seizure features and durations

| Variable | Seizures (n = 148), n | Results (mean ± SD [median, range]) |
|---|---|---|
| **Seizure phases duration, s** | | |
| **Tonic** | 108 | 8.7 ± 4.6 (8.5; 1–23) |
| **Jittery** | 125 | 9.5 ± 9.2 (7; 1–78) |
| **Clonic** | 148 | 34.9 ± 15.4 (32; 5–110) |
| **PGES duration, s** | 106 | 38.7 ± 23.7 (37; 1–169) |
| **EEG recovery duration, s** | 112 | 83.4 ± 119.2 (54; 1–1,091) |
| **Muscle artifact duration, s** | | |
| **Total** | 131 | 70.9 ± 45.4 (56; 10–180) |
| **Rhythmic** | 75 | 74.4 ± 42.3 (63; 18–180) |
| **Continuous** | 51 | 58.1 ± 42.2 (45, 10–180) |
| **Both rhythmic and continuous** | 5 | 148.6 ± 43.5 (92–180) |
| **Hypoxemia duration, s** | 95 | 130.5 ± 60.5 (119; 25–281) |
| **$Spo_2$, %** | | |
| **Nadir $Spo_2$** | 91 | 59.6 ± 14.1 (60; 22–87) |
| **Baseline minus nadir in $Spo_2$** | 91 | 35.8 ± 14.6 (34; 8–77) |
| **$tcCO_2$, mm Hg** | | |
| **Peak value $tcCO_2$** | 10 | 50.7 ± 9.6 (50.5, 39–66) |
| **Peak minus baseline $tcCO_2$** | 10 | 12 ± 6.5 (13; 2–20) |
| **ICA duration, s** | 49 | 16.4 ± 9.0 (15, 5–39) |
| **PCCA duration, s** | 31 | 12.0s ± 14.3 (8; 5–85) |
| **Immediate PCCA** | 10 | 8.7 ± 2.4 (8.5; 5–12) |
| **Delayed PCCA** | 18 | 9.2 ± 5 (7; 5–21) |
| **Both immediate and delayed PPCA** | 3 | 40.6 ± 38.4 (20; 17–85) |
| **Postictal breathing rate,[a] n** | | |
| **Bradypnea** | 13 | |
| **Eupnea** | 113 | |
| **Tachypnea** | 21 | |

Abbreviations: ICA = ictal central apnea; PCCA = postconvulsive central apnea; PGES = postictal generalized EEG suppression; $Spo_2$ = peripheral capillary oxygen saturation; $tcCO_2$ = transcutaneous carbon dioxide.
[a] Mean values for postictal breathing rate are not depicted because each 15-second epoch had a different mean.

(13 times the mean value of our study). The patient refused both epilepsy surgery and pacemaker implantation and remains under follow-up with sporadic seizures.

Patient 2 (video 2 and figure 3) was a 53-year-old right-handed man with intractable epilepsy of unknown etiology of 45 years' duration with 1 GCS per year. He had mild obstructive sleep apnea and coronary artery disease with stenting. He had 1 GCS during admission, out of sleep, that lasted 78 seconds. After clinical seizure end, the EEG seizure continued for 5 seconds. During the clonic and postconvulsive phase, the patient had progressive bradycardia. Asystole occurred 3 seconds after EEG seizure end. Asystole durations were 8 and 10 seconds. Cardiac rhythm was progressively restored with bradytachycardia and then normal sinus rhythm. Concurrently with asystole, the patient had delayed PCCA that recurred, with durations of 5 and 16 seconds each (total apnea duration 21 seconds). Oxygen was administered, and the patient was repositioned. PGES duration was 75 seconds. The patient is currently seizure free.

Patient 3 was a 21-year-old woman with genetic generalized epilepsy since 8 years of age with intractable absence seizures and 3 to 4 GCS per year. She was admitted with a 4-seizure cluster in 24 hours. One GCS of 58 seconds' duration was captured, arising from sleep. PGES duration was 42 seconds. She had 8 seconds of immediate PCCA, during which EEG seizure was evident. Breathing was restored spontaneously after EEG seizure end. No bradycardia or asystole was noted. Oxygen was administered. Seizures remained intractable. Two years after admission, the patient was found in cardiorespiratory arrest at home. CPR achieved recovery of pulse, but she died several hours later in hospital. Autopsy was declined, and death was classified as probable SUDEP.

## Postictal breathing rate and hypoxemia

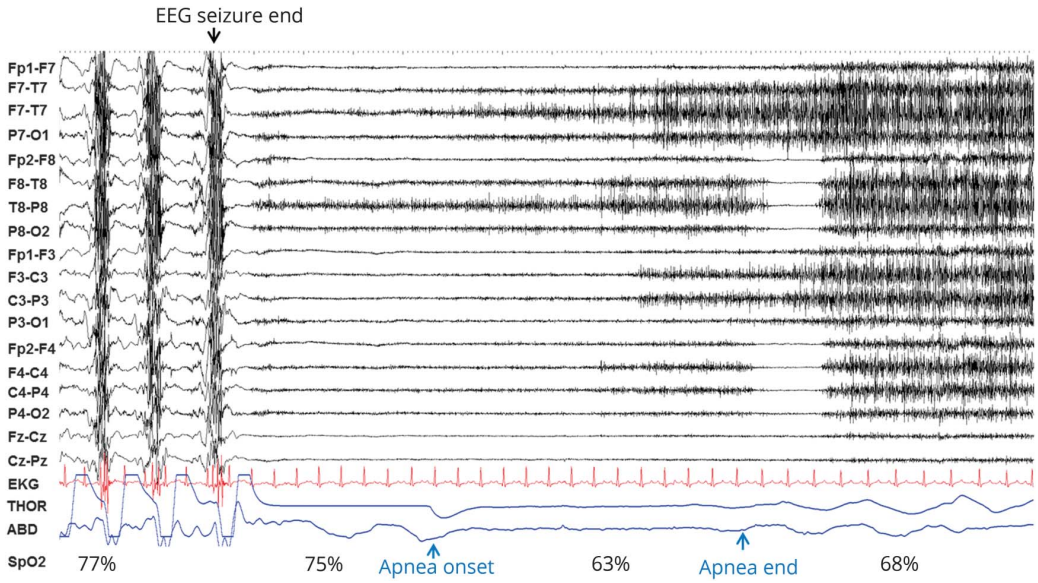
Breathing rate was available in 147 of 148 seizures (table 2). Bradypneic seizures had longer epilepsy duration, usually occurred in sleep, and were associated with severe hypoxemia and the presence of PCCA ($p < 0.05$). There was no association with age at study or at epilepsy onset or with seizure frequency and other epilepsy phenotypic or seizure characteristics (table e-2 available from Dryad, doi.org/10.5061/dryad.1k7d35q). Complete $Spo_2$ data were available in 91 seizures. All had at least moderate hypoxemia (moderate in 14 of 91 [15%] seizures, severe in 77 of 91 [85%] seizures). Nadir $Spo_2$ was detected postictally in 63 of 91 (69%) seizures and ictally in the rest (table 2). Early oxygen administration was related to shorter hypoxemia duration, with a mean in the early oxygen administration group of 120.33 ± 60.1 seconds vs 146.6 ± 57.4 seconds ($p = 0.018$).

## Postictal breathing effort and muscle artifact

Patients exhibited stertorous breathing in 109 of 147 (74.1%) seizures in 69 of 87 (79.3%) patients. Breathing sounds were expiratory in 60, both inspiratory and expiratory in 40, and solely inspiratory in 9. None exhibited ictal or postictal inspiratory stridor suggestive of laryngospasm. In 1 patient (smoker) with no known cardiorespiratory comorbidity, stereotypic wheezing occurred after clinical seizure end in all 3 recorded GCS, suggesting distal airway obstruction.

Postictal muscle artifact was present in 131 of 147 (89%) seizures (1 was excluded due to excessive electrode artifact),

**Figure 1** Postconvulsive central apnea




Generalized convulsive seizure end and subsequent postictal phase are shown in a 20-second page: EEG sensitivity 7 μV, time constant 0.1, high frequency filter 70 Hz. After seizure end, 2 noticeable breaths are followed by postconvulsive central apnea of 6 seconds, with pulse artifact identifiable in the plethysmography signal during this period. Oxygen desaturation and subsequent ongoing recovery are seen as the patient resumes breathing. ABD = abdominal; THOR = thoracic.

with a mean duration of 70.9 ± 45.4 seconds (56; 10–180 seconds). Muscle artifact was unrelated to epilepsy phenotypic features ($p > 0.05$), but longer hypoxemia duration ($p = 0.005$), lower mean $Spo_2$ nadir values ($p = 0.001$), higher decreases in $Spo_2$ ($p = 0.001$), stertorous breathing ($p = 0.005$), and presence of PGES ($p < 0.001$) were associated (table e-3 available from Dryad, doi.org/10.5061/dryad.1k7d35q). After binominal regression analysis, the presence of PGES remained an independent association (OR 11.630, 95% CI 1.631–82.945, $p = 0.014$). Duration of muscle artifact was longer in patients in the sleep state, those with tonic phases in GCS, and patients with stertorous breathing and correlated with PGES duration ($r = 0.286$, $p = 0.004$) and EEG recovery duration ($r = 0.405$, $p = 0.001$).

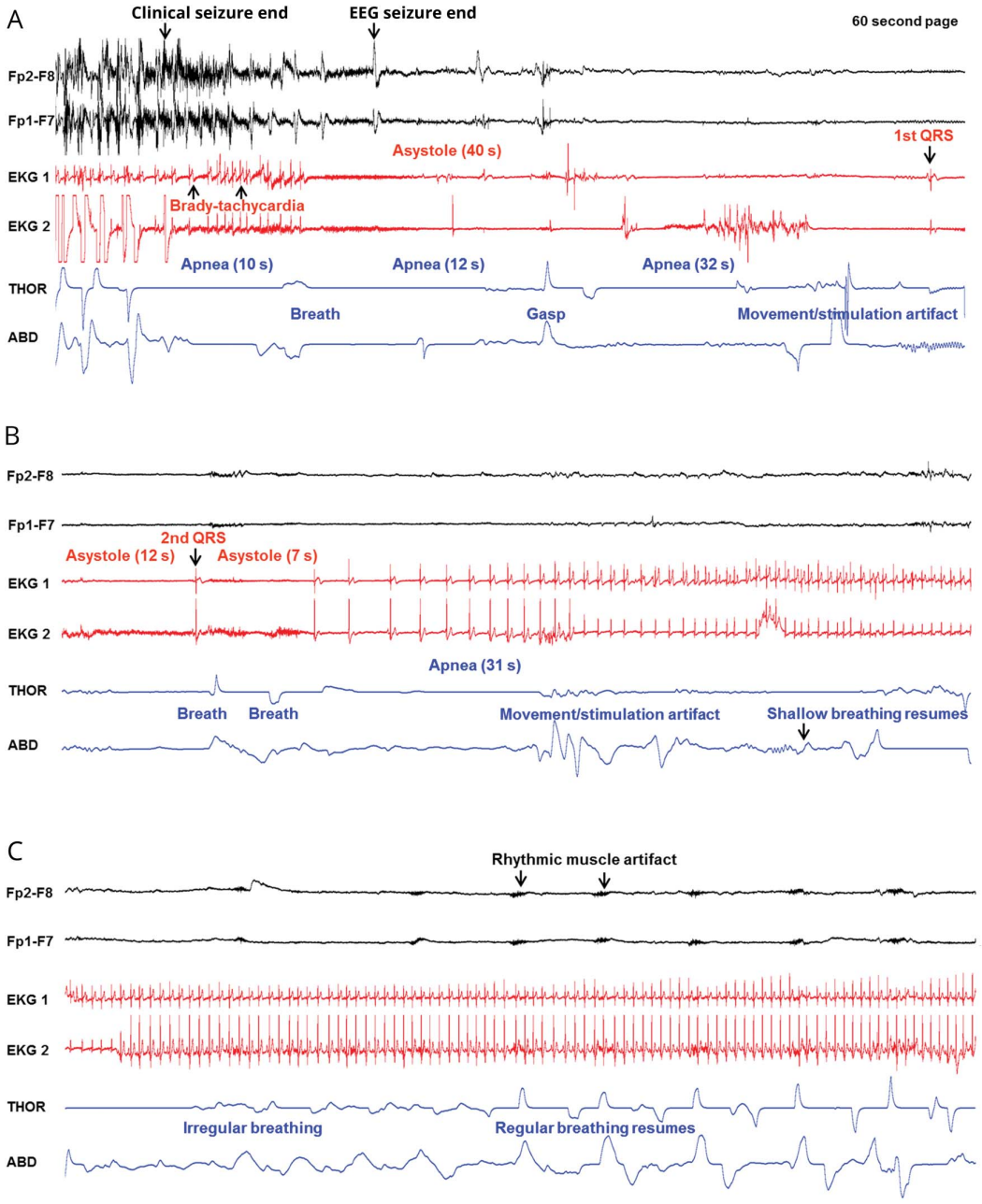
Two different muscle artifact patterns were noted: a rhythmic, intermittent pattern, synchronous with breathing, in 75 of 147 (51%) seizures in 53 patients (figure 4A) and a continuous, nonrhythmic pattern in 51 of 147 (34.6%) seizures in 35 patients (figure 4B). Five seizures (3.4%) in 5 patients successively exhibited both types of patterns.

Rhythmic muscle artifact was associated with older age at study, higher body mass index, longer seizure duration, and loud breathing ($p < 0.050$), whereas PCCA was less frequent in this group. After binominal regression analysis, presence of stertorous breathing (OR 3.856, 95% CI 1.395–10.663, $p = 0.009$), age at study (OR 1.032, 95% CI 1.001–1.064, $p = 0.040$), and longer clinical seizure duration (OR 1.026, 95% CI 1.001–1.051, $p = 0.045$) remained independently associated with rhythmic muscle artifact. It was also correlated with EEG recovery duration ($r = 0.303$, $p = 0.020$).

## Discussion

Our study suggests that PCCA is a possible SUDEP biomarker, occurring in only 22% of GCS. Consistent with MORTEMUS, PCCA was associated with near-SUDEP phenomena as well as SUDEP, the latter in a prospectively ascertained case. Its incidence was approximately half that of ICA, which appears more likely to be a benign semiologic feature of focal seizures unless prolonged (>60 seconds) or associated with severe hypoxemia (<75% $Spo_2$).[6] PCCA lasted 5 to 85 seconds, and 1 patient with only 8 seconds of PCCA in 1 recorded GCS went on to have an at-home, unmonitored SUDEP, suggesting that its presence may be a predictor of death. Prolonged PCCA may be especially dangerous. Our data suggest a distinction between the pathophenomenology of ICA and PCCA. The former is a preconvulsive phenomenon in focal epilepsy, likely driven by seizure discharges in cortical sites that modulate breathing[6,22,23]; on multivariate analysis, we found no association between ICA with PCCA. The latter, on the other hand, occurs in either focal or generalized epilepsy regardless of electrographic seizure discharge, suggesting that it is driven by brainstem mechanisms akin to a pontomedullary, rather than cortical, Todd paresis–like phenomenon. Whereas PCCA may be immediate or delayed, either can occur without postconvulsive electrographic seizure discharge, and the same patient may exhibit either or both types of PCCA. Thus, the 2 phenomena either are the same or share a common anatomic

**Figure 2** Sequence of EEG, ECG, and breathing changes in the near-SUDEP event of patient 1

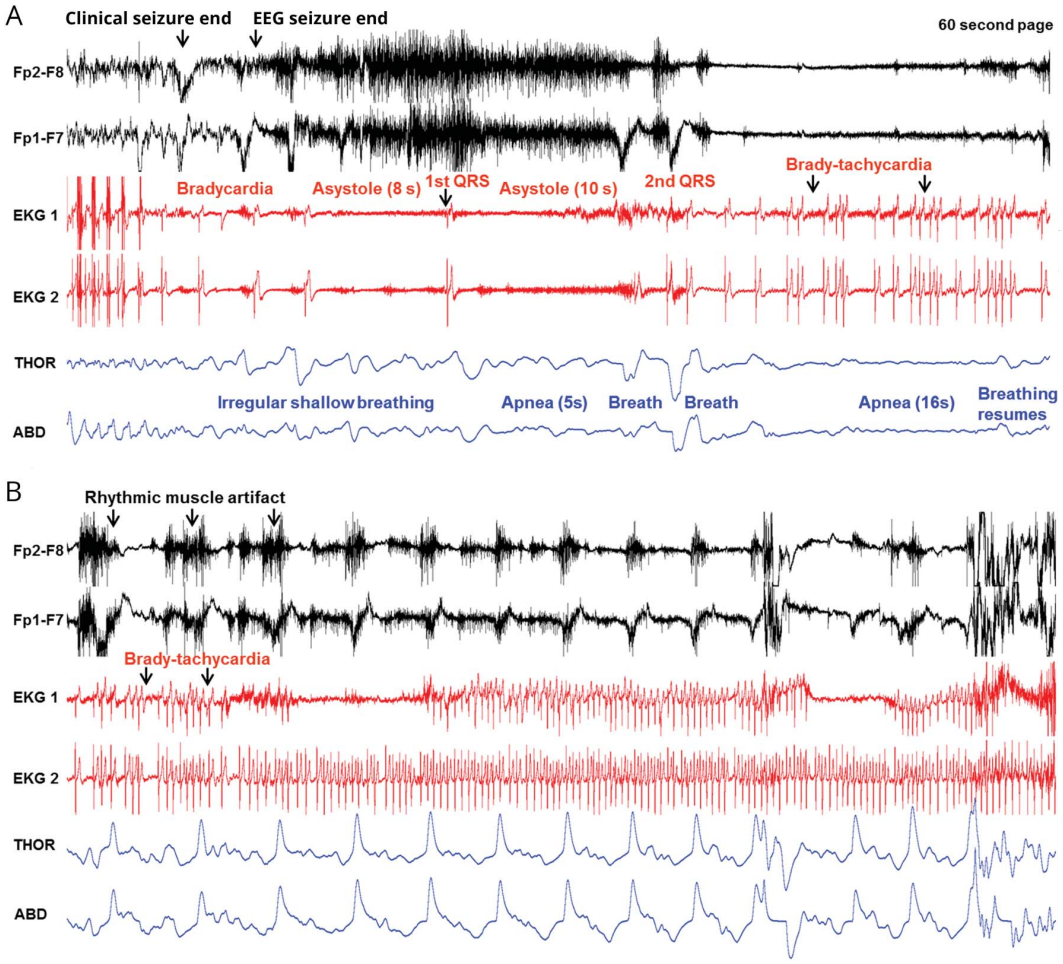



(A–C) Clinical seizure end and onset of the postictal convulsive phase are shown in 3 consecutive 60-second pages. Two channels of the EEG recording are displayed, along with 2 ECG channels and thoracic (THOR) and abdominal (ABD) belts. (A) After clinical seizure end, apnea is noted, accompanied by bradytachycardia that progresses into asystole. Three apneic periods are seen. The first QRS complex is seen at the end of the page. (B) Apnea and asystole continue from panel A until a second QRS complex and 2 breaths, followed by further apnea and asystole. Regular cardiac rhythm is progressively restored, although apnea persists until several seconds later. (C) Cardiac rhythm is re-established, and breathing excursions become more regular and increase in amplitude. Rhythmic muscle artifact becomes more evident on EEG. SUDEP = sudden unexpected death in epilepsy.

substrate of a compromised brainstem. Thus, in our patients with near-SUDEP/SUDEP, both immediate and delayed apnea occurred in patient 1, delayed apnea was seen in patient 2, and immediate apnea occurred in patient 3. Blunted $CO_2$ chemoreceptor responses due to preexisting obstructive sleep apnea in patient 2 may have played a role in his near-SUDEP, although his sleep apnea was uncomplicated and unlikely to have contributed.

ICA incidence (40.4%) was concordant with previous publications.[6] No patients with generalized epilepsy had preconvulsive ICA, supporting the contention that preconvulsive

**Figure 3** Sequence of EEG, ECG, and breathing changes in the near-SUDEP event of patient 2

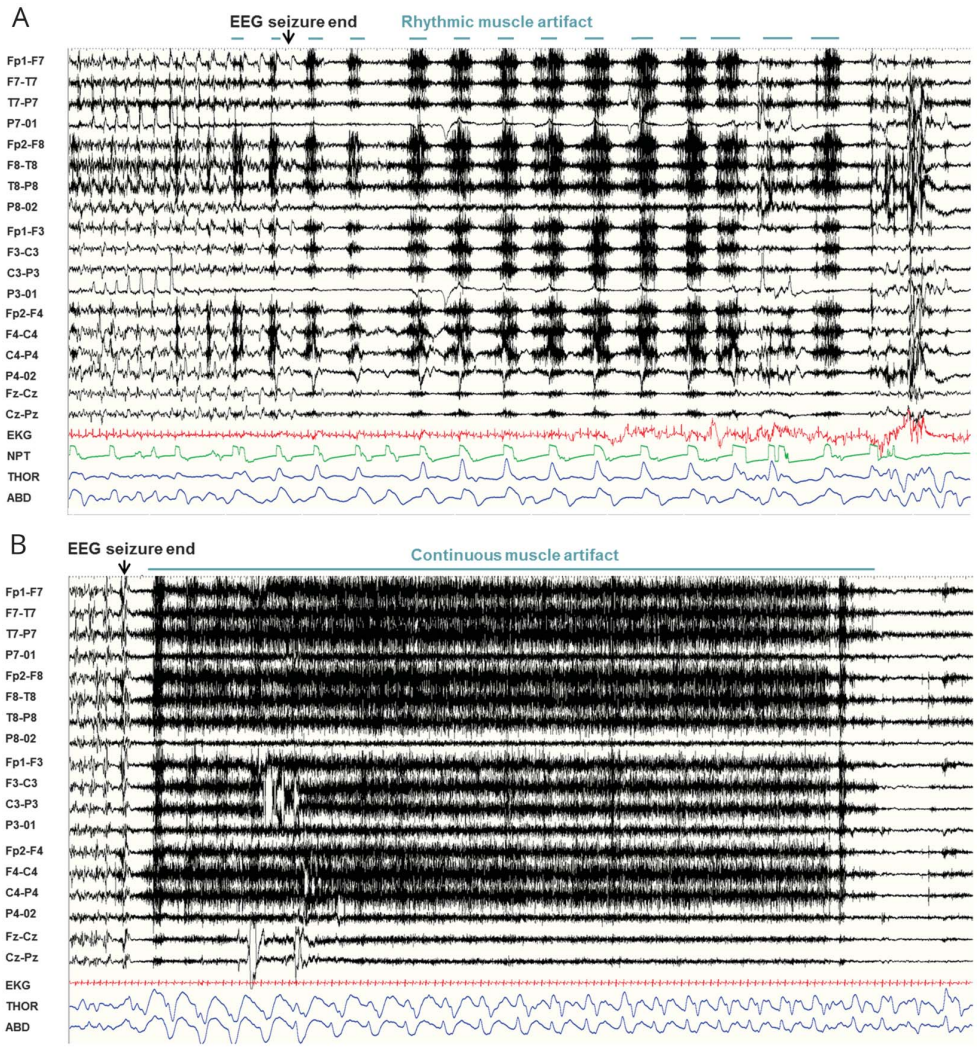



Seizure end and onset of the postconvulsive phase are shown in 2 consecutive 60-second pages. Two channels of the EEG recording are displayed, along with 2 ECG channels and thoracic (THOR) and abdominal (ABD) excursions. (A) After clinical end, progressive bradycardia is noted progressing to asystole after EEG end. After the first QRS complex, a brief period of apnea is noted. There are some isolated breaths followed by a longer period of apnea, even as cardiac activity is re-established, although in an arrhythmic fashion. Toward the end of the page, apnea ends and 2 breaths are noted. (B) A bradytachyarrhythmic pattern on the ECG is still present at the beginning of the page. Breathing excursions increase and become more regular accompanied by prominent rhythmic muscle artifact on EEG. SUDEP = sudden unexpected death in epilepsy.

ICA is a semiologic phenomenon unique to focal epilepsies.[22] On the other hand, PCCA occurred in both generalized and focal epilepsies, consistent with findings that SUDEP occurs in both categories. PCCA was more frequent in women and in the presence of PGES. However, PCCA duration was longer in men. Confirmed in multivariate analysis, female predilection is not easily explained because SUDEP is reported to more likely afflict men[14]; longer PCCA duration in men may be more indicative of risk. Imaging studies in our cohort with intractable epilepsy and GCS indicate sex-specific cortical changes in autonomic and breathing control sites such as preferential, lateralized orbitofrontal cortex thinning in women.[24] Bradypnea occurred more often in seizures arising from sleep, when most SUDEP occurs. Postconvulsive bradypnea or PCCA accompanied by asystole appears to be particularly rare, occurring in only 1 seizure each in the 2 near-SUDEP cases (<1% of all GCS), and thus may represent an especially important biomarker.

The apnea/bradycardia combination after seizures leading to death has been described in animal[25,26] and human[1,2] SUDEP, although its mechanisms are unclear. Apnea and the consequent hypoxemia and hypercapnia stimulate carotid body chemoreceptors, which may trigger bradycardia through vagal efferent activation.[27] However, in a Dravet syndrome animal model,[26] selective peripheral muscarinic receptor blockade did not prevent postictal apnea, bradycardia, and death. On the other hand, selective central, medullary muscarinic receptor blockade (intravenous methylatropine or intracerebroventricular N-methylscopolamin) did, suggesting that prevention of central apnea, rather than vagal output blockade, is more relevant. Medullary muscarinic receptors can stimulate

**Figure 4** Types of muscle artifact




(A) Rhythmic muscle artifact in a 60-second page. Note the one-to-one correspondence with thoraco (THOR)-abdominal (ABD) excursions and nasal flow assessed by nasal pressure transducer (NPT) (sensitivity 7 μV, time constant 0.03, high frequency filter 70). (B) Continuous muscle artifact in a 60-second page (sensitivity 7 μV, time constant 0.03, high frequency filter 70).

or inhibit breathing[28,29] and are involved in central $CO_2$ chemoreception.[30] Another critical brainstem component is the periaqueductal gray (PAG), which is an integrative center for breathing responses. Its afferents, including orbito-insular and dorsomedial projections, amygdalo-hippocampal complex, and thalamus, presumably participate in GCS seizure discharge. PAG functional and structural segregation can determine deep breathing, tachypnea, or apnea.[31] PAG efferents project to multiple nuclei, including medullary neurons involved in respiratory rhythm and pattern generation, shaping final breathing output. Stimulation of ventrolateral caudal PAG in the cat decreases spontaneous activity and responsiveness to surrounding stimuli and elicits irregular breathing, hypotension, and bradycardia.[32] Whereas significant GCS-driven disruption of brainstem-mediated breathing function may result in brief PCCA, severe and prolonged, fatal or near fatal PCCA may involve structures such as the PAG,[33] causing bradyarrhythmia, asystole, and hypotension.[34–36] Possible ineffective breathing during a seizure, along with a high metabolic load, could set the hypoxic stage for more catastrophic PCCA effects.

Postictal spreading depolarization in dorsal medulla after seizures, shown to produce cardiorespiratory arrest, preceded by EEG suppression and apnea, constitutes another potential mechanism.[37] Longer PGES duration was found in patients with delayed compared to immediate PCCA, suggesting a possible relationship between cerebral shutdown and brainstem dysfunction. Establishment of nonseizure SUDEP as an entity[38] suggests that brainstem dysfunction may initiate the agonal event independently of cortical seizures.[39,40] Whereas

spreading depression in cardiorespiratory suppression is unproven in humans, increasing evidence from imaging[41,42] and pathologic studies[43] suggests that key cardiorespiratory control structures are significantly damaged in patients with intractable epilepsy who succumb to SUDEP. Imaging studies[42] have shown increased right hippocampal and parahippocampal gray matter volume in patients experiencing SUDEP and high-SUDEP-risk patients, setting the stage for possible autonomic and respiratory output dysregulation.[44] Gray matter volume decline in the posterior thalamus and brainstem (superior colliculi, PAG, mesencephalic reticular formation, and raphe nuclei) in patients experiencing SUDEP and high-SUDEP-risk patients suggests damage to structures essential for breathing response modulation. Neuropathologic examination of brainstems of patients experiencing SUDEP[43] has shown structural injury in neuropeptidergic and monoaminergic systems, specifically somatostatin and neurokinin 1 receptor neurons in medullary raphe and ventrolateral medulla, where the pre-Botzinger complex[45] nucleus is located. The pre-Botzinger complex nucleus is an important site for inspiratory rhythm generation and a key PAG efferent. These findings provide crucial anatomic substrates for breathing and cardiac dysfunction seen in patients with PCCA and those experiencing near-SUDEP/SUDEP.

Recent studies[9,10] describe potentially greater ictal and postictal laryngospasm incidence in SUDEP phenomenology than previously reported in the literature.[7,46] Rodent laryngospasm models point to distinctive potential SUDEP biomarkers based on breathing effort and cardiorespiratory coupling.[10] One such is postconvulsive rhythmic breathing EMG artifact evident in ECG and EEG channels. Another is an abrupt increase in RR interval variance, indicating increased breathing effort. Further analysis of MORTEMUS SUDEP records has suggested the presence of 1 or more of these biomarkers, pointing to a role for laryngospasm and obstructive apnea in death. However, despite careful analysis of breathing in our study, aided by an expert pulmonologist, no convincing laryngospasm or obstructive apnea was seen despite the presence of rhythmic muscle artifact in 51% of GCS. The absence of such breathing compromise was further confirmed in the small subset of patients with airflow monitoring, in whom rhythmic muscle artifact occurred without airflow impediment (figure 4A). This suggests that the rarity of reported laryngospasm in the literature is deserved. Thus, rhythmic muscle artifact is more likely to represent enhanced, nonobstructive breathing effort in the aftermath of the physically vigorous seizure that is a GCS. Accordingly, its presence was related to older age, longer seizure duration, and stertorous breathing, reflecting strenuous seizure-related physical impact. On the other hand, rhythmic muscle artifact was not associated with objective markers of breathing drive such as oxygen desaturation or hypercarbia. PGES correlated with the presence of muscle artifact overall, although not with rhythmic artifact alone or continuous artifact alone. This finding suggests that PGES does not correlate with enhanced breathing effort but may correlate with increased muscle tone in the postictal state.[11]

PCCA, found in our cases of near-SUDEP/probable SUDEP and reported in all MORTEMUS SUDEP, may help stratify SUDEP risk. However, larger prospective studies are needed to confirm this and to standardize procedures of response. Whereas pacemaker implantation in ictal asystole may prevent fall-related injuries,[47,48] its role in postictal asystole with PCCA is uncertain. The accompanying apnea and centrally driven asystole may or may not render pacemakers futile. Optimization of seizure control, prevention of GCS, and potentially stimulation of ventilation remain critical.

Our study has limitations. Our near-SUDEP estimate (10.2 per 1,000 patient-years) may underestimate true incidence in the severely intractable population (but likely overestimates it in the general epilepsy population) because we could comment only on monitored seizures in this preliminary report and similar events at home may pass unnoticed. On the other hand, our definition of near-SUDEP did not include the institution of CPR[49]; the distinction between those with and those without CPR may be artificial because there is overreliance on the resuscitator's judgment as to its necessity. There is strong argument that all patients who have combined asystole and central apnea, regardless of CPR, be included in the definition. Our apnea definition may overestimate incidence because previous studies are based on sleep-study criteria. Our definition is more sensitive to brief disturbances of breathing that would otherwise be missed. While there was combined use of airflow and thoracoabdominal descriptions, precise distinction between obstructive and nonobstructive apnea can be made only by direct measures of chest wall/diaphragm EMG or measures of esophageal pressure. However, we assumed that even brief absences of ventilation in the postconvulsive phase, when most patients have enhanced breathing rates, could have important biological significance in the SUDEP context. Multiple apneic exposures may damage hypoxia-sensitive neural systems such as the long axons in the hippocampus and climbing fibers of the cerebellum; both structures serve significant breathing and blood pressure control roles, and progressive damage has the potential to lead to system collapse. Another limitation is that our study is based on surface EEG, and persistence of intracranial seizure cannot be completely ruled out in all patients with PCCA.[50] Exquisitely focal postconvulsive electrographic seizures in cortical sites that influence breathing such as the amygdala and hippocampus may account for sustained apnea, although it seems relatively unlikely to account for intermittent PCCA periods that were collectively as long as 85 seconds in our patients. Nasal outflow recordings were available in only a small subset, which may underestimate the true incidence of obstructive apnea/hypopnea. Limited airflow and $tcO_2$ datasets in this study reflect the clinical epilepsy monitoring unit setting, where data acquisition can be variable. However, it appears clear that clinically significant laryngospasm is probably rare in GCS.

PCCA is a relatively uncommon phenomenon. Its occurrence, regardless of epileptogenic zone or demonstrable seizure discharge, and an association with asystole indicate a functional

substrate in the brainstem akin to Todd paresis or even self-limited spreading depolarization. PCCA may serve as a SUDEP biomarker, and further follow-up of this large prospective cohort may further clarify its potential role. This study further highlights the role of polygraphic, multimodal recording in the epilepsy monitoring unit in peri-ictal breathing dysfunction diagnosis. We found that seizure-related laryngospasm is probably extremely rare, although it remains a potential mechanism of death. Breathing related rhythmic muscle artifact is more indicative of breathing effort than obstructed breathing and thus may not be a particularly useful biomarker for SUDEP.

## Acknowledgment

The authors thank Sarah J. Delozier (University Hospitals Cleveland Medical Center, OH) for her assistance with the statistical analysis.

## Study funding

No targeted funding reported.

## Disclosure

L. Vilella, N. Lacuey, J. Hampson, M. Sandhya Rani, R. Sanju, D. Friedman, M. Nei, K. Strohl, C. Scott, B. Gehlbach, B. Zonjy, N. Hupp, A. Zaremba, N. Shafiabadi, X. Zhao, V. Reick-Mitrisin, S. Schuele, J. Ogren, R. Harper, B. Diehl, L. Bateman, and O. Devinsky report no disclosures relevant to the manuscript. G. Richerson is funded by the Center for SUDEP Research: NIH/NINDS U01-NS090414. P. Ryvlin reports no disclosures relevant to the manuscript. S. Lhatoo is funded by the Center for SUDEP Research: NIH/NINDS U01-NS090405 and NIH/NINDS U01-NS090407. Go to Neurology.org/N for full disclosures.

## Publication history

Received by *Neurology* May 18, 2018. Accepted in final form August 29, 2018.

## References

1. Ryvlin P, Nashef L, Lhatoo SD, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. Lancet Neurol 2013;12:966–977.
2. Nashef L, Walker F, Allen P, Sander JW, Shorvon SD, Fish DR. Apnoea and bradycardia during epileptic seizures: relation to sudden death in epilepsy. J Neurol Neurosurg Psychiatry 1996;60:297–300.
3. Blum AS, Ives JR, Goldberger AL, et al. Oxygen desaturations triggered by partial seizures: implications for cardiopulmonary instability in epilepsy. Epilepsia 2000;41:536–541.
4. Bateman LM, Li CS, Seyal M. Ictal hypoxemia in localization-related epilepsy: analysis of incidence, severity and risk factors. Brain 2008;131:3239–3245.
5. Seyal M, Bateman LM, Albertson TE, Lin TC, Li CS. Respiratory changes with seizures in localization-related epilepsy: analysis of periictal hypercapnia and airflow patterns. Epilepsia 2010;51:1359–1364.
6. Lacuey N, Zonjy B, Hampson JP, et al. The incidence and significance of periictal apnea in epileptic seizures. Epilepsia 2018;59:573–582.
7. Tavee J, Morris H III. Severe postictal laryngospasm as a potential mechanism for sudden unexpected death in epilepsy: a near-miss in an EMU. Epilepsia 2008;49:2113–2117.
8. So EL, Sam MC, Lagerlund TL. Postictal central apnea as a cause of SUDEP: evidence from near-SUDEP incident. Epilepsia 2000;41:1494–1497.
9. Nakase K, Kollmar R, Lazar J, et al. Laryngospasm, central and obstructive apnea during seizures: defining pathophysiology for sudden death in a rat model. Epilepsy Res 2016;128:126–139.
10. Stewart M, Kollmar R, Nakase K, et al. Obstructive apnea due to laryngospasm links ictal to postictal events in SUDEP cases and offers practical biomarkers for review of past cases and prevention of new ones. Epilepsia 2017;58:e87–e90.
11. Gastaut H, Broughton R. Epileptic Seizures: Clinical and Electrographic Features, Diagnosis and Treatment. Springfield: Charles C Thomas; 1972.
12. Schuele SU, Bermeo AC, Alexopoulos AV, Burgess RC. Anoxia-ischemia: a mechanism of seizure termination in ictal asystole. Epilepsia 2010;51:170–173.
13. van der Lende M, Surges R, Sander JW, Thijs RD. Cardiac arrhythmias during or after epileptic seizures. J Neurol Neurosurg Psychiatry 2016;87:69–74.
14. Hesdorffer DC, Tomson T, Benn E, et al. Combined analysis of risk factors for SUDEP. Epilepsia 2011;52:1150–1159.
15. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the Ad Hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;51:1069–1077.
16. Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the international league against epilepsy: position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58:522–530.
17. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58:512–521.
18. Alexandre V, Mercedes B, Valton L, et al. Risk factors of postictal generalized EEG suppression in generalized convulsive seizures. Neurology 2015;85:1598–1603.
19. Azar NJ, Tayah TF, Wang L, Song Y, Abou-Khalil BW. Postictal breathing pattern distinguishes epileptic from nonepileptic convulsive seizures. Epilepsia 2008;49:132–137.
20. Lhatoo SD, Faulkner HJ, Dembny K, Trippick K, Johnson C, Bird JM. An electroclinical case-control study of sudden unexpected death in epilepsy. Ann Neurol 2010;68:787–796.
21. Theeranaew W, McDonald J, Zonjy B, et al. Automated detection of postictal generalized EEG suppression. IEEE Trans Biomed Eng 2018;65:371–377.
22. Lacuey N, Zonjy B, Londono L, Lhatoo SD. Amygdala and hippocampus are symptomatogenic zones for central apneic seizures. Neurology 2017;88:701–705.
23. Dlouhy BJ, Gehlbach BK, Kreple CJ, et al. Breathing inhibited when seizures spread to the amygdala and upon amygdala stimulation. J Neurosci 2015;35:10281–10289.
24. Ogren JA, Tripathi R, Macey PM, et al. Regional cortical thickness changes accompanying generalized tonic-clonic seizures. Neuroimage Clin 2018;20:205–215.
25. Johnston SC, Siedenberg R, Min JK, Jerome EH, Laxer KD. Central apnea and acute cardiac ischemia in a sheep model of epileptic sudden death. Ann Neurol 1997;42:588–594.
26. Kim Y, Bravo E, Thirnbeck CK, et al. Severe peri-ictal respiratory dysfunction is common in Dravet syndrome. J Clin Invest 2018;128:1141–1153.
27. Paton JF, Boscan P, Pickering AE, Nalivaiko E. The yin and yang of cardiac autonomic control: vago-sympathetic interactions revisited. Brain Res Brain Res Rev 2005;49:555–565.
28. Muere C, Neumueller S, Miller J, et al. Atropine microdialysis within or near the pre-Botzinger complex increases breathing frequency more during wakefulness than during NREM sleep. J Appl Physiol 2013;114:694–704.
29. Lydic R, Baghdoyan HA. Pedunculopontine stimulation alters respiration and increases ACh release in the pontine reticular formation. Am J Physiol 1993;264:R544–R554.
30. Dev NB, Loeschcke HH. A cholinergic mechanism involved in the respiratory chemosensitivity of the medulla oblongata in the cat. Pflugers Arch 1979;379:29–36.
31. Subramanian HH, Balnave RJ, Holstege G. The midbrain periaqueductal gray control of respiration. J Neurosci 2008;28:12274–12283.
32. Carrive P. The periaqueductal gray and defensive behavior: functional representation and neuronal organization. Behav Brain Res 1993;58:27–47.
33. UEDA H. Arrhythmias produced by cerebral stimulation. Jpn Circ J 1962;26:225–230.
34. Bozorgi A, Chung S, Kaffashi F, et al. Significant postictal hypotension: expanding the spectrum of seizure-induced autonomic dysregulation. Epilepsia 2013;54:e127–e130.
35. Hampel KG, Jahanbekam A, Elger CE, Surges R. Seizure-related modulation of systemic arterial blood pressure in focal epilepsy. Epilepsia 2016;57:1709–1718.
36. Hampel KG, Elger CE, Surges R. Impaired baroreflex sensitivity after bilateral convulsive seizures in patients with focal epilepsy. Front Neurol 2017;8:210.
37. Aiba I, Noebels JL. Spreading depolarization in the brainstem mediates sudden cardiorespiratory arrest in mouse SUDEP models. Sci Transl Med 2015;7:282ra46.
38. Ba-Armah DM, Donner EJ, Ochi A, et al. "Saved by the bell": near SUDEP during intracranial EEG monitoring. Epilepsia Open 2018;3:98–102.
39. Devinsky O, Friedman D, Duckrow RB, et al. Sudden unexpected death in epilepsy in patients treated with brain-responsive neurostimulation. Epilepsia 2018;59:555–561.
40. Lhatoo SD, Nei M, Raghavan M, et al. Nonseizure SUDEP: sudden unexpected death in epilepsy without preceding epileptic seizures. Epilepsia 2016;57:1161–1168.
41. Mueller SG, Bateman LM, Laxer KD. Evidence for brainstem network disruption in temporal lobe epilepsy and sudden unexplained death in epilepsy. Neuroimage Clin 2014;5:208–216.
42. Wandschneider B, Koepp M, Scott C, et al. Structural imaging biomarkers of sudden unexpected death in epilepsy. Brain 2015;138:2907–2919.
43. Patodia S, Somani A, O'Hare M, et al. The ventrolateral medulla and medullary raphe in sudden unexpected death in epilepsy. Brain 2018;141:1719–1733.
44. Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. Neurology 1992;42:1727–1732.
45. Feldman JL, Del Negro CA. Looking for inspiration: new perspectives on respiratory rhythm. Nat Rev Neurosci 2006;7:232–242.
46. Lacuey N, Vilella L, Hampson JP, Sahadevan J, Lhatoo SD. Ictal laryngospasm monitored by video-EEG polygraphy: a potential SUDEP mechanism. Epileptic Disord 2018;20:146–150.
47. Moseley BD, Ghearing GR, Munger TM, Britton JW. The treatment of ictal asystole with cardiac pacing. Epilepsia 2011;52:e16–e19.
48. Hampel KG, Thijs RD, Elger CE, Surges R. Recurrence risk of ictal asystole in epilepsy. Neurology 2017;89:785–791.
49. Nashef L, So EL, Ryvlin P, Tomson T. Unifying the definitions of sudden unexpected death in epilepsy. Epilepsia 2012;53:227–233.
50. Altenmüller DM, Schulze-Bonhage A, Elger CE, Surges R. Local brain activity persists during apparently generalized postictal EEG suppression. Epilepsy Behav 2016;62:218–224.

**Appendix 1** Author contributions

| Name | Location | Role | Contribution |
|---|---|---|---|
| **Laura Vilella, MD** | Epilepsy Center, University Hospitals Cleveland Medical Center, Cleveland, OH | Author | Major role in the acquisition and analysis of data; interpreted the data; drafted the manuscript for intellectual content |
| **Nuria Lacuey, MD** | Epilepsy Center, University Hospitals Cleveland Medical Center, Cleveland, OH | Author | Design and conceptualized study; interpreted the data; revised the manuscript for intellectual content |
| **Johnson P. Hampson, MSBME** | Epilepsy Center, University Hospitals Cleveland Medical Center, Cleveland, OH | Author | Analysis of data; statistical analysis; images and video editing |
| **Sandhya Rani, PhD** | NINDS Center for SUDEP Research (CSR), Cleveland, OH | Author | Recruiter; Revised the manuscript for intellectual content |
| **Rup K. Sanju, MBBS** | University of Iowa School of Medicine, Iowa City, IA | Author | Revised the manuscript for intellectual content |
| **Daniel Friedman, MD** | NYU Langone School of Medicine, New York, NY | Author | Revised the manuscript for intellectual content |
| **Maromi Nei, MD** | Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA | Author | Revised the manuscript for intellectual content |
| **Kingman Strohl, MD** | Division of Pulmonary, Critical Care and Sleep Medicine, University Hospitals Medical Center, Cleveland, OH | Author | Interpreted the data; revised the manuscript for intellectual content |
| **Catherine Scott** | Institute of Neurology, University College London, London, UK | Author | Data acquisition |
| **Brian K Gehlbach, MD** | University of Iowa School of Medicine, Iowa City, IA | Author | Revised the manuscript for intellectual content |
| **Bilal Zonjy, MD** | NINDS Center for SUDEP Research (CSR), Cleveland, OH | Author | Data acquisition |
| **Norma J. Hupp, R.EEG.T.CLTm** | Epilepsy Center, University Hospitals Cleveland Medical Center, Cleveland, OH | Author | Data acquisition |
| **Anita Zaremba, BA** | NINDS Center for SUDEP Research (CSR), Cleveland, OH | Author | Led and coordinated communication among sites. Revised the manuscript for intellectual content |
| **Nassim Shafiabadi, MD** | Epilepsy Center, University Hospitals Cleveland Medical Center, Cleveland, OH | Author | Data acquisition |
| **Xiuhe Zhao, MD** | Epilepsy Center, University Hospitals Cleveland Medical Center, Cleveland, OH | Author | Data acquisition |
| **Victoria Reick-Mitrisin** | Epilepsy Center, University Hospitals Cleveland Medical Center, Cleveland, OH | Author | Data acquisition |
| **Stephan Schuele, MD MPH** | Feinberg School of Medicine, Northwestern University, Chicago, IL | Author | Revised the manuscript for intellectual content |
| **Jennifer Ogren, PhD** | Department of Neurobiology and the Brain Research Institute, University of California, Los Angeles (UCLA), Los Angeles, CA | Author | Revised the manuscript for intellectual content |
| **Ronald M. Harper, PhD** | Department of Neurobiology and the Brain Research Institute, University of California, Los Angeles (UCLA), Los Angeles, CA | Author | Revised the manuscript for intellectual content |
| **Beate Diehl, MD PhD FRCP** | Institute of Neurology, University College London, London, UK | Author | Revised the manuscript for intellectual content |
| **Lisa Bateman, MD** | Department of Neurology, Columbia University, New York, NY | Author | Revised the manuscript for intellectual content |
| **Orrin Devinsky, MD** | NYU Langone School of Medicine, New York, NY | Author | Revised the manuscript for intellectual content |
| **George B. Richerson MD PhD** | University of Iowa School of Medicine, Iowa City, IA | Author | Revised the manuscript for intellectual content |
| **Philippe Ryvlin, MD PhD** | Department of Clinical Neuroscience, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland | Author | Conceptualized study; revised the manuscript for intellectual content |
| **Samden D. Lhatoo, MD FRCP** | Epilepsy Center, University Hospitals Cleveland Medical Center, Cleveland, OH | Author | Designed and conceptualized study; analysis and interpretation of data; revised the manuscript for intellectual content |