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The incidence and significance of peri-ictal apnea in epileptic seizures

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SUMMARY

Objective

The aim of this study was to investigate peri-ictal central apnea as a seizure semiological feature, its localizing value, and possible relationship with sudden unexpected death in epilepsy (SUDEP) pathomechanisms.

Methods

We prospectively studied polygraphic physiological responses, including inductance plethysmography, peripheral capillary oxygen saturation (SpO_2), electrocardiogram (EKG), and video electroencephalogram (VEEG) in 473 patients in a multicenter study of SUDEP. Seizures were classified according to a semiological seizure classification based on the most prominent clinical signs during VEEG. The putative epileptogenic zone was defined based on clinical history, seizure semiology, neuroimaging and scalp electroencephalography (EEG).

Results

Complete datasets were available in 126 patients in 312 seizures. Ictal central apnea (ICA) occurred exclusively in focal epilepsy (51/109 patients [47%] and 103/312 seizures [36.5%]) ($p<0.001$). ICA was the only clinical manifestation in 14/103 (14%) seizures, and preceded EEG seizure onset by 8 ± 4.9 seconds, in 56/103 [54.3%] seizures). ICA $\geq$ 60 seconds was associated with severe hypoxemia (SpO_2 <75%). Automotor and dialeptic semiologies were associated with ICA presence ($p<0.001$), ICA duration ($p=0.002$) and moderate/severe hypoxemia ($p=0.04$). Temporal lobe epilepsy was highly associated with ICA in comparison to extratemporal epilepsy ($p=0.001$) and frontal lobe epilepsy ($p=0.001$). Isolated post-ictal central apnea was not seen; in 3/103 seizures (3%), ICA persisted into the post-ictal period.

Significance

ICA is a frequent, self-limiting semiological feature of focal epilepsy, often starting before surface EEG onset, and may be the only clinical manifestation of focal seizures. However, prolonged ICA ($\geq$60 seconds) is associated with severe hypoxemia and may be a potential SUDEP biomarker. ICA is more frequently seen in temporal than extratemporal seizures, and in typical temporal seizure semiologies, such as dialeptic and automotor seizure types. ICA rarely persists after seizure end. ICA agnosia is typical, and thus may remain unrecognized without polygraphic measurements that include breathing parameters.

INTRODUCTION

Hypoventilation and hypoxemia are typically seen in generalized tonic clonic seizures (GTCS), [1, 2 3] and severe alteration of breathing after GTCS has been suggested as a possible mechanism of Sudden Unexpected Death in Epilepsy (SUDEP) [1]. However, oxygen desaturations are also found in 30-60% of focal seizures without generalized convulsions [2]. Desaturations are more commonly seen with temporal lobe than extratemporal seizures [2, 4]. Electrical stimulation of mesial temporal structures, consistently elicits central apnea, potentially explaining this observation [5]. Ictal apnea has also been noted in 44-48 % of non-generalizing focal seizures, [2, 4, 6, 7] and has been reported as the main manifestation of focal seizures in a few case reports[8, 9]. Ictal and post-ictal central apnea has been suggested as a potential mechanism in some SUDEP[10] and near-SUDEP[11] cases. However, the role of ictal and post-ictal central apnea in SUDEP remains to be definitively demonstrated. We set out to examine the phenomenology, localizing value, and impact of ictal and post-ictal central apnea in patients with intractable epilepsy, in the epilepsy monitoring unit setting.

METHODS

Patients and clinical settings. All patients were prospectively consented and recruited participants in the NINDS Center for SUDEP Research's Autonomic and Imaging Biomarkers of SUDEP project (U01-NS090407). Patients with epilepsy aged ≥16 years undergoing video electroencephalogram (EEG) evaluation were studied in the epilepsy monitoring units of University Hospitals Cleveland Medical Center, University of Iowa, Northwestern University, New York University, Thomas Jefferson University, University of California at Los Angeles, University College London, and Columbia University. Inclusion criteria were patients in whom inductance plethysmography (abdominal and/or thoracic belts) and video EEG recording were carried out during the evaluation in the epilepsy unit. Exclusion criteria were movement or electrical artifacts obscuring plethysmographic signal, or obstructed or unavailable video.

Cardiorespiratory monitoring and VEEG monitoring. All patients had prolonged surface video EEG monitoring using the 10-20 International Electrode System. EEG and electrocardiogram (EKG) were acquired using the Nihon Kohden (Tokyo, Japan), Micromed (Modigliani Veneto, Italy) and Xltek (Natus) acquisition platforms. Peripheral capillary oxygen saturation (SpO_2) and heart rate were monitored using pulse oximetry (Nellcor OxiMax N-600x [Convidien], Masimo Radical-7 [Irvine] and SenTec Digital Monitoring System [Therwil BL]). Chest and abdominal excursions were recorded using inductance plethysmography (Ambu [Ballerup, Denmark] Sleepmate and Perfect Fit 2 [Dymedix]). Oxygen desaturations were classified as mild (SpO_2 of 90-94%), moderate (75-89%) and severe (< 75%). We defined central apnea as cessation of breathing movements lasting for ≥ 10 seconds in the absence of generalized tonic or clonic movements, since such movements invariably produced movement artifact in breathing channels. Tachycardia and bradycardia were defined as heart rate >100 beats per minute and <60 beats per minute respectively, or a >20% deviation from baseline. Seizures were classified according to a semiological seizure classification[12] based on the most prominent clinical signs: aura (subjective feeling, usually at the beginning of the seizure); complex motor seizure (motor seizures in which the movements simulate natural, but inappropriate movements); automotor (complex motor seizure with prominent automatisms of distal limb segments or mouth and tongue, and usually with dyscognitive features), dialeptic (alteration of consciousness without motor disturbance), aphasic (patient cannot speak and often cannot understand spoken language), hypermotor (high amplitude movements involving

proximal limb segments and trunk), focal motor (simple motor seizures), SGTCS= secondary generalized tonic-clonic seizures (tonic posturing of all limbs followed by a clonic phase, in focal epilepsy); no clinical signs (electrographic seizures with no clinical signs other than central apnea). In order to distinguish focal from primary generalized epilepsy, the dialeptic seizures of the latter were classified as absence seizures, and generalized tonic-clonic seizures were classified as PGTCS= primary generalized tonic-clonic seizures. The putative epileptogenic zone was defined based on clinical history, seizure semiology, neuroimaging and scalp EEG.

Statistical analysis. Statistical analysis was performed using Statistical Package for Social Science (SPSS - IBM, corp. version 24). Summary statistics were reported as mean±SD (median, range). Chi-square test and binary logistic regressions were used to assess the association between dichotomous variable apnea (yes/no), with other variables and combinations. Since the 103 apneic seizures were not normally distributed, non-parametric testing (Kurskal-Wallis test) was used to assess apnea duration with other variables.

RESULTS

473 patients underwent polygraphic study of seizures. Reliable inductance plethysmography recordings and unobstructed seizure videos for the assessment of breathing responses were available in 312 seizures in 126 patients (77 female). Mean age was 40.09±14.71 years (median 38.5; 16-77). 109 patients had focal epilepsy and 17 patients had primary generalized epilepsy. Mean epilepsy duration was 17.8±13.5 years (17; 0-52).

A) Ictal central apnea (ICA) incidence and duration. ICA was found in 103/312 (36.5%) seizures in 51/126 (40.5%) patients (29 female). Mean ICA duration was 28±18.8 (22; 10-97) seconds (s). Oxygen saturation data was available in 227/312 seizures overall, and in 79/103 seizures with ICA. In the remaining seizures, data was rendered unreliable because of dislodged sensors and movement. Prolonged ICA (≥ 60 seconds) occurred in eight patients and was associated with severe hypoxemia (SpO_2 <75%) in six. Seizure and epilepsy details of patients with and without ICA are shown in table 1.

Influence of type and duration of epilepsy, age and gender on apnea. ICA was seen exclusively in focal epilepsy (36.5% of all partial seizures; p<0.001); none of the 17 primary generalized epilepsy patients (15 primary generalized tonic-clonic seizures [PGTCS] and 7 absence seizures), had ICA. None of the 15 PGTCS were preceded by central apnea. In the focal epilepsy group, 10/22 secondary generalized tonic-clonic seizures (SGTCS) had preceding ICA; ICA was the sole clinical manifestation in all ten. We found that older age was significantly associated with ICA presence (p<0.001), but not with ICA duration or hypoxemia severity (p=0.6). There were no gender differences in ICA incidence (p=0.2). Although longer duration of epilepsy was not significantly associated with the presence of ICA (p=0.3), it was associated with longer ICA duration (p<0.001). Examples of presence or absence of ICA are shown in figures 1 and 2.

Epileptogenic and ictal onset zones and seizure semiology. Temporal lobe epilepsy was highly associated with ICA presence in comparison to extratemporal epilepsy (odds ratio (OR) 10.1; 95% CI (5.5-18.5); P=0.001) and to frontal lobe epilepsy (OR 8.3; 95% (4-17.3); P=0.001) (Figure 3). Temporal lobe ictal onset zone was accordingly significantly associated with ICA (p<0.001). We then assessed whether ictal discharge at ICA onset involved one or both

hemispheres. The ictal discharge was unilateral in 75/103 apneic seizures (72.8%), bilateral in 21/193 (20.4%) and obscured by artifact at ICA onset in 7/103 (6.8%). ICA was significantly more likely to be associated with unilateral (left or right) ictal discharge at apnea onset compared to bilateral or non-lateralizable discharges ($p<0.001$). Temporal lobe epilepsy ($p<0.001$) and unilateral temporal lobe EEG ictal onset ($p=0.001$) were both significantly associated with longer ICA duration. There was a higher incidence of ICA in automotor (71.4%) and dialeptic seizures (55.9%) compared to other seizure types (figure 3). Both were highly associated with ICA presence ($p<0.001$), as well as ICA duration ($p=0.002$) and severe hypoxemia ($p=0.04$).

Awake and sleep states. Mean duration of ICA in seizures during the awake state was 27.87±19.38 seconds and 28.13±18.43 seconds during the non-REM (rapid-eye movement) sleep state; the awake/sleep states at seizure onset did not significantly impact either ICA presence or ICA duration ($p=0.6$). No seizures arose during REM sleep.

Apnea-induced oxygen desaturation of hemoglobin (SpO_2). Ictal hypoxemia was present in 56/79 (70.8%); desaturation was mild in 26/56 (46%) seizures (mean 92.5±1.2 [93; 90-94]), moderate in 22/56 (39%) (mean 81.5±4.0 [82.5; 75-89]) and severe in 8/56 (14%) (mean 64.7±9.3 [69.5; 46-72]). Mean oxygen desaturation nadir was 87.7±10.3 (92; 46-98). Duration of ICA was significantly negatively correlated with SpO_2 nadir ($r=-0.89$; $p<0.001$) (Figure 4). 53% of automotor seizures had moderate or severe hypoxemia compared to all other semiologies combined ($p=0.04$). Temporal lobe seizures were more likely to have moderate or severe ictal hypoxemia compared to other epileptogenic zones ($p=0.03$).

Ictal apnea characteristics and relationship with EEG onset/clinical onset. In 14/103 (14%) of seizures, ICA was the only clinical manifestation during the entirety of the seizure. In 56/103 (54.3%) of seizures, ICA onset occurred before EEG seizure onset (mean 8±4.9 [7.7; 1-29] seconds). In 15/103 (14.5%), EEG onset and ICA onset were simultaneous, and in 32/103 (31%) EEG seizure onset preceded ICA (mean 7.7±7.9 [7.7; 1-28] seconds). In 61/103 seizures (68.5%), ICA onset occurred before clinical onset (mean 12.3±9.7[10; 1-50] seconds). These ICA onsets were simultaneous in 15/103 (16.8%), and in 13 seizures (14.6%), clinical onset preceded ICA onset (mean 13.6±9.6[12; 1-33] seconds). ICA always occurred in the expiratory phase and all patients were agnostic to their apneas, confirmed by questioning.

Apnea and bradycardia. During ICA periods, heart rate increased in all 103 seizures; it was always seen at or after EEG seizure onset, rather than with ICA onset. Peri-ictal bradycardia was not observed in any seizure.

B) Post-ictal central apnea. Spontaneous restoration of breathing before seizure end was seen in 100/103 (97%). In 3 automotor seizures (3%), in 2/126 patients (2%), apnea persisted into the postictal period for 16-22 seconds (total peri-ictal apnea periods were 46-97 seconds). None had apnea beginning exclusively in the post-ictal period.

DISCUSSION

This study suggests that ICA is a semiological feature exclusive to focal epilepsy, most commonly starts before surface EEG onset, and can be the only clinical manifestation of focal seizures. ICA might help to distinguish focal from primary generalized epilepsies although this

possibility requires confirmation in a larger cohort of patients. Temporal lobe epilepsy and frontal lobe epilepsy accounted for the majority of focal epilepsies associated with apnea; temporal lobe epilepsy not only had an eightfold greater association with apnea than frontal lobe epilepsy, it was also significantly more likely to be associated with longer apneas and more severe hypoxemia. Automotor and dialeptic seizure semiologies, typical of temporal lobe epilepsy, were similarly much more likely to produce ICA, and longer ICA durations. Thus, ICA presence and ICA duration may not only help distinguish focal epilepsies, they may enhance localization to the temporal lobe. Temporal lobe symptomatogenicity for ICA is in concordance with direct electrical cortical stimulation studies in humans that point to highly reproducible apneic responses with [13, 14]low intensity, unilateral (left or right) amygdalar and hippocampal stimulation. [5, 15, 16] Although seizure spread to bilateral temporal structures has been considered necessary to produce ICA, these unilateral stimulation experiments, and the focal, unilateral ictal discharges at the time of ICA in many of our patients, suggest that such spread is not always the case.

It is likely that seizure discharges impair involuntary suprapontine (amygdalo-hippocampal) breathing control, resulting in ICA. Since ICA occurred after expiration in all our patients, it is likely that inspiration is immediately inhibited by seizure discharge, whereas expiration is mostly passive and allowed to occur to completion. The most likely downstream driver for ICA is seizure induced inhibition or disruption of brainstem inspiratory neuronal function. Descending amygdala projections to the parabrachial structures which exert critical roles in phase switching from expiration to inspiration have been described in cats[17]; single pulse amygdala stimulation triggers inspiratory onset[18]. Hippocampal activity increases before apnea termination in cats [19] and some hippocampal neurons phase-lock with the respiratory cycle in humans[20]. Thus, the relatively frequent occurrence of ICA in temporal lobe epilepsy patients is unsurprising. Whether ICA in extratemporal epilepsy patients reflects spread to amygdalohippocampal structures, or whether this implies involvement of symptomatogenic extra-temporal breathing control structures is uncertain; shorter duration of apnea in these patients may indicate the involvement of breathing network nodes that are distinct from those involved in temporal lobe seizures. Anterior cingulate, orbitofrontal and anterior insular regions, extratemporal sites have been also implicated in cortical breathing control[16].

The apnea agnosia described in stimulation studies, [5, 15] appeared to be true of ICA in our patients, and cessation of apnea in partial seizures was not followed by breathing distress, air hunger or dyspnea despite significant oxygen desaturations. Breathing resumption in ICA patients, prior to seizure end, was the rule (97%) with few exceptions (3%). Lack of ICA awareness may only be dangerous in prolonged apnea. We observed that ICA cessation did not appear to be driven by hypoxemia. Although hypercarbia cannot be commented upon here since carbon dioxide was not measured, ictal central apneas are not reversed by augmentations in ventilatory drive from increasing carbon dioxide in previous human[2] and animal[21] studies and similar observations have been made in stimulation experiments[5]. ICA durations were highly varied, and hence changes in seizure discharge intensity in breathing control structures are a more likely explanation.

In our patients, the complete absence of ictal bradycardia with ICA, reported in a minority of seizures in one series,[6] is surprising since bradycardia is a normal response to hypoventilation. Asphyxia in animal models results in heart rate decline and cardiac arrest in approximately 5 minutes[22]. Consistent with the literature, [11, 23] even in the rare, prolonged ICA epochs (up to 97

seconds), no bradycardia was observed in our study. Seizure-driven tachycardia is common[24], and may conceivably have overcome any physiological tendency to bradycardia in these patients. Combined peri-ictal apnea and bradycardia, therefore, appears rare, but when it does occur, may comprise a potentially deleterious, high vagal tone, phenotype in seizure patients in the SUDEP context; the observed tachycardia apnea combination in this study, may reflect a more benign, self-limiting seizure manifestation.

Is ictal apnea a SUDEP biomarker? The majority of patients had a brief, self-limiting apnea with mild or moderate hypoxemia, suggesting that ICA poses no danger in most cases. Mean and median ICA durations in this cohort were 28 and 22 seconds respectively; the sheer frequency of ICA in this cohort, their short durations, and cessation before seizure end, suggest that in the majority of cases, ICA is self-limiting and unlikely to be a SUDEP concern. However, prolonged ICA ($\geq$60 seconds) was associated with severe hypoxemia (SpO_2<75%) (Figure 4) and hence this combination may prove to be a biomarker of SUDEP that deserves prospective study. Indeed, two non-fatal ICA durations of 57 and 58 seconds, with SpO_2 of 68% and 62%, respectively were recorded in a previously reported patient who subsequently died of SUDEP at home. [11]

Post-ictal apnea appears to be a rare phenomenon. Only 3% of ICA persisted (for 16-22 seconds) beyond electroclinical seizure end in this study. None had isolated post-ictal central apnea beginning exclusively after seizure end. Duration of apnea continuance beyond seizure end was short (16-22 seconds) with total peri-ictal apnea periods between 46 and 97 seconds. Post-ictal apneic bradycardia, frequently reported in the post-ictal, agonal phases of MORTEMUS SUDEP cases, and near-SUDEP cases, after a partial seizure[10] or GTCS[25], did not occur in any of our patients. The persistent apnea observed into the post-ictal period may not have been truly post-ictal, as epileptiform discharges can persist in deep regions, such as amygdala or hippocampus, and not been seen on scalp EEG. However, persistent apnea could also represent a phenomenon similar to Todd's paralysis or postictal aphasia, due to dysfunction or "exhaustion" in the major breathing control sites in in the human brainstem.

Some limitations of our study need to be considered. Our conclusions are based on a relatively small number of seizures in the primary generalized epilepsy group. Additionally, by considering PGTCS or SGTCS onset as ICA end, we may have underestimated ICA duration since central apnea may conceivably commence in or continue into the tonic-clonic phase. The invariable loss of plethysmographic breathing signal due to movement artifact and the contribution of respiratory muscle spasm to hypoxia render comment on ICA difficult.

CONCLUSION

ICA is a frequent, self-limiting semiological feature in focal epilepsy and can be its only clinical manifestation. However, prolonged ICA and severe hypoxemia together may comprise a potential biomarker of SUDEP. ICA is ten times more frequently seen at the beginning of temporal than extratemporal seizures; and in typical temporal (dialeptic and automotor) seizure semiologies. The apnea is frequently seen before scalp EEG or clinical seizure onset. ICA rarely persists after seizure end. Without polygraphic monitoring, including pulse oximetry and breathing plethysmography during VEEG, ICA may go unrecognized, since patients are agnostic to the apnea.

Legends:

Figure 1. A left temporal lobe seizure is shown in three consecutive 30 second-pages, in polygraphic detail. In A), the patient is awake before seizure onset. Breathing movements' cessation was noted six seconds before epileptiform discharges began. In B), during a 50 second apnea period, complete absence of breathing movement is seen, along with oxygen desaturation, with only pulse artifacts identifiable in the plethysmography signal. In C), the patient re-starts breathing 15 seconds before seizure end, when he is interviewed by nurses. The patient was apnea agnostic.

Figure 2. Differences in polygraphy studies are represented in a typical A), generalized seizure with 3 Hz spike and wave's discharges where no apnea is observed and B), focal epilepsy and right temporal lobe seizure where central apnea is clearly seen.

Figure 3. Plot with error bars of ictal central apnea duration in seconds by epileptogenic zone (A) and seizure semiology (B), showing 95% confident intervals (CI) for temporal compared to extra-temporal ($p<0.001$) (A) and automotor and dialeptic compared to other seizure semiologies ($p<0.001$) (B).

Figure 4. Oxygen saturation of hemoglobin ($SpO_{2)}$ nadir and ictal central apnea duration. The abscissa is apnea duration (in seconds) and the ordinate is the SpO_2 at apnea end. The robust simple linear regression line and 95% confidence intervals are shown. Dashed lines show that apnea duration of 60 seconds approximately correlates with SpO_2 <75%.

Seizures were classified according to a semiological seizure classification[12]: aura (subjective feeling, usually at the beginning of the seizure); CMS = complex motor seizure (motor seizures in which the movements simulate natural, but inappropriate movements); automotor (complex motor seizure with prominent automatisms of distal limb segments or mouth and tongue, and usually with dyscognitive features), dialeptic (alteration of consciousness without motor disturbance), hypermotor (high amplitude movements involving proximal limb segments and trunk), focal motor (simple motor seizures), SGTCS = secondary generalized tonic-clonic seizures of focal epilepsy; no clinical signs (electrographic seizures with no clinical signs other than central apnea).

s= seconds; w/o= without.

Table 1. Seizure and epilepsy characteristics in 129 patients, with and without apnea

	Number	Apnea	No apnea
Total of seizures	312	103	209
Type of seizures			
Focal	285	103*	182
Generalized	27	0	27
State at the seizure onset			
Awake	146	50	96
Sleep	166	53	113
Epileptogenic zone			
Temporal	156	84*	72
Frontal	79	10	69
Parietal	11	0	11
Occipital	24	4	20
Insula	2	2	0
Generalized	30	0	30
Unknown	10	3	7
Seizure semiology**			
Automotor	63	45*	18
Dialeptic	34	19*	15
Aura	28	3	25
Complex motor, hypermotor or focal motor seizure	99	10	89
Aphasic	17	0	17
SGTCS	22	10	12
Absence	7	0	7
PGTCS	15	0	15
Non-clinical signs	27	16	11
EEG seizure onset			
Temporal	132	71*	61
Frontal	51	10	41
Parietal	6	0	6
Occipital	14	2	12
Bilateral	64	6	58
Obscured or non-focal	45	14	31

EEG seizure hemisphere at the apnea onset			
Unilateral Right	94	34*	60
Unilateral Left	120	51*	69
Bilateral	59	7	52
Obscured	39	11	28

**Significant values (p<0.05)*

*** According to a semiological seizure classification[12]*

SGTCS = secondarily generalized tonic-clonic seizures (of focal epilepsy)

PGTCS = primary generalized tonic-clonic seizures (of primary generalized epilepsy)

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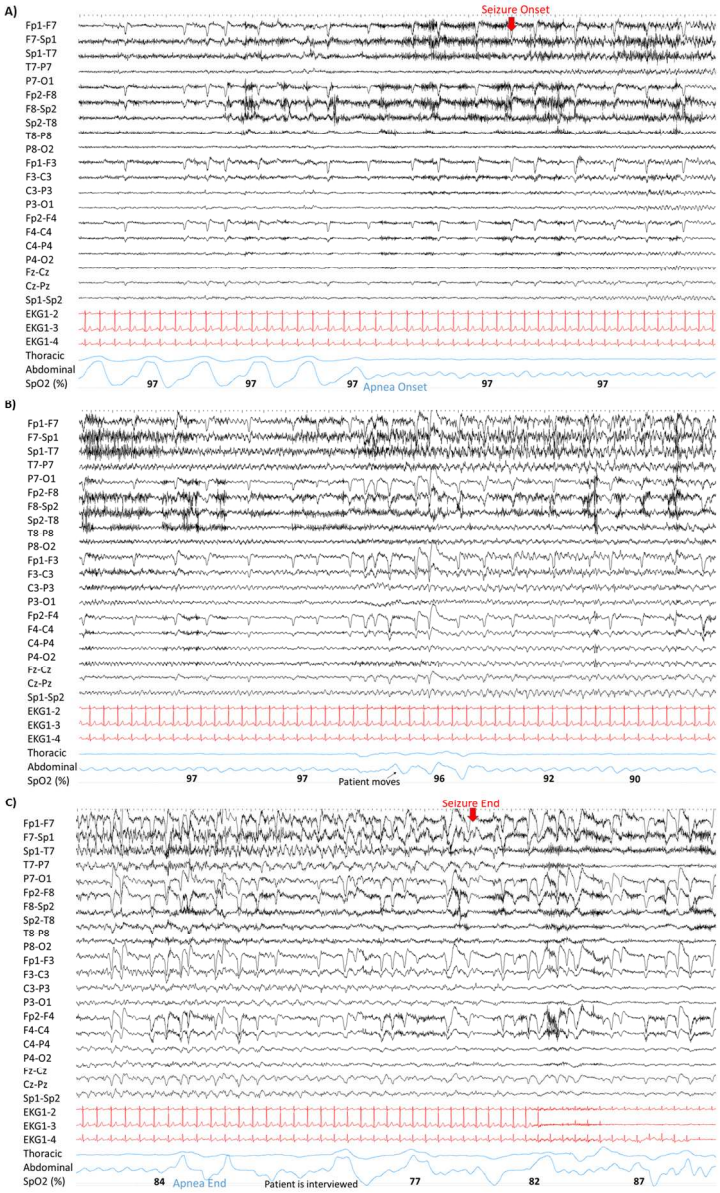
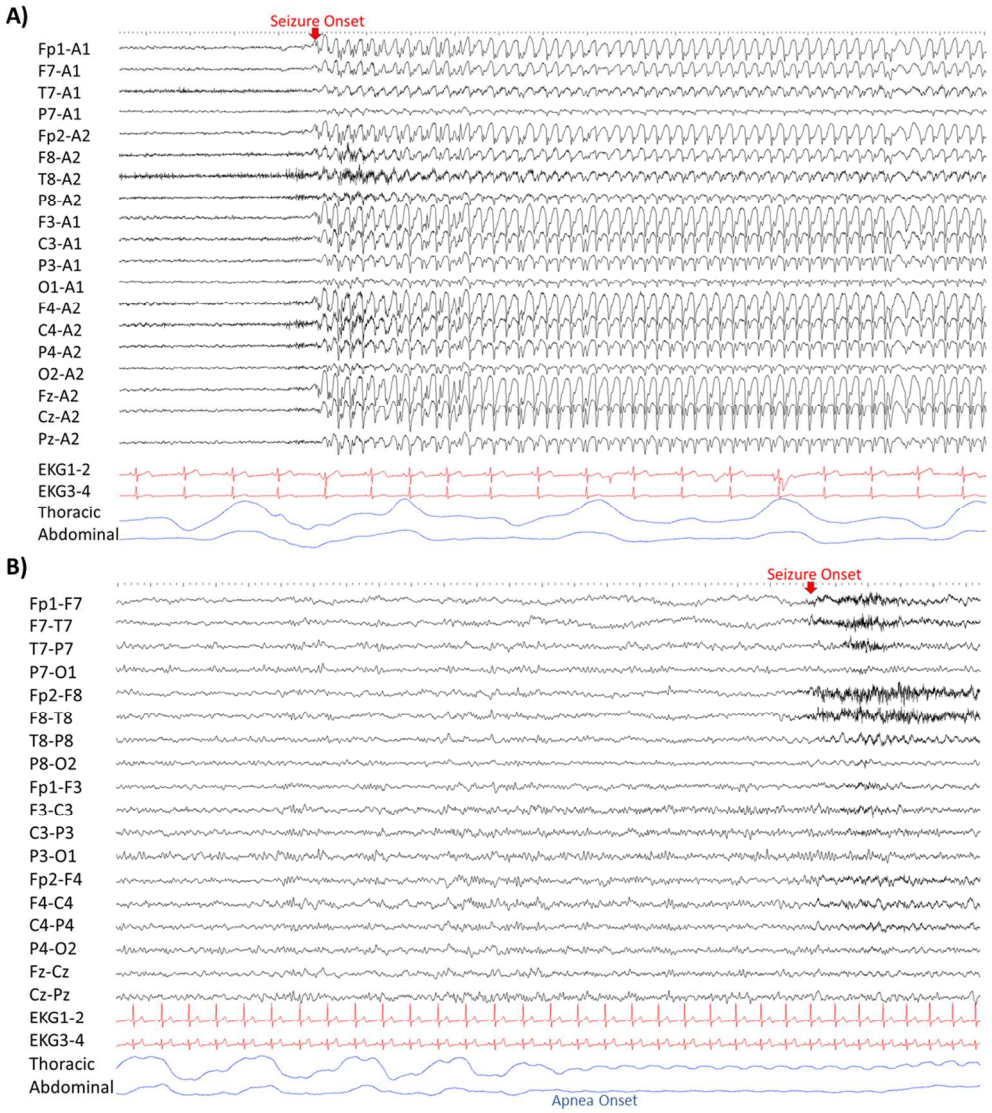


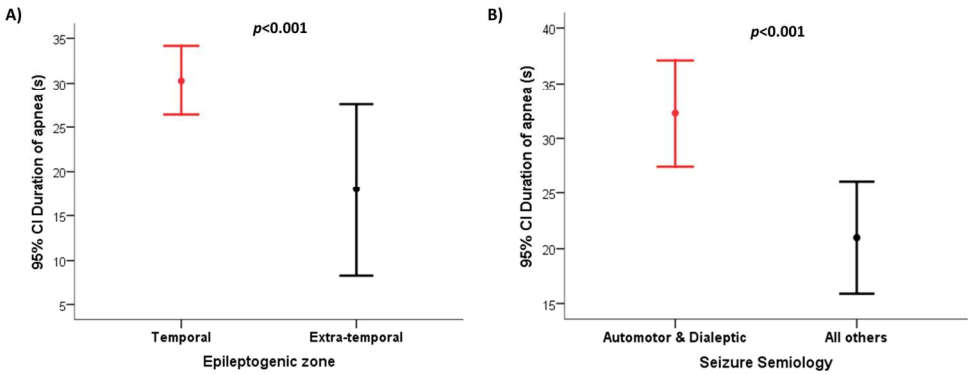
A left temporal lobe seizure is shown in three consecutive 30 second-pages, in polygraphic detail. In A), the patient is awake before seizure onset. Breathing movements' cessation was noted six seconds before epileptiform discharges began. In B), during a 50 second apnea period, complete absence of breathing movement is seen, along with oxygen desaturation, with only pulse artifacts identifiable in the plethysmography signal. In C), the patient re-starts breathing 15 seconds before seizure end, when he is interviewed by nurses. The patient was apnea agnostic.

338x558mm (96 x 96 DPI)



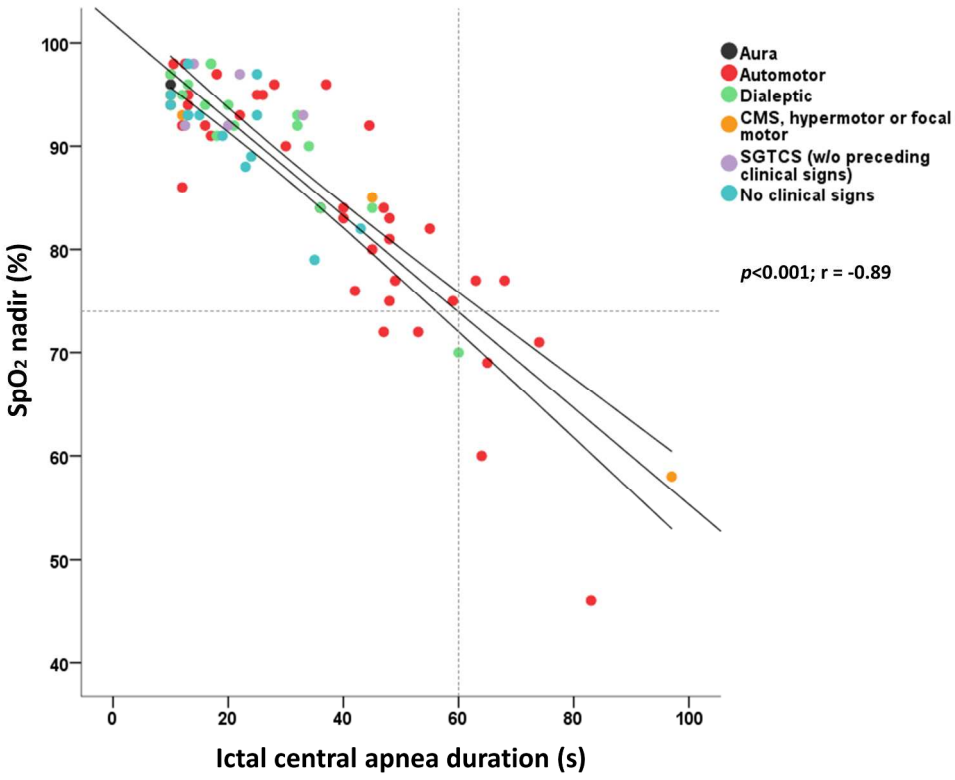
Differences in polygraphy studies are represented in a typical A), generalized seizure with 3 Hz spike and wave's discharges where no apnea is observed and B), focal epilepsy and right temporal lobe seizure where central apnea is clearly seen.

338x381mm (96 x 96 DPI)



Plot with error bars of ictal central apnea duration in seconds by epileptogenic zone (A) and seizure semiology (B), showing 95% confident intervals (CI) for temporal compared to extra-temporal (p<0.001) (A) and automotor and dialeptic compared to other seizure semiologies (p<0.001) (B).

152x59mm (300 x 300 DPI)



Peripheral capillary oxygen saturation (SpO2) nadir and ictal central apnea duration. The abscissa is apnea duration (in seconds) and the ordinate is the SpO2 at apnea end. The robust simple linear regression line and 95% confidence intervals are shown. Dashed lines show that apnea duration of 60 seconds approximately correlates with SpO2 <75%.

266x210mm (300 x 300 DPI)