Association of peri-ictal brainstem posturing with seizure severity and breathing compromise in patients with generalized convulsive seizures

Laura Vilella MD[1,2,3], Nuria Lacuey MD, PhD[1,2], Johnson P. Hampson MSBME[2], Liang Zhu[4] PhD, Shirin Omidi MD[1,2], Manuela Ochoa-Urrea MD[1,2], Shiqiang Tao PhD[1,2], M. R. Sandhya Rani PhD[1,2], Rup K. Sainju MBBS[1,5], Daniel Friedman MD[1,6], Maromi Nei MD[1,7], Kingman Strohl MD[8], Catherine Scott[1,9], Luke Allen[1,9], Brian K Gehlbach MD[1,5], Norma J. Hupp R.EEG.T.CLTm[2], Jaison S Hampson MD[1,2], Nassim Shafiabadi MD[10], Xiuhe Zhao MD[10,], Victoria Reick-Mitrisin[10], Stephan Schuele MD MPH[1,11], Jennifer Ogren PhD[1,12], Ronald M. Harper PhD[1,12], Beate Diehl MD PhD FRCP[1,9], Lisa M Bateman MD[1,13], Orrin Devinsky MD[1,6], George B. Richerson MD PhD[1,4], Philippe Ryvlin MD PhD[1,14], GQ Zhang MS PhD[1,2] ,Samden D Lhatoo MD FRCP[1,2]

[1]NINDS Center for SUDEP Research (CSR), McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA

[2]Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA

[3]Departament de Medicina. Universitat Autonoma de Barcelona, Barcelona, Spain.

[4]Biostatistics & Epidemiology Research Design Core, Division of Clinical and Translational Sciences, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA

[5]University of Iowa Carver College of Medicine, Iowa City, IA, USA

[6]NYU Langone School of Medicine, New York, NY, USA

[7]Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, USA

[8]Division of Pulmonary, Critical Care and Sleep Medicine, University Hospitals Medical Center, Cleveland, OH, USA

[9]Institute of Neurology, University College London, London, UK

[10]Case Western Reserve University, Cleveland, OH, USA

[11]Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

[12]Department of Neurobiology and the Brain Research Institute, University of California, Los Angeles (UCLA), Los Angeles, CA, USA

[13]Department of Neurology, Columbia University, New York, NY, USA

[14]Department of Clinical Neuroscience, Centre Hospitalier Universitaire Vaudois,

Lausanne, Switzerland

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Corresponding Author**:** Laura Vilella (Lvilellabertran@gmail.com)

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ABSTRACT

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

Methods: 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. Post-ictal posturing was also assessed. Respiration was monitored using thoraco-abdominal belts, video and pulse oximetry.

Results: 295 seizures (180 patients) were analyzed. Ictal decerebration was observed in 122/295 (41.4%), decortication in 47/295 (15.9%) and hemi-decerebration in 28/295 (9.5%) seizures. Tonic phase was absent in 98/295 (33.2%) seizures. Postictal posturing occurred in 18/295 (6.1%) seizures. PGES risk increased with ictal decerebration [OR 14.79, 95% 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]. Post-ictal posturing was associated with post-convulsive 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. Post-ictal posturing is associated with a threefold increased risk of PCCA, longer hypoxemia and SpO_2 recovery. Peri-ictal

brainstem posturing may be surrogate biomarkers 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.

INTRODUCTION

Sudden Unexpected Death in Epilepsy (SUDEP) is the leading category of death in patients with refractory epilepsy, with an incidence of 6.3-9.3 per 1000 person-years in this population.[1, 2] Frequent generalized convulsive seizures (GCS) in patients with longstanding, early onset epilepsy, comprise 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), post-convulsive central apnea (PCCA), hypoxemia severity, post-ictal blood catecholamine rise and prolonged (>50 seconds) post-ictal generalized electroencephalographic suppression (PGES).[4-9] PGES was observed in all monitored SUDEP cases in the MORTEMUS study 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 is 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 post-ictal although its symptomatogenic brain areas, and its relationship to post-ictal cardiorespiratory compromise are unknown.[16] Brainstem seizure spread may potentially explain both.[14, 17] Semiological clinical features such as posturing, can be recognized without 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 post-ictal 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 prospectively obtained from all the participants in the NINDS Center for SUDEP Research's Autonomic and Imaging Biomarkers of SUDEP multi-center 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 (IRB) of the participating centers.

Patient selection

Patients with intractable epilepsy (failure of adequate trials of two or more antiepileptic medications)[18] aged $\geq$18 years who were undergoing video-electroencephalography (VEEG) evaluation in the adult epilepsy monitoring units of participating centers from February 2011 until April 2018 were selected. Inclusion criteria were patients with recorded GCS and successfully analyzed until April 2018, including generalized tonic-clonic seizures (GTCS), focal to bilateral tonic-clonic seizures (FBTCS) and focal onset motor bilateral clonic seizures.[19] Exclusion criteria were status epilepticus (SE) and/or obscured or unavailable video. Demographic and clinical data were collected, including epilepsy duration, seizure type and frequency, semiological seizure features, awake or asleep states at seizure onset, and presence of major cardiac (cardiac ischemic disease, known arrhythmia, valvulopathy) or respiratory disease (obstructive sleep apnea, asthma, chronic obstructive pulmonary disease, bronchiectasis, cystic fibrosis).

We considered the use of serotonin or serotonin-noradrenaline reuptake inhibitors (SRIs). We assessed the impact of AEDs 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 one 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 1-3.**

Post-ictal 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 using the 10-20 International Electrode System. EEG and electrocardiogram (EKG) were acquired using Nihon Kohden (Tokyo, Japan), Micromed (Modigliani Veneto, Italy) and Xtlek (Natus)

and Nicolet (Natus) acquisition platforms. Peripheral capillary oxygen saturation (SpO_2) was monitored using pulse oximetry (Nellcor OxiMax N-600x [Convidien], Masimo Radical-7 [Irvine] and SenTec Digital Monitoring System [Therwil BL]) and chest wall and abdominal excursions were recorded using inductance plethysmography (Ambu [Ballerup, Denmark] Sleepmate and Perfect Fit 2 [Dymedix]).

Breathing analysis for apnea used composite analysis of inductance plethysmography, EEG breathing artifact and visually inspected thoraco-abdominal excursions two minutes before seizure onset (clinical or electrographic, whichever occurred first) and up to three minutes after clinical seizure end. Central apnea (cessation of thoraco-abdominal breathing movements) was defined as >one missed breath without other explanation (i.e. speech, or intervention), with a minimum duration of five seconds (s). ICA referred to apnea occurring in the pre-convulsive phase of GCS. PCCA referred to apnea after GCS; we preferred this term to post-ictal central apnea since 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 two minutes before EEG onset or clinical onset, whichever occurred first. We defined change in SpO_2 as 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 termed "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 two epilepsy neurophysiologists in all cases when the tool gave no solution. The visual inspection was masked to video EEG results for one of the neurophysiologist, but not for the other one.

Statistical analysis

Descriptive statistics (mean, standard deviation, 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 standard deviation 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-subject correlation. For continuous demographic and clinical variables, covariate coefficient estimates, standard error, and corresponding p values from GEE method were provided. Descriptive statistics for dichotomous outcomes (PGES, PCCA) are provided in **Tables 4**. Frequency and percentage, mean and standard deviation were provided for categorical and continuous variables, respectively. P values were obtained from GEE as well, with the binomial distribution and logit link. Based on the univariate analysis shown in **Tables 2, 3 and 4**, we present the multivariable analysis in **Tables 5 and 6**. Variables from the univariant analysis with p value less than 0.1 were included in the final models, and age at study and sex were treated as force-in variables. P value < 0.05 in the final models were considered significant. All analyses were performed in SAS 9.4 (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 and thirty-seven seizures were included in two previous publications on peri-ictal breathing dysfunction.[5, 22] Mean age at monitoring was 36.7±13.3 years (34; 18-77). Mean age at epilepsy onset

was 19.6±15.5 years old (16; 1-68) 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 patients (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 and forty-eight seizures occurred during wakefulness, 144 during sleep, and three during post-ictal stupor in a seizure cluster in one patient.

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

Postictal posturing occurred in 18/295 (6.1%) seizures in 12 patients (6.6%). In 16/18(88.8%) seizures in 10/12 patients (83.3%) tonic flexion of the upper extremities, identical to ictal decortication was observed. In the remaining 2/18 seizures (2/10 patients), tonic extension of upper extremities was noted, similar to ictal decerebration.

Electrographic burst discharge was simultaneous with decortication in two seizures (two patients) followed by PGES. In the remainder, this occurred concurrently with PGES. Posturing occurred 7 ± 7.9 s (4; 1-30) after the last clonic jerk.

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

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

Hypoxemia duration, available in in 127 seizures, was 142.6 ± 65.5 s (124; 25-314). When analyzing SpO_2 recovery from clinical seizure end, available in 120 seizures, it was 43.2 ± 34.2 s (35.5; -27-179). 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), nor with change in SpO_2 (p=0.822). There was also no association of tonic phase duration with ictal (p=0.965) or postictal apnea (p=0.712). Postictal posturing was associated with PGES (p=0.001). **Tables 2, 3 and 4.** In multivariate analysis, presence of either ictal decerebration [OR 14.79, 95% 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, when compared to absence of any tonic phase. PGES duration was significantly longer in those seizures with ictal decerebration [Est 20.45s, 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, 26.59), p=0.161] or hemi-decerebration [Est 5.22 (-10.16, 20.61), p=0.506] and those seizures without tonic phase.PGES duration was also longer with increasing age at time of study [Est 0.51s, 95% CI (0.13, 0.89), p=0.008]. **Table 5.**
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 comorbidities [Est -9.38%, 95% CI (-15.26,-3.50, p=0.002]. **Table 6.**
Post-ictal 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, RR 0.26, 95% CI (0.09-0.73), p=0.010], epilepsy type [focal, RR 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]. Post-

ictal posturing was associated with prolonged hypoxemia duration [Est 47.87s, 95% CI (24.47,71.27), p<0.001). Hypoxemia duration was also longer in male [Est 40.14s, 95%CI (16.61-63.67), p<0.001], it increased with GCS duration [Est 0.87s, 95% CI (0.03,1.70), p=0.041] and decreased with increasing age at study [Est -1.61s, 95%CI (-2.44,-0.78), p<0.001]. Post-ictal posturing was also associated with longer SpO_2 recovery [Est 27.84s, 95% CI (1.98-53.69), p=0.035]. Conversely, SpO_2 recovery was shorter with early administration of oxygen [Est -17.69s, 95% CI -29.56, -5.83) p=0.003] and with increased duration of the GCS [Est -0.53s, 95% CI (-0.92, -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, and its association with overall GCS duration. An increase in tonic/clonic duration ratio, was associated with a decrease in total GCS duration [Est -19.29s, 95% CI (-29.52,-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 semiological severity, such that presence of ictal decerebration, decortication and hemi-decerebration during was associated with the most striking signs of compromise (presence of PGES and larger drops in SpO_2), with 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 post-ictal “brainstem” type posturing is related to a

threefold increased risk for PCCA and to longer hypoxemia duration and SpO_2 recovery periods after GCS seizures. Since PCCA has been observed in SUDEP and near-SUDEP, post-ictal brainstem posturing may suggest a semiological 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 also 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 anatomical 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 non-structural causes of coma.[30, 31] Similar posturing can occur in the post-ictal state. Immediate post-ictal, tonic contractions were described by Gastaut,[32] at times “as intense as that of the tonic phase of the tonic-clonic attack”, with trismus, and limb and back extension, indicating what he 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, the putative pre-Botzinger area, raphe nuclei, solitary tract nucleus, nucleus ambiguus and.[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 SUDEP patients; seizure spread to such brainstem levels, as evidenced by characteristic posturing, may produce post-ictal 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 post-ictal 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 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 (4-AP) induced hippocampal seizures, only those rats receiving high doses of 4-AP with tonic-clonic seizures and longer hippocampal discharges exhibited brainstem discharges. Longer brainstem discharges (>30 s) were associated with a respiratory arrest and accompanying cortical and hippocampal EEG flattening. In this study, spreading depression in the brainstem was not noted prior to respiratory dysfunction.[17] Similarly, in Kv1.1 KO and Scn1a mice, an animal model of SUDEP, post-ictal spreading depolarization in the dorsal medulla following seizures produced cardiorespiratory arrest, preceded by EEG suppression and apnea. [42] Spreading depolarization has also been recently reproduced in a homozygous Cacna1a mouse model, in this case, coincident with apnea.[43] Specific subcortical structures such as superior olivary complex, PAG, pontine and midbrain reticular formation, substantia nigra pars reticularis (SNRr) and amygdala, as well as Kolliker-Fuse, facial nucleus and rostroventrolateral medullar were significantly activated in a magnetic resonance imaging 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 (non-epileptic mice) produced significant intensity-related decreases in inter-breathing interval in both strains.[45] However, the effects were significantly reduced in DBA/1 mice, compared to C57BL/6, 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 neuropathological studies 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 post-ictal 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 tonic phase brainstem posturing to be associated with PGES when 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 deafferentiation, reflected by longer PGES duration. Thus, ictal decerebration may be a potential clinical biomarker of SUDEP.

Our finding of a relationship between post-ictal brainstem posturing and PCCA is novel and intriguing. The former is a known phenomenon[32] further described in 31 GCS in 16 patients, where 48% of seizures had post-ictal 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 only found in a minority of our study seizures (6%). Such post-ictal 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 post-ictal brainstem posturing although it is clear that ictal brainstem posturing is associated with larger changes in SpO_2, and 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 post-ictal brainstem posturing and PCCA in such patients may prove fatal. The threefold elevation in PCCA risk with post-ictal brainstem posturing, and the prolongation in SpO_2 recovery and hypoxemia duration is a striking finding, and encourages scrutiny of the post-ictal video-EEG recording in patients with high-risk SUDEP phenotypes.

Our study is a multicenter, prospectively designed study, with large sample size, and detailed cardio-respiratory 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 values< 0.01 or 0.001), even after adjusting for multiple testing on six primary outcomes, and thus our conclusions remain.** Our definition of apnea differs from previous extended definitions (10 seconds duration) based on sleep studies. Our definition is pragmatic, reflecting stimulation studies for symptomatogenic zones underpinning ICA, which has a consistent minimum duration of five seconds, even with brief two seconds stimulation bursts.[49] Thus our definition is more sensitive to transient disturbances of breathing, but may over-detect 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, SpO_2 recovery decreased with longer GCS duration. However, shorter duration of the GCS was associated with a more prolonged tonic phase when compared to clonic. 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 post-ictal 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 post-ictal brainstem posturing are 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 elucidate the role of peri-ictal semiology and SUDEP risk.

TABLE 1- Demographic and phenotypic variables

	Patients (n= 180)	Seizures (n=295)
Age at study, $\bar{x}$ ± sd (med; R), yo	36.7 ± 13.3 (34; 18-77)	-
Age at epilepsy onset, $\bar{x}$ ± sd (med; R), yo	19.6 ± 15.5 (16; 1-68)	-
Epilepsy duration, $\bar{x}$ ± sd (med; R); 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 comorbidities, n	6 (3.3%)	8 (2.7%)
Unknown	7 (3.4%)	8 (2.7%)
Respiratory comorbidities, 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%)

GCS: generalized convulsive seizure; Med: median; n: number; R: range; sd: standard deviation; $\bar{x}$: mean, y: years; yo: years old

TABLE 2- Univariate analysis for continuous variables with categorical independent variables

	PGES duration, s		Change in SpO2, %		Hypoxemia duration, s	
	$\bar{x}$ ± sd	p value	$\bar{x}$ ± sd	p value	$\bar{x}$ ± sd	p value
Sex		0.377*		0.032*		0.014*
Male	35.1±22.2		31.2±12.7		159.8±70.2	
Female	38.0±20.7		36.8±15.4		129.0±58.5	
State		0.551		0.845		0.072*
Awake	37.5±23.8		34.9±15.2		154.0±69.2	
Asleep	35.7±18.4		34.4±14.2		130.1±60.3	
Epilepsy type		0.359		0.096*		0.818
Focal	35.8±22.5		32.6±13.3		143.3±64.0	
Generalized	39.0±15.6		38.2±16.3		139.4±69.9	
MRI		0.168		0.311		0.405
Negative	38.9±22.4		35.4±14.7		146.7±65.7	
Positive	33.8±22.3		32.4±14.2		134.8±70.0	
Tonic Phase semiology		0.034*		0.024*		0.093*
Decerebrate	40.1±22.7		36.9±14.4		155.4±65.5	
Decorticate	38.9±21.8		37.6±14.8		115.3±47.2	
Hemi-decerebration	31.3±17.5		38.4±13.2		126.0±46.7	
No tonic phase	26.4±15.4		26.2±12.2		144.7±76.2	
Post-ictal posturing		0.261		0.989		0.075*
No	35.8±19.3		34.4±14.8		139.4±65.5	
Yes	46.2±36.7		34.4±9.3		179.3±54.7	
Early O2 administration		0.076*		0.343		0.130
No	40.4±23.7		36.7±14.7		157.3±64.8	
Yes	34.8±20.0		33.6±14.4		136.5±65.1	

ICA		0.091*		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 comorbidities		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 comorbidities				0.024*		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	
GCS frequency the year prior		0.624		0.055*		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	
Chronic 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	

Mean ($\bar{x}$) and standard deviation (sd) are provided with p values obtained from GEE. GCS: generalized convulsive seizure; ICA: ictal central apnea; PCCA: post-convulsive central apnea; PGES: post-ictal generalized EEG suppression; s; seconds; SpO_2: capillary peripheral oxygen saturation; SRI: serotonin or serotonin-noradrenaline reuptake inhibitors *variables introduced in multivariate analysis since $p<0.1$, including age and sex as force-in variables

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, yo	0.440	0.130	0.001*	-0.070	0.087	0.423*	-1.295	0.460	0.005*	-0.026	0.371	0.945
Age at epilepsy onset, yo	0.304	0.131	0.020*	-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*	-0.752	0.221	0.010*

Covariate coefficient estimates, standard error, and corresponding p values from GEE method. Est: beta estimate; GCS: generalized convulsive seizure; s: seconds; SE: standard error; SpO2: capillary peripheral oxygen saturation; yo: years old; *variables introduced in multivariate analysis since $p<0.1$, including age and sex as force-in variables

TABLE 4- Univariate analysis for categorical variables.

	PGES, n			PCCA, n		
	No	**Yes**	**p**	**No**	**Yes**	**p**
Sex, n			*0.188			*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; yo	34.4±13.7	37.2±13.2	*0.229	36.7±13.3	34.4±14.0	*0.397
Age at epilepsy onset, $\bar{x}$ ± sd; yo	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			*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			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%)	
Post-ictal posturing, n			*0.001			*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	*0.010
Early O2 administration, n			*0.091			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			-
No	81 (33.9%)	158 (66.1%)		-	-	

Yes	9 (20.5%)	35 (79.5%)		-	-	
Cardiac comorbidities, 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%)	
Respiratory comorbidities, 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%)	
Chronic SRI treatment			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%)	

Frequency and percentage, mean ($\bar{x}$) and standard deviation (sd) were provided for categorical and continuous variables, respectively, with p values obtained from GEE method. GCS: generalized convulsive seizure; ICA: ictal central apnea; n: number; PCCA: post-convulsive central apnea; PGES: post-ictal generalized EEG suppression; SpO2: capillary peripheral oxygen saturation; ; SRI: serotonin or serotonin-noradrenaline reuptake inhibitors; yo: years old; *variables introduced in the multivariate analysis since $p<0.1$, including age and sex as force-in variables.

TABLE 5- Multivariate analysis for PGES incidence and duration

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

Cardiac comorbidities	-	-	-	-	-	-
Respiratory comorbidities	-	-	-	-	-	-
GCS frequency	-	-	-	-	-	-
1-2						
3-12						
>12						

CI: confidence interval; Est: beta estimate; GCS: generalized convulsive seizure; ICA: ictal central apnea; PCCA: post-convulsive central apnea; PGES: post-ictal generalized EEG suppression; RR: relative risk; SpO_2: capillary peripheral oxygen saturation; *statistically significant, $p<0.05$

TABLE 6- Multivariate analysis for respiratory outcomes

	Presence of PCCA			Change in SpO2 (%)			Hypoxemia duration (s)			SpO_2 recovery (s)		
	OR	**CI 95%**	**P**	**Est**	**CI 95%**	**p**	**Est**	**CI95%**	**p**	**Est**	**CI95%**	**p**
Sex, male	0.26	(0.09,0.73)	0.010*	-3.47	(-8.95, 2.01)	0.214	40.14	(16.61, 63.67)	<0.001*	5.44	(-7.38, 18.26)	0.406
Age at study	0.99	(0.95, 1.03)	0.622	-0.06	(-0.26, 0.31)	0.526	-1.61	(-2.44,-0.78)	<0.001*	-0.06	(-0.62, 0.50)	0.834
Age at epilepsy onset	-	-	-	-	-	-	-	-	-	-	-	-
State, asleep	-	-	-	-	-	-	3.85	(-20.02,27.72)	0.752	-11.00	(-22.01, 0.02)	0.050
Epilepsy type, focal	0.29	(0.11, 0.80)	0.017*	-3.061	(-9.57, 3.45)	0.356	-	-	-	-	-	-
Neuroimaging, positive	-	-	-	-	-	-	-	-	-	-	-	-
Tonic Phase semiology	-	-	-							-	-	-
Decerebration				9.57	(3.83-15.32)	0.001*	14.48	(-12.24,41.20)	0.288			
Decortication				11.37	(4.32, 18.42)	0.002*	-11.86	(-41.45,17.73)	0.432			
Hemi-decerebration				12.52	(4.19, 20.84)	0.003*	-5.40	(-32.45, 21.64)	0.695			
Post-ictal posturing	6.06	(1.76-20.89)	0.004*	-	-	-	47.87	(24.47, 71.27)	<0.001*	27.84	(1.98-53.69)	0.035*

Clinical GCS duration	0.95	(0.91-0.99)	0.017*	-	-	-	0.87	(0.03, 1.70)	0.041*	-0.53	(-0.92, -0.14)	0.009*
Early O_2 administration	-	-	-	-	-	-	-	-	-	-17.69	(-29.56, -5.83)	0.003*
ICA	-	-	-	-	-	-	-	-	-	-	-	-
PCCA	-	-	-	-	-	-	-	-	-	-	-	-
Cardiac comorbidities	-	-	-	-	-	-	-	-	-	-	-	-
Respiratory comorbidities	-	-	-	-9.38	(-15.26, -3.50)	0.002*	-	-	-	-	-	-
GCS frequency	-	-	-				-	-	-	-	-	-
0				2.49	(-4.24,9.22)	0.469						
1-2				-5.43	(-11.67,0.82)	0.089						
2-12				3.67	(-3.11,10.44))	0.289						

CI: confidence interval; Est: beta estimate; GCS: generalized convulsive seizure; ICA: ictal central apnea; PCCA: post-convulsive central apnea; RR: relative risk; SpO_2: capillary peripheral oxygen saturation; *statistically significant, $p<0.05$

APPENDIX 1: Authors

Name	Location	Contribution
Laura Vilella, MD	NINDS Center for SUDEP Research (CSR), McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA Departament de Medicina. Universitat Autonoma de Barcelona, Barcelona, Spain	Major role in the acquisition and analysis of data; design 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, Houston, TX, USA	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, Houston, TX, USA	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, Houston, TX, USA	Analysis of data; statistical analysis; reviewed the manuscript for intellectual content
Shirin Omidi, MD	NINDS Center for SUDEP Research (CSR), McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA Department of Neurology, McGovern Medical School, University of Texas Health Science	Data acquisition

	Center at Houston, Houston, TX, USA	
Manuela Ochoa-Urrea	NINDS Center for SUDEP Research (CSR), McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA	Data acquisition
Shiqiang Tao PhD	NINDS Center for SUDEP Research (CSR), McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA	Analysis of data
Sandhya Rani, PhD	NINDS Center for SUDEP Research (CSR), McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA 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 (CSR), McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA University of Iowa Carver College of Medicine, Iowa City, IA, USA	Data acquisition; interpreted the data
Daniel Friedman, MD	NINDS Center for SUDEP Research (CSR), McGovern Medical School, University of	Revised the manuscript for intellectual content

	Texas Health Science Center at Houston, Houston, TX, USA NYU Langone School of Medicine, New York, NY, USA	
Maromi Nei, MD	NINDS Center for SUDEP Research (CSR), McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, USA	Revised the manuscript for intellectual content
Kingman Strohl, MD	Division of Pulmonary, Critical Care and Sleep Medicine, University Hospitals Medical Center, Cleveland, OH, USA	Interpreted the data;
Catherine Scott	NINDS Center for SUDEP Research (CSR), McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA Institute of Neurology, University College London, London, UK	Data acquisition
Luke Allen	NINDS Center for SUDEP Research (CSR), McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA Institute of Neurology, University College London, London, UK	Data acquisition
Brian K Gehlbach, MD	NINDS Center for SUDEP Research (CSR), McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA University of Iowa Carver College of Medicine, Iowa City, IA, USA	Data acquisition; interpreted the data
Norma J. Hupp, R.EEG.T.CLTm	Department of Neurology, McGovern Medical School, University of Texas Health Science	Data acquisition

	Center at Houston, Houston, TX, USA	
Jaison Hampson, MD	NINDS Center for SUDEP Research (CSR), McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA	Data acquisition
Nassim Shafiabadi, MD	Department of Neurology, Case Western Reserve University, Cleveland, OH, USA	Data acquisition
Xihue Zhao, MD	Epilepsy Center, University Hospitals Cleveland Medical Center, Cleveland, OH, USA	Data acquisition
Victoria Reick-Mitrisin	Epilepsy Center, University Hospitals Cleveland Medical Center, Cleveland, OH, USA	Data acquisition
Stephan Schuele, MD MPH	NINDS Center for SUDEP Research (CSR), McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA Feinberg School of Medicine, Northwestern University, Chicago, IL, USA	Revised the manuscript for intellectual content
Jennifer Ogren, PhD	Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA Department of Neurobiology and the Brain Research Institute, University of California, Los Angeles (UCLA), Los Angeles, CA, USA	Data acquisition
Ronald M. Harper, PhD	Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA	Revised the manuscript for intellectual content

	Department of Neurobiology and the Brain Research Institute, University of California, Los Angeles (UCLA), Los Angeles, CA, USA	
Beate Diehl, MD PhD FRCP	Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA Institute of Neurology, University College London, 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, Houston, TX, USA Department of Neurology, Columbia University, New York, NY, USA	Revised the manuscript for intellectual content
Orrin Devinsky, MD	Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA NYU Langone School of Medicine, New York, NY, USA	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, Houston, TX, USA University of Iowa Carver College of Medicine, Iowa City, IA, USA	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
GQ Zhang, MS PhD	NINDS Center for SUDEP Research (CSR), McGovern Medical School, University of	Analysis of data

	Texas Health Science Center at Houston, Houston, TX, USA Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA	
Samden D. Lhatoo, MD FRCP	NINDS Center for SUDEP Research (CSR), McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA	Designed and conceptualized study; analysis and interpretation of data; revised the manuscript for intellectual content

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