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Letter to the Editor

## Picking up the pace

The most important goal of an intracranially-implanted electrode evaluation in an Epilepsy Monitoring Unit is to further define the seizure onset zone to determine the optimal surgical intervention. Ideally, the electrographic onset must come before or soon after the clinical onset of seizures to ensure the seizure focus has been adequately sampled prior to planning intervention. However, one "electrographic" sign may easily be overlooked – the EKG. Here we present a patient who underwent intracranial evaluation and was found to have two independent seizure foci. One focus in the left frontal region was associated with typical electroclinical seizures, and resection of that particular focus led to clinical seizure freedom. The second focus in the left anterior temporal region only occurred two days after medication withdrawal, and its first electrographic sign of seizure onset was the triggering of pacemaker spikes visible in the EKG lead. To our knowledge, this is the first case with intracranially-implanted electrodes for epilepsy surgery evaluation in which the electrographic seizure onset was defined by pacer spikes on the EKG lead.

In this case, a 49-year-old left handed female with a history of anxiety and medically intractable focal epilepsy was admitted to the epilepsy monitoring unit (EMU) of a tertiary referral center for intracranial monitoring as part of an epilepsy surgery evaluation. Despite multiple trials of antiepileptic drugs, she continued to experience an average of two focal impaired awareness seizures per week. In her late 30s, she began having episodes of behavioral arrest associated with slight head turns to either side. She was initially evaluated at an outside health system and had her first EMU admission in 2005. This revealed left temporal interictal epileptiform discharges and one non-lateralized seizure, complicated by an episode of ictal asystole. She then underwent placement of a permanent cardiac pacemaker. She was admitted again to the EMU in 2013 which captured seven left frontotemporal complex partial seizures along with left temporal interictal epileptiform discharges. MRI of the brain showed a nonexpansile lesion in the subcortical white matter of the anterior left superior frontal gyrus (Fig. 1A).

Based on her non-invasive testing, she underwent placement of a 2 × 8 double-sided interhemispheric grid, 6 × 8 left frontal convexity grid, 1 × 4 left temporal grid strip, 1 × 4 left orbitofrontal grid strip, and 1 × 8 parietal-occipital grid strip (Fig. 1B and C). Her home doses of levetiracetam and lamotrigine were held immediately following intra-operative electrode placement. There were four seizures which arose from the left frontal perilesional area. One of these seizures began clinically with dizziness, a shaking feeling, and subtle buccal automatisms without a loss of consciousness, and another seizure was associated with ictal confusion upon interrogation by the technician. These were reported as her typical events. The electrographic onset of these seizures was low voltage fast activity in the left frontal perilesional area which quickly evolved into 6–8 Hz spike discharges with regional spread before evolving into 1 Hz polyspike and slow wave activity and terminating after 23–70 seconds. In all of these seizures, electrographic onset preceded clinical onset.

Interestingly, 7 atypical clinical and subclinical seizures were also captured which did not arise from a peri-lesional region, including 5 from the left anterior temporal region with clinical arousal, perioral, and hand automatisms and ictal bradyarrhythmia with pacer spikes on single lead EKG. Two of these events were characterized only by ictal bradyarrhythmia with pacemaker activation without any intracranial correlation, one of which was associated with clinical arousal and a confusional state. The pacer spikes on single lead EKG were confirmed on cardiac telemetry. The onset of the bradyarrhythmia and pacemaker activation preceded electrocorticographic onset from 7 seconds up to 50 seconds (Fig. 1D).

Given the findings of her typical clinical seizure and three subclinical seizures arising from the left frontal peri-lesional area, it was felt that this represented the epileptogenic zone for her habitual events. She underwent intracranial language mapping followed by a language-sparing lesionectomy. The pathology revealed focal cortical dysplasia, ILAE Type IIIB, and a low grade angiocentric glioma. On 18 months follow up, she remains seizure free on her previous doses of medication and without any abnormalities on pacer interrogation.

This is the first case to our knowledge where electrographic seizure onset is defined by pacer spikes in a patient with placement of intracranial electrodes for the evaluation of epilepsy surgery. Video-EEG recording showing pacer spikes after pacemaker implantation has previously been described using scalp EEG recordings (Strzelczyk et al., 2008; AlKhawajah et al., 2013; Gregg et al., 2019). In all of these prior cases, ictal bradycardia triggering the pacemaker occurred after seizure onset. While pre-ictal heart rate increase is common and well described, pre-ictal heart rate reduction is exceedingly rare and virtually non-existent in adults (Bruno et al., 2018). Therefore, the findings in the present case suggest that the patient has a second seizure focus in the left temporal lobe that was likely undersampled with intracranial electrodes. Since this focus only became active 2 days after medication withdrawal and the patient had no further seizures or pacer activations in the 18 months after her resection, this second seizure focus is likely well controlled with medication. Nonetheless, the patient was counseled that stopping medications will result in a high risk of seizure recurrence and/or pacemaker activation given our findings. In addition, these atypical seizures were subclinical or had only subtle clinical features, so future pacemaker interrogation may be the best method of detecting this seizure type in the long term.

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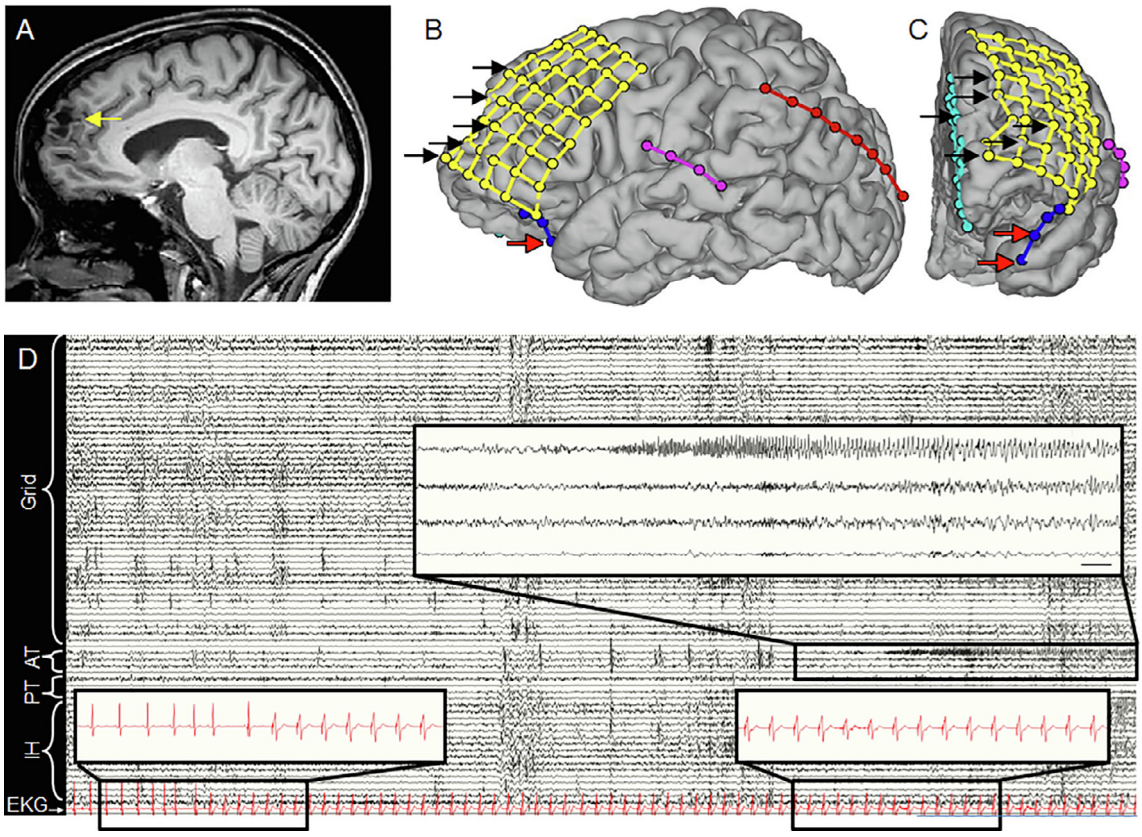


**Fig. 1.** Pacer spiking as the first sign of electrographic seizure onset. (A) Sagittal MRI near the midline showing region of cystic encephalomalacia in the left frontal lobe (arrow). (B and C) Reconstruction after placement of intracranial grid and strips showing contacts for onset of Type 1 (black arrows) and Type 2 (red arrows) seizures. Yellow = left frontal grid; Blue = anterior temporal/orbitofrontal strip; Pink = posterior frontal/temporal strip; Red = parieto-occipital strip; Light blue = Interhemispheric grid. (D) 75 s recording capturing the onset of Seizure 11 (Type 2/atypical). Lower left inset: onset of bradycardia followed by initiation of pacer spikes. Upper right inset: first electrocorticography onset in the anterior temporal contact. Lower right inset: Continued pacing through electrocorticographic onset. Note: some contacts were removed to improve visibility. AT = anterior temporal/orbitofrontal strip; PT = posterior frontal/temporal trip; IH = interhemispheric grid. Bar = 1 s.

Patients with ictal bradycardia/asystole are generally referred for cardiac pacemaker placement, with good outcomes reported over time (Moseley et al., 2011). However, persistent seizures despite pacemaker placement warrants further investigation for one or more seizure foci, and attention to the EKG lead can be an important clue for identifying seizure onset. Altogether, we find that patients with pacemaker placement secondary to ictal asystole should continue to be evaluated as needed to achieve seizure freedom, and the pacemaker can itself be a helpful marker for electroclinical seizure onset.

## Declaration of Competing Interest

None of the authors have potential conflicts of interest to be disclosed.

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