INCIDENCE AND TYPES OF CARDIAC ARRHYTHMIAS IN THE PERI-ICTAL PERIOD IN PATIENTS HAVING A GENERALIZED CONVULSIVE SEIZURE

ABSTRACT

Background and objectives: Generalized convulsive seizures (GCS) are the main risk factor for Sudden Unexpected Death in Epilepsy (SUDEP), likely due to peri-ictal cardiorespiratory dysfunction. The incidence of GCS-induced cardiac arrhythmias, their relationship to seizure severity markers and their role in SUDEP physiopathology are unknown. The aim of this study is to analyze the incidence of seizure-induced cardiac arrhythmias, their association with electroclinical features and seizure severity biomarkers as well as their specific occurrences in SUDEP cases.

Methods: this is a prospective, multicentric study of patients with epilepsy ≥18 years of age with recorded GCS during inpatient video-EEG monitoring. Exclusion criteria were status epilepticus, and obscured video. We analyzed semiological and cardiorespiratory features through video-EEG, EKG, thoraco-abdominal bands and pulsi-oximetry. We investigated the presence of bradycardia, asystole, supraventricular tachyarrhythmias (SVT), premature atrial beats, premature ventricular beats, non-sustained ventricular tachycardia (NSVT), atrial fibrillation (Afib), ventricular fibrillation (VF), atrioventricular block (AVB), exaggerated sinus arrhythmia (ESA) and exaggerated sinus arrhythmia with bradycardia (ESAWB). We classified bradycardia, asystole, SVT, NSVT, Afib, VF, AVB and ESAWB as arrhythmias of interest. The main outcome was the occurrence of seizure-induced arrhythmias of interest.

Results: Complete EKG data was available for 397 seizures (228 patients). ESA was the commonest seizure-induced arrhythmia, with an incidence of 137/382 (35.9%) seizures (106/224 [47.3%] patients). The incidence of arrhythmias of interest was 50/352 (14.2%) in

41/204 (20.1%) patients. ESAWB was the commonest, in 22/394 (5.6%) seizures (18/225 [8%] patients), followed by SVT in 18/397 (4.5%) seizures (17/228 [7.5%] patients). During follow-up (48.36±31.34 months), eight SUDEPs occurred. Seizure-induced bradycardia (3.8% vs 12.5%, z:-16.66, p<0.01) and ESAWB [6.6% vs 25%; z; -3.03, p: < 0.01] were over-represented in patients who later died of SUDEP. There was no association between arrhythmias of interest and seizure severity biomarkers (p >0.05).

Discussion: Markers of seizure severity are not related to seizure-induced arrhythmias of interest. Seizure induced ESAWB and bradycardia were more frequent in SUDEP cases.

INTRODUCTION

Frequent generalized convulsive seizures (GCS) in early onset, longstanding epilepsy is a common phenotype in sudden unexpected death in epilepsy (SUDEP).[1-3] The precise pathomechanisms of SUDEP are unknown, but monitored evidence suggests a combination of cardiac rhythm and breathing dysfunction.[4,5] The role of cardiac arrhythmias in near SUDEP and SUDEP, and their relationship to GCS severity (duration and degree of oxygen desaturation, prolonged ictal central apnea [ICA], post-convulsive central apnea [PCCA], and prolonged post-ictal generalized EEG suppression [PGES] duration), are unknown. [6-9] We lack systematic prospective incidence data on benign and malignant cardiac arrhythmias in SUDEP. Sinus tachycardia, the most common peri-ictal arrhythmia (80% of GCS and non-GCS), is likely benign[10] whereas peri-ictal bradycardia and asystole are rare (< 1% of epileptic seizures), and may not be benign.[10,11] Postictal bradycardia is commonly observed in monitored near SUDEP and SUDEP cases.[10] Rarely, dangerous arrhythmias, including atrio-ventricular conduction block, atrial flutter/fibrillation and ventricular fibrillation/tachycardia,[10] can occur during or after seizures and result in falls, injuries, and potential deaths. Since GCS represent the strongest SUDEP risk factor,[1,3] and almost all monitored deaths occurred after GCS,[4,12] we prospectively assessed the incidence of GCS-related cardiac arrhythmias. We also investigated the potential relationship between seizure-induced arrhythmias of interest and electroclinical GCS characteristics, including seizure severity markers.[13]

MATERIALS AND METHODS

Patient selection

All patients were prospectively consented participants in the NINDS Center for SUDEP Research's Autonomic and Imaging Biomarkers of SUDEP multi-center project (U01-NS090407), and the Prevention and Risk Identification of SUDEP Mortality Project

(P20NS076965). This study was approved by the Institutional Review Boards of all participating centers. Patients with epilepsy ≥18 years of age undergoing video-electroencephalography (VEEG) evaluation in epilepsy monitoring units (EMU) from April 2010 until October 2019 were enrolled. Inclusion criteria were patients with recorded GCS (generalized tonic-clonic seizures, focal to bilateral tonic-clonic seizures and focal onset motor bilateral clonic seizures).[14] Exclusion criteria were status epilepticus, and obscured video. Demographic and clinical data collected included gender, age, age at epilepsy onset and epilepsy duration, epilepsy type,[15] GCS frequency in the year prior to admission, VNS therapy, peri-ictal semiological features,[16] state at seizure onset, presence of major cardiac (coronary artery disease, arrhythmia, valvulopathy) or respiratory [obstructive sleep apnea (OSA), asthma, chronic obstructive pulmonary disease (COPD)] comorbidities and Body Mass Index. Chronic antiseizure medication (ASM) use was classified as no therapy, monotherapy and polytherapy. Information regarding treatment with sodium channel blockers (phenytoin, carbamazepine, oxcarbazepine, eslicarbazepine, lamotrigine, lacosamide and rufinamide) was also collected.[17-20]

Cardiorespiratory and VEEG monitoring

Prolonged VEEG monitoring followed the 10-20 International Electrode System. Electrocardiogram (EKG), pulsi-oximetry and inductance plethysmography acquisition were carried out using previously described methodology.[6,7,16,21-23]

We analyzed a two-minute period before clinical or electrographic seizure onset (pre-ictal period), the ictal period (limited to the available technically satisfactory portions of the recording) and three minutes after clinical seizure end (post-convulsive period). For the pre-ictal and post-convulsive period, if EKG data was lost or had an artifact for > 6 consecutive seconds, the full period was disregarded. For the ictal period, this applied only to the non-convulsive phase of the seizure, since all of them had an unavoidable artifact during the tonic-clonic movements.

Maximal HR, and lowest HR in case of bradycardia, were determined by measurement of shortest and longest RR intervals, respectively, through visual beat to beat analysis.

In all three periods, cardiac rhythm abnormalities were reviewed by a board-certified cardiac electrophysiologist (CYM). These included sinus tachycardia (>100 beats per minute [bpm]), bradycardia (<60 bpm), asystole (R-R interval ≥ 3s), supraventricular tachyarrhythmias (atrial or junctional tachycardia [SVTs]), atrial fibrillation (Afib), premature atrial complexes (PACs), premature ventricular complexes (PVCs), non-sustained ventricular tachycardia (three or more consecutive ventricular beats at least 20% higher than baseline sinus rhythm [NSVT]), ventricular fibrillation (VF) and atrioventricular block (first, second or third degree [AVB]). We also noted the presence of "exaggerated sinus arrhythmia" (ESA) when variations in sinus rhythm were found without apparent correlation to breathing pattern, and the presence of "exaggerated sinus arrhythmia with bradycardia" (ESAWB) defined by the presence of ESA with at least one R-R interval >1s and < 3s. If RR interval was >1s in more than three consecutive beats, this was labelled as bradycardia. If multiple arrhythmia types were recorded in the same period, all were considered in the analysis. For the purposes of this study, bradycardia, asystole, SVT, NSVT, Afib, VF, AVB and ESAWB were classified as "arrhythmias of interest". Arrhythmias occurring during the ictal or post-convulsive period (but not present in the pre-ictal period) were considered seizure-induced.

Breathing analysis used composite analysis of inductance plethysmography, EEG breathing artifact and visually inspected thoraco-abdominal excursions, following published methods.[7,16]. 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).[24] ICA referred to central apnea occurring in the pre-convulsive phase of GCS and it could only be determined if thoracoabdominal belts were available.[6] PCCA referred to central apnea after GCS and was determined either using thoracoabdominal belts or through

visual inspection, given that breathing is usually stertorous and deep after GCS, while the patient is immobile.[7] Incidences and durations of ICA and PCCA were determined.

SpO_2 was assessed using validated methods.[7,16] 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 the difference between baseline and lowest SpO_2 value (nadir SpO_2) recorded up to 3 minutes after clinical seizure end. Hypoxemia was defined as SpO_2<90%. When baseline SpO_2 was already <90%, a >1% drop was considered significant. If a transient loss of SpO_2 signal occurred during monitoring, SpO_2 nadir (and thus change in SpO_2) were not determined. Hypoxemia duration prior to the convulsive phase of the seizure (hypoxemia pre-GCS duration) and SpO_2 value at GCS onset (SpO_2 at GCS onset) was collected. To avoid the effect of seizure duration, following previous studies, we determined the time to hypoxemia recovery after clinical seizure end, which we termed "SpO_2 recovery".[16,25] We considered early oxygen administration and early suction when these were applied during the seizure, or within 5 s of seizure termination.[25,26]

Presence and duration of PGES [8] were determined by a validated automated EEG suppression detection tool,[27] and supplemented with visual analysis by two epilepsy neurophysiologists (SDL and LV) when the tool results were indeterminant.

Yearly follow up was conducted through a combination of clinic visits, chart review and telephone interviews. Three researchers (SDL, MOU and SR) reviewed autopsy reports (when available), circumstances of death reported in death certificates, chart reviews and telephone interviews with next of kin.[28]

Statistical analysis

Descriptive statistics for continuous variables were reported as mean ± standard deviation and median (first quartile, third quartile). For categorical variables number and percentage were provided.

Binary Logistic Generalized estimating equations (BL-GEEs), were used to determine clinical-demographic and peri-ictal variables that were predictive of the presence of seizure-induced arrhythmias of interest in those seizures that did not have arrhythmias of interest in the pre-ictal period. The BL-GEE model was corrected for within-participant effects. A value of $P < 0.05$ was considered significant. Asymmetric distribution of predictive variables between the binary categories of the response variable and/or a collinearity among the predictor variables are likely to cause errors in the GEE model. Under such circumstances we eliminated the collinear variables which possessed the greater amount of missing data instead of merging the variables (a common practice to avoid Hessian singularity error). Hence, two-staged BL-GEEs were constructed to determine seizure-induced arrhythmias of interest. The first BL-GEE would help determine the significant clinical-demographic and peri-ictal seizure characteristics that were predictive of seizure-induced arrhythmias of interest. In the second stage BL-GEE, we included these significant predictors along with peri-ictal respiratory variables, to determine the final set of predictors of seizure-induced arrhythmias of interest. This helped negate the Hessian singularity error without compromising the outcome prediction.

The z-score test for two population proportions was used to test if the proportion of seizures and patients with post-convulsive ESAWB or bradycardia differed between SUDEP and survivors.

Data availability

Data is available from the corresponding author, upon reasonable request.

RESULTS

A total of 492 GCS were reviewed in 270 patients. 455 GCS in 249 patients [137 female (55%) with 214 (53%) seizures] met inclusion criteria and had no exclusion criteria, with a mean of 1.8 seizures per patient (minimum 1, maximum 12). Demographic and seizure characteristics are shown in **table 1** and **e-table 1 in supplement**.

Frequency and incidence of cardiac arrhythmias and tachycardia

Complete pre-ictal, ictal and post-convulsive period EKG data was available for 397 seizures in 228 patients. Exaggerated sinus arrhythmia was the most common seizure-induced arrhythmia, with an incidence of 137/382 (35.9%) seizures (106/224 [47.3%] patients).

The incidence of arrhythmias of interest was 50/352 (14.2%) seizures in 41/204 (20.1%) patients. Although rare, the most common seizure-induced arrhythmia of interest was ESAWB in 22/394 (5.6%) seizures (18/225 [8%] patients), followed by SVT in 18/397 (4.5%) seizures (17/228 [7.5%] patients). Further details are described below, and in **table 2, e-table 2 and e-table 3 in supplement.**

Ictal arrhythmia occurred in 48/424 (11.3%) seizures (44/237 [18.6%] patients). In 4/424 (0.9%) seizures (4/237 [1.7%] patients) two ictal arrhythmia types were seen.

Post-convulsive arrhythmia was observed in 254/400 (63.5%) seizures (164/229 [71.6%] patients). Two to four different arrhythmias occurred in 54/400 (21.6%) seizures in 50/229 (21.8%) patients. The most common combination was ESA with PVCs.

Ictal sinus tachycardia occurred in 352/431 (81.7%) seizures (204/262 [77.9%] patients), and post-convulsive sinus tachycardia in 422/428 (98.6%) seizures (238/244 [97.5%] patients).

Asystole. Post-convulsive asystole was seen in 2/400 (0.5%) seizures in 2/229 (0.9%) patients. Both were monitored near-SUDEP cases, reported in a prior study.[7] In both cases, asystole was followed by SVT. In one case, there was pre-ictal bradycardia (that briefly persisted after EEG onset and was replaced by tachycardia). Asystole had a duration of 18 s and 59s respectively.

Atrioventricular block (AVB). Post-convulsive (Mobitz type I) AVB arose *de novo* in 1/400 (0.3%) seizure in 1/229 (0.4%) patient.

Bradycardia. Ictal bradycardia occured in 6/424 (1.4%) seizures in 6/237 (2.5%) patients. Heart rate change was -40±19.6 (-32 (-61,-24) bpm. Two patients had multiple seizures included in the study; bradycardia was recurrent in one patient.

Post-convulsive bradycardia occurred *de novo* in 7/400 (1.8%) seizures in 4/229 (1.7%) patients. Change in HR from pre-ictal to lowest HR was -23.4±11 [-26 (-32,-12)] bpm. In two of three patients with multiple seizures, post-convulsive bradycardia recurred in two. In the other, EKG signal was lost.

Exaggerated sinus arrhythmia with bradycardia (ESAWB). Ictal ESAWB was seen in 6/424 (1.4%) seizures in 5/237 (2.1%) patients. None of the patients had pre-ictal arrhythmias of interest, except for one, who had pre-ictal bradycardia. All except one, had multiple seizures and ictal ESAWB recurred in 1/4 (25%) patient.

De novo post-convulsive ESAWB occurred in 16/400 (4%) seizures in 13/229 (5.9%) patients. In 2 of these seizures (2 patients), pre-ictal bradycadia was seen, and one also had post-convulsive bradycardia. Nine patients with *de novo* post-convulsive ESAWB had multiple seizures, and recurrences occurred in 2/9 (22.2%) patients.

Supraventricular tachycardia (SVT). Ictal SVT was seen in 2/424 (0.5%) seizures in 2/237 (0.8%) patients. These patients had only one seizure each.

De novo post-convulsive SVT occurred in 16/400 (4%) seizures in 15/229 (6.5%) patients. Two were near-SUDEP patients in whom post-convulsive asystole was also seen, as described earlier in this manuscript. Seven out of the 15 patients had more than one seizure included in the study and SVT recurred in one patient(14.3%).

Atrial fibrillation (Afib). Non-sustained post-convulsive Afib was seen in 1/400 (0.3%) seizure in 1/229 (0.4%) patient, who had only one seizure.

Non-sustained ventricular tachycardia (NSVT). Post-convulsive NSVT was seen in 3/400 (0.8%) seizures in 3/229 (1.3%) patients. Only one patient had multiple seizures and NSVT did not occur again.

Arrhythmias of interest and their relationship with electroclinical variables

386 seizures without arrhythmias of interest in the pre-ictal period were considered for analysis. Of these, 198 seizures (115 patients) had complete data. None of variables was associated with occurrence of seizure-induced arrhythmias of interest. **Table 3.**

When considering only those seizures in which complete respiratory data (both pulsi-oximetry and thoraco-abdominal belts) was available, a total of 111 seizures (73 patients) were analyzed. None of the respiratory variables were associated with the presence of seizure-induced arrhythmias of interest. **Table 4.**

Arrhythmias of interest and SUDEP

Eleven patients (accounting for 18 seizures) were lost for follow up and their vital status could not be ascertained. Five patients died of non-SUDEP related etiologies. In a follow-up period of 48.36±31.34 (43.97 [23.7, 69.23]) months, there were eight SUDEPs (two female [two definite, five probable, one possible]), with 18 seizures. Two had idiopathic generalized epilepsy, and the remaining had focal epilepsy. One patient with one seizure already had an arrhythmia of interest in the pre-ictal period (bradycardia). Three out of the remaining seven patients (42%) had at least one seizure with seizure-induced arrhyrhmias of interest. One patient had post-convulsive SVT, one patient had ictal and postconvulsive bradycardia in one seizure and post-convulsive ESAWB in another seizure, and one patient had post-convulsive ESAWB. The proportion of seizures with postconvulsive-ESAWB was higher in SUDEP [11%] compared to

non-SUDEP cases [4.6%][z: -12.39, p: < 0.01]. Accordingly, the proportion of patients with postconvulsive-ESAWB was also higher in SUDEP [25%] compared to non-SUDEP cases [6.6%][z: -3.03, p: < 0.01]. The proportion of non-SUDEP patients with post-convulsive bradycardia was 3.8% (3% of seizures) and that of SUDEP patients was 12.5% (5.5% of seizures) [z:-16.66, p<0.01].

DISCUSSION

In this large, prospective multicenter study of cardiac arrhythmia incidence in GCS and SUDEP, we found that potentially fatal arrhythmias are rare, occurring in fewer than 1% of patients, and none are associated with electroclinical markers of GCS severity. Only three patients (1.3%) had NSVT, none of whom went on to die of SUDEP. On the other hand, two out of eight SUDEP patients had transient post-convulsive bradycardia (sinus bradycardia and/or ESAWB), which deserves further investigation as a cardiac biomarker of SUDEP risk. This is in line with monitored deaths in the MORTEMUS study, where bradycardic/asystolic arrest was preceded by terminal apnea in all SUDEP, and some cases had transient post-ictal bradycardia/asystole prior to, or simultaneous with onset of breathing dysfunction.[4] Thus, the role of bradycardia and ESAWB in abnormal post-seizure homeostasis and SUDEP pathophysiology is of interest. Neither is likely to be the primary mechanism of death, but together with breathing dysfunction, may produce fatal scenarios. SUDEP has been averted in animal models with strategies that restore breathing after seizures.[29-31] Given that patients have succumbed to probable SUDEP despite well-functioning pacemakers at the time of death, the benefit of cardiac pacemakers remains unproven. Additional strategies that target breathing dysfunction may be needed to prevent death.[32,33]

The fact that electroclinical seizure severity markers of PGES, hypoxemia, peri-ictal central apnea, and brainstem posturing in seizures had no consistent association with any ictal or post-convulsive seizure-induced arrhythmia of interest is interesting. This, coupled with the fact that in patents with multiple seizures, peri-ictal arrhythmias were not consistently seen in all of them, suggest that these arrhythmias are not induced by hypoxia or seizure features, and may not be part of the patient's habitual seizure semiology. However, only 17% of the patients with seizure-induced arrhythmias of interest had ≥3 seizures, and hence conclusions on semiological consistency versus stochastic phenomena cannot be conclusively inferred from the present study. The thesis that hypoxemia duration during GCS[9,34,35] is arrhythmogenic is somewhat refuted by our findings, as is the theory that ictal involvement of central autonomic structures[36-39] is responsible, given the poor reproducibility of arrhythmia features in consecutive seizures. An exception to arrhythmias as a seizure phenomenon may be ictal asystole,[40] which did not occur in any of our patients. Other potential explanations include catecholamine surges, which may vary in extent between seizures and possibly cause myocardial damage. Myocardial damage is also hypothesized to occur from repeated seizure induced ischemia; myocardial fibrosis is seen in SUDEP hearts[41,42] and regardless of the mechanism of causation, may predispose to arrhythmias and an "epileptic heart".[43] It is unlikely that ASMs played any role in generating arrhythmias given that we did not find an association between chronic treatment with sodium channel blockers and seizure-induced arrhythmias of interest. Indeed, no individual ASM has been consistently associated with an increased SUDEP risk.[18,44]

82.6% of seizures had no pre-ictal period arrhythmias in our study. Two thirds developed ictal and post-convulsive period arrhythmias, in line with prior observations that seizures induce cardiac arrhythmias.[13,35,45,46] Seizure-induced ESA, initially described in temporal lobe seizure patients,[47] was the most frequent arrhythmia, occurring in more than one third of seizures. In a previous study, ESA was the second most common cardiac arrhythmia in GCS (18.8%, second

only to PAC)[46] and the most common (42%) in another study of GCS and non-GCS.[13] Sinus arrhythmia may be a surrogate of vagal tone, highly modulated by breathing changes, showing an inverse correlation with breathing rate and a direct correlation with tidal volume.[48] In a minority of seizures, ESA was associated with bradycardic beats (ESAWB). Its genesis is uncertain and may represent post-seizure parasympathetic overdrive. It was over-represented in the SUDEP group as compared to non-SUDEP cases and is worthy of further study, although given the small number of SUDEP cases, this requires cautious interpretation.

The incidence of arrhythmias of interest in our prospective study largely confirmed some findings and others differed from smaller retrospective studies. The incidence of ictal/post-convulsive bradycardia was 3.6%, comparable to the 2.7% described in another study.[35] SVT incidence was 4.5%, similar to the 0.5-6.3% reported previously.[35,46] Incidence of NSVT was 0.8%, ranging similarly from 0-2.7% in previous literature.[35,46] In accordance with prior studies, we did not see any cases of VF.[35,46] However, only one seizure (0.25%) in our study induced Afib, whereas other series have reported an incidence of 0-6.3%.[35,46] Notably, ictal asystole was not observed, otherwise reported in 2.2%-6.3% of GCS series.[35,46] Our data, is also comparable to a recent long-term monitoring study with implantable loop-recorders that used similar criteria for defining clinically significant arrhythmias, and jointly reported GCS and non-GCS.[13] In contrast, one smaller long-term monitoring study that used stricter arrhythmia definitions (and excluded ictal asystole) did not detect any clinically significant arrhythmias.[49]

This study has several limitations. Arrhythmia evaluation during the ictal phase could only be made during segments with readable data due to inevitable artifact on EKG channels. Thus, the presence of transient ictal arrhythmias is likely underestimated. Our definition of arrhythmias of interest was deliberately less stringent than definitions used in other studies, in order to capture phenomena such as ESAWB, in case these are of biomarker value in SUDEP assessments. We chose this approach because tachycardia is the norm during and after GCS whereas postictal

bradycardia has been mainly observed in (near) SUDEP cases.[10,35] Given the rarity of SUDEP, research is focused on understanding the most common responses (likely physiological) and flagging those that are rare. We did not analyze outside the pre-ictal, ictal and post-convulsive periods; therefore, it is possible that some of the arrhythmias (i.e bradycardia) were present intermittently at baseline, and were not truly seizure-induced. Seizure-induced cardiac arrhythmias were analyzed as a group due to the rarity of certain arrhythmia types. Even larger prospective studies designed to assess the association of seizure severity biomarkers with individual arrhythmia types and SUDEP risk may yield additional information, although we found no correlation. Another limitation is that associations between VNS treatment, cardiac comorbidities and seizure-induced cardiac arrhythmias could not be analyzed due to insufficient number of patients in each of the groups. Lastly, information about other medications potentially affecting cardiac rhythms (i.e. beta-blockers) was not available.

In conclusion, serious, potentially fatal GCS induced cardiac arrhythmias are rare. When they occur, markers of seizure severity appear unrelated, suggesting that other factors, such as occult cardiac abnormalities may be relevant. Less than seven percent of patients had either exclusive post-convulsive ESAWB or bradycardia, compared to two out of eight SUDEP patients. Our observations are based on a very limited number of SUDEP patients and further case control-studies are needed to evaluate the yield of arrhythmias of interest along with respiratory changes as potential SUDEP biomarkers.

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VARIABLES	Patients (n=249)	Seizures (n=455)
Age at study, $\bar{x}$ sd, y.o (median [IQR])	37.1 ± 13.5 (34 [26-47])	-
Age at epilepsy onset, $\bar{x}$ ± sd, y.o. (median [IQR])	21.6 ± 15.4 (19 [10-31])	-
Epilepsy duration, $\bar{x}$ ± sd, y.o. (median [IQR])	15.4 ± 12.1 (13.8 [5-23])	-
BMI, $\bar{x}$ ± sd kg/m^2 (median [IQR])	28.5±6.9 (26.9 [16.4-46.9])	-
GCS frequency in the year prior to admission, n		
0	35 (16.4%)	59 (14.8%)
1-2	54 (25.4%)	78 (19.5%)
3-12	66 (31%)	127 (31.8%)
>12	69 (32.4%)	135 (33.8%)
Unknown	36	56
Cardiac comorbidities, n	7 (2.9%)	9 (2%)
Unknown	6	6
Respiratory comorbidities, n	25 (10.3%)	56 (12.5%)
Unknown	6	6
Epileptogenic zone, n		
Temporal	124 (51%)	216 (48.3%)
Frontal	31 (12.8%)	72 (16.1%)
Parietal	2 (0.8%)	2 (0.4%)
Occipital	1 (0.4%)	1 (0.2%)
Multifocal	21 (8.6%)	44 (9.8%)
Generalized	37 (15.2%)	52 (11.6%)
Lateralized	25 (10.3%)	56 (12.5%)
Insula	1 (0.4%)	2 (0.4%)
Both focal and generalized	1 (0.4%)	2 (0.4%)
Unknown	6	8
Neuroimaging, n		
Negative	112 (50.2%)	211 (51.1%)
Positive	111 (49.8%)	202 (48.9%)
Unavailable	26	42
VNS, n	4 (1.6%)	10 (2.3%)
Unknown	6	11
ASM		
None	5 (2%)	6 (1.4%)
Monotherapy	79 (32.4%)	120 (27%)
Polytherapy	160 (65.6%)	318 (71.6%)
Unknown	6	11
Na channel blockers, n	175 (72%)	340 (76.6%)
Unknown	6	11

473 **Table 1. Demographic characteristics per patient and per seizure.** ASM: antiseizure medications; BMI:
474 body mass index; GCS: generalized convulsive seizure; IQR: interquartile range; n: number; Na: sodium
475 sd: standard deviation ; VNS: vagus nerve stimulator; $\bar{x}$: mean; y.o: years old. Of note, for GCS
476 frequency and ASM variables, the total percentage of patients adds up above 100%, since some patients
477 with more than one admission have had different GCS frequency and therapeutic regimens among
478 admissions.

	Pre-ictal Arr (szs) n= 436	**Pre-ictal 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**	**Post-convulsive Arr (szs) n= 400**	**Post-convulsive Arr (pts) n= 229**	**Post-convulsive *de novo* Arr (szs) n= 400**	**Post-convulsive *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%)

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Table 2. Frequency of different cardiac arrhythmia (Arr) types for the different periods and incidence. In bold, the most frequent Arr of interest occurring during the pre-ictal, ictal and post-convulsive periods respectively, as well as the most incident Arr of interest. In italics, the most frequent Arr type occurring during pre-ictal, ictal and post-convulsive 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%.

Variable	OR	95% CI	p-value
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
Post-ictal 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 3. Electroclinical variables associated with presence of seizure induced arrhythmias of interest. ASM: antiseizure medications; BMI: body mass index; GCS: generalized convulsive seizure; CI: confidence interval; IQR: interquartile range; n: number; Na: sodium; OR: odds ratio; O_2: oxygen; PGES: Post-ictal Generalized Electroencephalographic Suppression;

Variable	OR	95% CI	p-value
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

493 **Table 4. Respiratory variables associated with presence of seizure induced arrythmias of interest.** GCS:
494 generalized convulsive seizure; ICA: ictal central apnea; n: number; PCCA: post-convulsive central apnea;
495 SpO_2: oxygen saturation;

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