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Ictal Central Apnea (ICA) may be a useful semiological sign in invasive epilepsy surgery evaluations

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ABSTRACT

Introduction: Ictal central apnea (ICA) occurs in up to 44% focal seizures (temporal > extratemporal) and precedes scalp electrographic (EEG) seizure onset in 54% of them. Central apnea can be elicited by electrical stimulation of mesial temporal structures (amygdala, hippocampus, and anteromesial parahippocampal and fusiform gyri), known symptomatogenic anatomical substrates for ICA. We aimed to analyze ICA value as an early semiological sign in invasive evaluation of suspected mesial temporal lobe epilepsy (MTLE).

Methods: We examined seizure records of intractable, suspected MTLE patients undergoing intracranial EEG (ICEEG) evaluations who had simultaneous respiratory belts with artifact-free signal.

Results: We analyzed 32 seizures (11 patients). ICA was seen in 22/32 (68.7%) seizures in 9 patients, was the first clinical manifestation in all of them, and the only clinical sign in 5/32 (15.6%). ICA onset occurred simultaneously or after ICEEG seizure onset in 20/22 (91%) seizures by 4.9 ±4.6 [0–14] seconds. In one patient with bilateral amygdalar and hippocampal implantation, ICA occurred before ICEEG seizure onset, indicating seizure discharge in an untargeted, probably extra amygdalohippocampal, symptomatogenic location.

Conclusions: ICA incidence in mesial temporal lobe (MTL) seizures is 68.7%. ICA is often the first clinical sign and sometimes the only clinical manifestation in MTLE, but usually goes unrecognized. ICA recognition may help anatomo-electro-clinical localization of clinical seizure onset to known symptomatogenic areas. ICA preceding ICEEG onset may indicate inadequate putative epileptogenic zone coverage, and may impact surgical outcomes. Respiratory monitoring in surgical evaluations is of critical importance and should be carried out as standard of care.

1. Introduction

Ictal central apnea (ICA) occurs in 36.5–44% of focal onset seizures (Bateman et al., 2008; Lacuey et al., 2018; Vilella et al., 2018), preceding electrographic (EEG) seizure onset by up to 29 s in 54% of seizures and before any other clinical manifestation by up to 50 s in 68.5% seizures (Lacuey et al., 2018). ICA is the sole clinical manifestation in 16.5% of focal, surface recorded EEG seizures (Lacuey et al., 2018). Suspected temporal lobe epilepsy is highly associated with ICA presence in comparison to extratemporal epilepsy (odds ratio [OR] 10.1, 95% confidence interval [CI] 5.5–18.5; $p = 0.001$) and to frontal lobe epilepsy (OR 8.3, 95% CI 4–17.3; $p = .001$). ICA occurred in 84/156 (54%) scalp vEEG monitored temporal lobe seizures as opposed to 16/116 (13%) extratemporal seizures and 0/30 of idiopathic generalized seizures, suggesting that ICA as an isolated sign, is more likely to indicate a temporal lobe epilepsy than any other type of epilepsy (Lacuey et al., 2018). Electrical stimulation studies in patients undergoing intracranial EEG (ICEEG) evaluations, have shown that stimulation of mesial temporal lobe structures (hippocampus, amygdala and anteromesial fusiform and parahippocampal gyri), induces central apnea in the absence of induced seizures/afterdischarges, and represent symptomatogenic anatomical substrates of ICA (Dlouhy et al., 2015; Lacuey et al., 2017, 2019; Nobis et al., 2018). Despite strong association with focal, particularly temporal lobe epilepsy, ICA has not previously been used as a semiological sign in presurgical epilepsy evaluations. Given recent knowledge, there is an urgent requirement for study of the utility of ICA in this setting. Here, we assessed the correlation between ICA and ICEEG seizure onset in patients with suspected mesial temporal lobe epilepsy (MTLE), to evaluate the value of ICA as a semiological sign in epilepsy surgery.

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2. Methods

We retrospectively studied patients undergoing SEEG evaluations for intractable, suspected MTLE at University Hospitals Cleveland Medical Center (UHCMC) from May 2015 to March 2019. The local Institutional Review Board at UHCMC approved the study (UH 10-14-03), and all patients signed informed consent. We included patients with video-ICEEG monitored suspected mesial temporal lobe (MTL) seizures with simultaneous artifact-free respiratory monitoring with thoraco-abdominal belts. Additionally, patients had simultaneous surface EEG (using the 10–20 International Electrode System) as part of the evaluation. We excluded patients with obstructed video and artifact at or before seizure onset. Thoraco-abdominal excursions were recorded using inductance plethysmography (Ambu [Ballerup, Denmark] Sleepmate). EEG and ECG were acquired using a diagnostic system (EEG-1200; Nihon Kohden). Peripheral capillary oxygen saturation (SpO_2), and heart rate were monitored using pulse oximetry (Nellcor OxiMax N-600x; Covidien). We defined ictal central apnea (ICA) as an abrupt drop in peak signal excursion by > 90% of pre-event baseline, lasting for at least 6 s (Lacuey et al., 2019) and before any apparent thoraco-abdominal movements (for example, generalized tonic movements) altered or obscured breathing signal. The EEG seizure onsets were determined by visual analysis, agreed by two epileptologists (SDL, NL). As per our EMU protocol, all patients were interviewed during the ictal/postictal period. Summary statistics were reported as mean ±standard deviation (SD; median, range). Fisher test was used to assess association between dichotomous variable apnea (yes/no) and state at seizure onset (awake/sleep). Significance was set at 2-sided $p < .05$.

3. Results

Nineteen of 51 seizures were excluded due to absent belt signal (4 seizures) or artifact-ridden breathing signal (15). Thus, 11 patients (6 females) had 32 seizures with artifact-free data. Mean age was 41.4±15.6 [41; 18–69] years. The epileptogenic zone was right hemispheric in 6/11(55%), and left in 5/11 (45%) [Table 1]. Ten of 32 (31%) were sleep onset seizures and 22/32 (69%) were awake. Only depth electrodes were used in the intracranial implantations. Each patient had approximately 8 electrodes with 10–12 contacts each (patient 8 had bilateral coverage) covering on average amygdala (3 contacts), hippocampus head (3), hippocampus body (2), mesial temporal pole (2), lateral temporal pole (2), lateral temporal (9), mesial orbitofrontal (3), anterior subcallosal (2), lateral orbitofrontal (6), posterior cingulate (2) and lateral parietal (2) cortices. The remaining electrode contacts traversed white matter. Additionally, patients 10 and 11 had two occipito-temporal (postero-anterior trajectory) hippocampal electrodes with 10 electrode contacts each, covering antero-mesial fusiform (2), parahippocampal (2), posterior fusiform (2), and lingual gyri (2) and hippocampus head and body (5). Thus, all 11 patients had amygdalo-hippocampal electrodes (one with bilateral implantation); two patients had additional electrodes in antero-mesial parahippocampal and fusiform gyri. SEEG onset was hippocampal in 19/32 (59.3%), amygdala in 10/32 (31.2%) and antero-mesial fusiform gyrus in 3/32 (10%). All patients had surgery and > 90% seizure reduction with a mean follow up of 21.3 ±9.7 [21; 6–43] months; patient 9 continued to have seizures.

ICA occurred in 22/32 (68.7%) seizures in 9/11 (82%) patients with mean duration of 38.8±25.5 [28.5; 10–25] seconds. SpO_2 was recorded in 13/22 (59%) ICA seizures; 9/13 (69%) ICA seizures had hypoxemia (SpO_2 < 95%) at ICA end, with mean desaturation of 81±11.6 [87; 64–94] %. ICA onset occurred simultaneously or before scalp EEG onset by 7.8±6.8 [6.5; 0–28] seconds in all seizures except one, where no scalp EEG ictal discharges were seen. Examples of ICA in scalp EEG (Fig. 1A) and ICEEG (Fig. 1B and 1C) recordings in patient 7 are shown in Fig. 1. Of 10 sleep-onset seizures, 7 (70%) had ICA, and preceded arousal. ICA onset occurred simultaneously or after ICEEG seizure onset by 4.9 ±4.6 [3; 0–14] seconds in 20/22 (91%). In two seizures in patient 9, ICA occurred before SEEG seizure onset by 7 and 20 s (Fig. 2). Three patients experienced an aura during 7 seizures, classified as abdominal aura in 4 seizures, non-specific aura ("lightheaded" and "head

Table 1
Patients, epilepsy surgery and ictal central apnea (ICA) characteristics.

Case	Age	Sex	Electrodes in MTL	Side	ICA presence in ICEEG sz	ICA = 1st clinical sign	ICA onset from ICEEG sz onset	ICA duration	Sz Onset	Surgery	Outcome (Engel)**	Follow up (m)
1	28	F	Am, H	R	1/1 (100%)	1/1 (100%)	+1s	29	H	TP + Am + H*	IA	14
2	34	M	Am, H	R	2/ 3 (66.7%)	2/ 3 (66.7%)	+2 s, +2s	11, 11	H (3 sz)	MTP + Am + H	IIA	21
3	44	F	Am, H	L	2/2 (100%)	2/2 (100%)	+10 s, 0 s	44, 27	H, H	H*	IIA	43
4	26	M	Am, H	R	0/5 (0%)	0/5 (0%)	n/a	n/a	Am (5sz)	TP + Am	IA	29
5	18	M	Am, H	L	4/4 (100%)	4/4 (100%)	+7 s, +2 s, +4 s, +9s	17, 16, 12, 16	H, H, H, H	TP + Am + H	IIA	17
6	66	M	Am, H	L	2/2 (100%)	2/2 (100%)	+4 s, +6s	36, 82	H, H	H*	IA	29
7	49	F	Am, H	L	3/3 (100%)	3/3 (100%)	0 s, 0 s, +2s	60, 68, 34	H, H, H	TP + Am + H*	IA	25
8	69	F	Am, H	R	0/5 (0%)	0/5 (0%)	n/a	n/a	Am (5sz)	Am	IA	24
9	41	M	Am, H	L, R	2/2 (100%)	2/2 (100%)	−20 s[a], -7s[a]	22, 10	H, H	H*	IIIA	17
10	39	F	Am, H, PH, AFG	R	3/3 (100%)	3/3 (100%)	+14 s, +12 s, +13s	85, 75, 80	AFG, AFG, AFG	TP + Am	IA	6
11	42	F	Am, H, PH, AFG	R	2/2 (100%)	2/2 (100%)	+1 s, +1s	24, 28	H, H	MTP + Am + H	IA	6

MTL: mesial temporal lobe; ICA: ictal central apnea; ICEEG: intracranial; Am: amygdala, H: hippocampus, PH: parahippocampal gyrus; AFG: anterior fusiform gyrus; TP: temporal pole; MTP: mesial temporal pole; F: female; M: male, m: months; sz: seizures; R: right; L: left.

* Hippocampal transections instead or resection (as memory sparing produce).

** Engel's Classification of Postoperative Outcome (Engel et al., 1993).

[a] ICA onset was seen before ICEEG seizure onset.

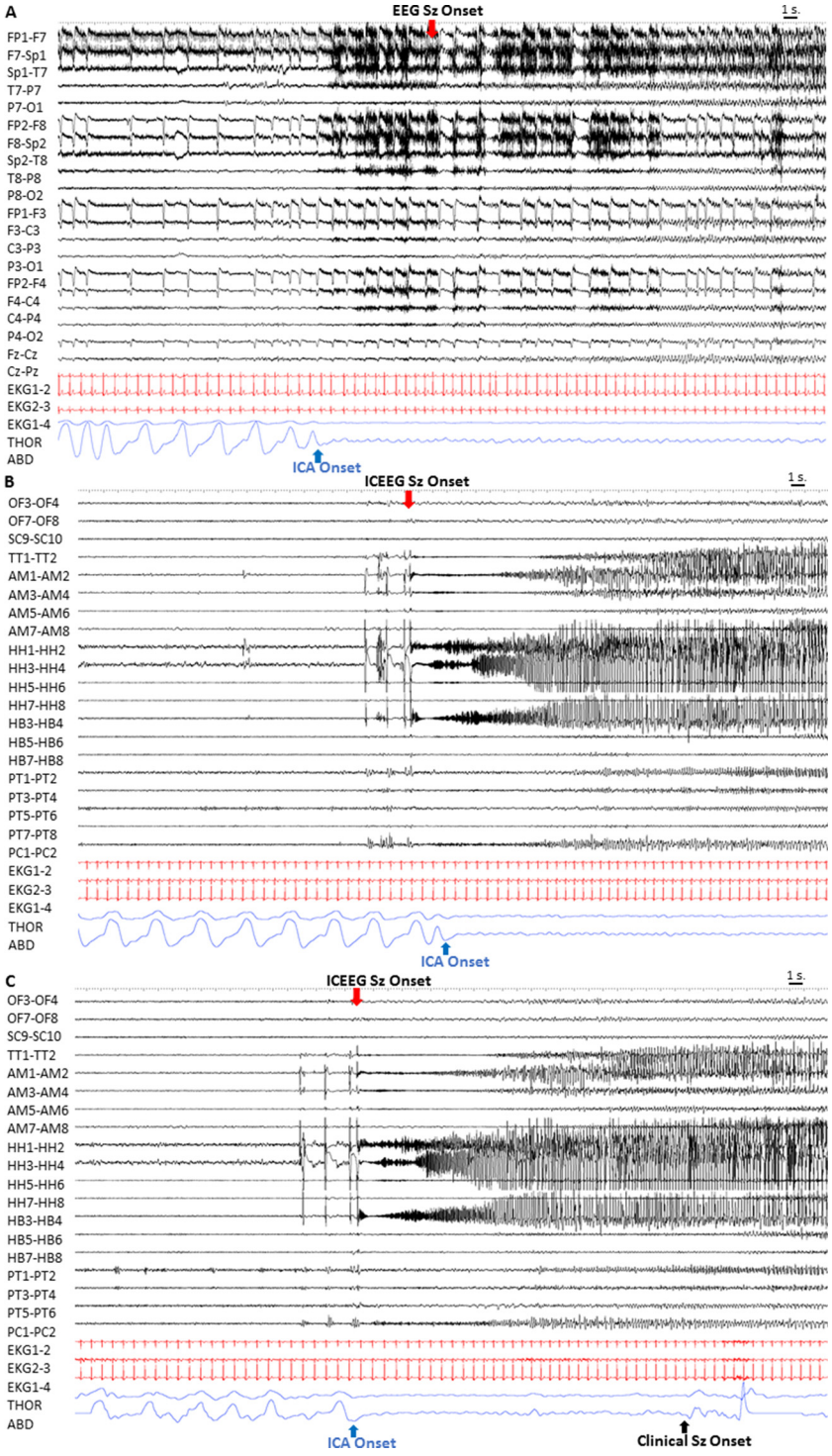

Fig. 1. Mesial temporal pole seizure-induced ictal central apnea (ICA) as the first clinical sign.
Focal seizures in patient 7, characterized by ictal central apnea (ICA) followed by impaired consciousness and oral automatisms. He underwent left temporal intracranial depth electrode implantation (including amygdala, hippocampus head and body, lateral temporal, temporal tip and lateral temporo-polar cortex in the left hemisphere); simultaneous respiratory belts recordings are shown. **A)** During scalp video EEG recording, a typical seizure was recorded. ICA was noted 7 s before epileptiform discharges began in the scalp EEG. **B)** During a left amygdalo-hippocampal, intracranially monitored seizure, ICA occurred within 2 s after ICEEG seizure onset. The patient was awake, and 29 s after ICA onset became unresponsive. **C)** ICEEG recording of spontaneous left amygdalo-hippocampal seizure onset with concurrent thoraco-abdominal signal cessation. The patient was awake and after 30 s of ICEEG seizure and ICA onsets, she became unresponsive. Peripheral capillary oxygen saturation (SpO_2) at ICEEG seizure onset was 96%, and went down to 77% at seizure end. The patient had no seizure recollection and was ICA agnostic.

feels fuzzy") in 2 seizures, and autonomic aura (nausea) in 1. Out of 7 seizures with aura, 3 (42.8%) had ICA. In all of these, ICA preceded aura by 22, 57 and 136 s.

Of 22 awake seizures, 14 (63.6%) had ICA. No association was seen between ICA presence and state ($p = 1$). ICA was the first clinical sign in all seizures, and followed by automatisms in 10 (45%), complex motor movements in 4 (18%), aura in 2 (9%) and altered awareness in 1 (4.5%). ICA was the sole clinical sign in 5/32 (15.6%), otherwise classified as EEG seizures. None showed or reported breathing distress.

4. Discussion

Hitherto, ICA has not been used as a semiological sign in the presurgical evaluation of patients with intractable focal epilepsy. This is mainly because the incidence of ICA in focal seizures, and the role of mesial temporal structures in the generation of ICA, have only recently been systematically described on a large scale. Moreover, the traditionally held view of mesial temporal seizure semiology has been that spread to nearby symptomatogenic areas is necessary for the emergence of semiological features. Our study suggests that ICA is an important semiological sign of MTLE and has important relevance in the

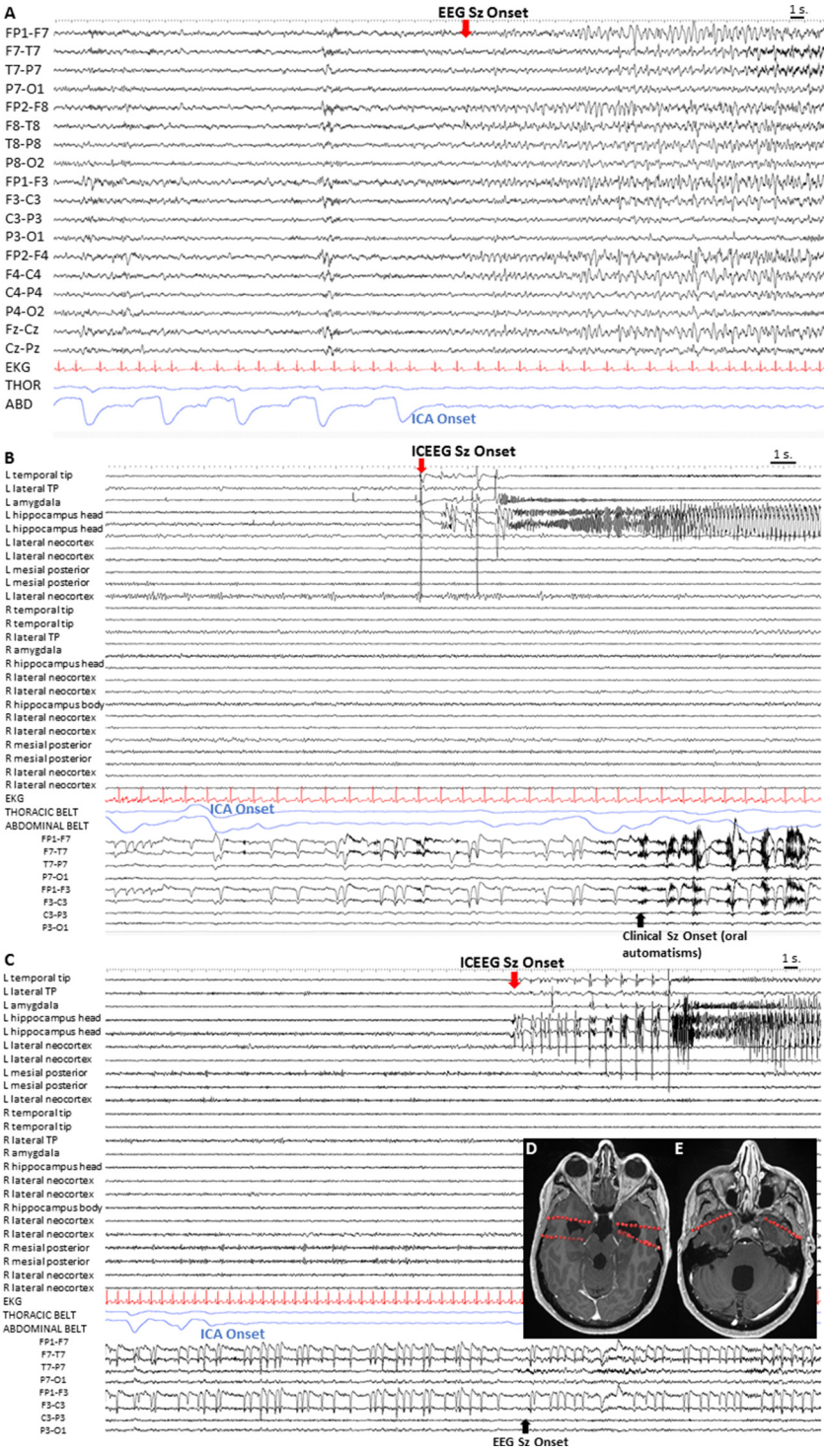

Fig. 2. Ictal central apnea (ICA) onset preceding intracranial EEG (ICEEG) seizure onset.
Figure shows patient 9, with focal seizures, comprising ictal central apnea (ICA) followed by impaired consciousness with oral automatisms, who underwent bilateral temporal intracranial depth electrode implantation (including amygdala, hippocampus head and body, lateral temporal, temporal tip and lateral temporo-polar cortex in both hemispheres. **A)** During scalp video EEG recording, a typical seizure was recorded. Cessation of breathing movements was noted 3 s before epileptiform discharges began in the scalp EEG. The patient was asleep at ICA and ICEEG seizure onset and started having oral automatisms and became unresponsive 16 s after ICA onset. **B)** During a monitored ICEEG habitual seizure, ICA was seen 7 s before unequivocal ICEEG seizure onset arising from the left hippocampal body. The patient had oral automatisms and became unresponsive 16 s after ICA onset. **C)** During a second monitored ICEEG seizure, ICA preceded EEG and ICEEG seizure onset by 20 s. Patient was awake and talking to the nurse when the seizure started. ICA was the only clinical sign of this seizure. Patient was apnea agnostic. Electrode contact locations targeting amygdala and hippocampus head **(D)** and **(E)** temporal tip in both hemispheres.

evaluation of the ictal onset zone in epilepsy surgery patients.

In this study, we found that ICA incidence in intra-cranially documented mesial temporal lobe (MTL) seizures is 22/32 (68.7%). In all, ICA was the initial clinical manifestation and the solitary clinical manifestation in 5/32 (15.6%). ICA may thus prove to be a valuable clinical sign of MTL seizure discharge, helping to localize the true clinical seizure onset in two thirds. Its primary value lies in the fact that hippocampal seizures are non-symptomatogenic until seizure spread to nearby eloquent structures. ICA is easily recognizable at the very onset of MTL seizures, often well before patients report auras. Recent human brain mapping studies using electrical stimulation provide robust evidence that sites within limbic/paralimbic (amygdala, hippocampus, anterior parahippocampal gyrus and antero-mesial fusiform gyrus [mesial temporo-polar region]) structures have the potential to suppress breathing and likely provide the symptomatogenic substrate for ICA (Dlouhy et al., 2015; Lacuey et al., 2019; Nobis et al., 2018). Higher ICA incidence in invasively recorded MTL seizures (68.7%) in our study compared to surface recorded temporal lobe seizures (53%) is consistent with MTL structures representing the symptomatogenic zone for ICA, distinct from usually silent lateral temporal neocortex. Thus, ICA recognition may help anatomo-electroclinical localization of clinical seizure onset to areas known to be symptomatogenic substrates of ICA.

In our study, we observed that ICA occurred more frequently in seizures arising from the hippocampus and longest ICA periods in seizures arising from the antero-mesial fusiform gyrus (in the mesial part of the temporal pole) [Table 1]. However, because of the small sample size and imbalanced groups, we were not able to assess any possible association.

We found ICA presence not to be preferentially associated with awake/sleep states at seizure onset. Additionally, ICA in the sleep state always occurred before arousal. We also found ICA to usually start before unequivocal surface EEG onset, consistent with a previous study that analyzed the correlation between ICA and scalp EEG seizure onset (Lacuey et al., 2018). Here, we analyzed the correlation between ICA and intracranial EEG (ICEEG) seizure onset. ICA onset occurred simultaneously or after intracranial EEG seizure onset within a mean of 4.9 s in over 90% of seizures. The rest occurred in one patient whose hippocampal head, body and amygdala were implanted bilaterally, but without coverage of the anterior parahippocampal and fusiform gyri in the mesial temporo-polar cortex (Fig. 2). ICA was the first clinical sign (similar to habitual seizures) and preceded intracranial left hippocampal seizure onset by 7 and 20 s (Fig. 2B and C). In this case, the unequivocal demonstration of ICA as the marker of clinical seizure onset, in the absence of seizure discharge on invasive electrodes, indicates that unexplored parts of the amygdala or hippocampus or extra-amygdalo-hippocampal cortical structures critical to generation of ICA, were not covered in the invasive evaluation. Given current knowledge, these structures are likely to have been the anteromesial parahippocampal and fusiform gyri. The patient continued to have seizures after left hippocampal transections, which were carried out as a memory sparing procedure. On the other hand, patients with ICA at or after ICEEG seizure onset, seem to have a better outcome (Table 1). For example, patient 7 (Fig. 1), with ICA onset within 2 s of the EEG seizure onset, underwent left hippocampal transections and amygdala resection and the patient is currently seizure free. Similarly, patient 10, with ICEEG seizure onset 12–14 second after ICA onset, underwent right amygdala and temporal pole resection, and is seizure free since surgery (Table 1). Thus, a case is made for respiratory monitoring in epilepsy surgery evaluations. Since patients are typically ICA agnostic, self-reporting is unreliable, and systematic monitoring with respiratory belts is highly recommended. This may help seizure detection, and provide information on respiratory symptoms essential for seizure localization. Further, ICA recognition may prove crucial for identification of the true region of clinical seizure onset in ICEEG evaluation, where ICA occurrence before ICEEG seizure onset indicates inadequate coverage of brain areas responsible for seizure onset. Our conclusions are based on a small number of seizures in MTLE patients. A larger study that includes extra-MTLE patients is necessary to confirm the value of ICA presence in localizing the epileptogenic zone (temporal vs extratemporal; mesial vs lateral temporal) in epilepsy surgery assessments.

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References

Bateman, L.M., Li, C.S., Seyal, M., 2008. Ictal hypoxemia in localization-related epilepsy: analysis of incidence, severity and risk factors. Brain 131, 3239–3245.
Dlouhy, B.J., et al., 2015. Breathing inhibited when seizures spread to the amygdala and upon amygdala stimulation. J. Neurosci. 35, 10281–10289.
Engel Jr., J., et al., 1993. Outcome with Respect to Epileptic Seizures. Book: Surgical Treatment of the Epilepsies. pp. 609–621.
Lacuey, N., et al., 2017. Amygdala and hippocampus are symptomatogenic zones for central apneic seizures. Neurology 88, 701–705.
Lacuey, N., et al., 2018. The incidence and significance of periictal apnea in epileptic seizures. Epilepsia 59, 573–582.
Lacuey, N., et al., 2019. Limbic and paralimbic structures driving ictal central apnea. Neurology 92, 1–15.
Nobis, W.P., et al., 2018. Amygdala-stimulation-induced apnea is attention and nasal-breathing dependent. Ann. Neurol. 83, 460–471.
Vilella, L., et al., 2018. Postconvulsive central apnea as a biomarker for sudden unexpected death in epilepsy (SUDEP). Neurology 92, 171–182.