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Ictal high-frequency oscillations and hyperexcitability in refractory epilepsy

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HIGHLIGHTS

- High-frequency oscillations captured at the onset of seizure may help determine surgical outcome in patients with refractory epilepsy.
- Cortical areas demonstrating hyperexcitability may be associated with ictal high-frequency oscillations.
- By examining hyperexcitability and ictal high-frequency oscillations, the decision-making process for surgical resection to treat refractory epilepsy may be improved with values of sensitivity and specificity that are more optimal.

ABSTRACT

Objective: High-frequency oscillations (HFOs, 80–500 Hz) from intracranial electroencephalography (EEG) may represent a biomarker of epileptogenicity for epilepsy. We explored the relationship between ictal HFOs and hyperexcitability with a view to improving surgical outcome.
Methods: We evaluated 262 patients with refractory epilepsy. Fifteen patients underwent electrode implantation, and surgical resection was performed in 12 patients using a semi-prospective design. Ictal intracranial EEGs were examined by continuous wavelet transform (CWT). Significant ictal HFOs were denoted by normalized wavelet power above the 50th percentile across all channels. Each patient underwent functional mapping with cortical electrical stimulation. Hyperexcitability was defined as the appearance of afterdischarges or clinical seizures after electrical stimulation (50 Hz, biphasic, pulse width = 0.5 ms, 5 s, 5 mA).
Results: Among the group of patients achieving Engel Class I/II outcome at 1+ year, the mean proportion of significant ictal HFOs among resected channels for any given patient was 69% (33.3–100%). The respective figures for conventional frequency ictal patterns (CFIPs), hyperexcitability, and radiological lesion were 68.3% (26.3–100%), 39.6% (0–100%), and 52.8% (0–100%). Statistical significance was only achieved with ictal HFOs when comparing patients with Engel Class I/II outcomes versus III/IV outcomes (12.6% vs. 4.2%, the number of channels as the denominator, $p = 0.005$).
Results: Further analysis from all patients irrespective of the surgical outcome showed that ictal HFOs co-occurred with CFIP ($p < 0.001$), hyperexcitability ($p < 0.001$), and radiological lesion ($p < 0.001$). The combination of ictal HFOs/hyperexcitability improved the sensitivity from 66.7% to 100%, and the specificity from 66.7% to 75% when compared with ictal HFOs or hyperexcitability alone.
Conclusions: We confirmed the utility of ictal HFOs in determining surgical outcome. Ictal HFOs are affiliated to cortical hyperexcitability, which may represent a pathological manifestation of epileptogenicity.
Significance: Presurgical evaluation of refractory epilepsy may incorporate both ictal HFOs and cortical stimulation in determining epileptogenic foci.

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1. Introduction

The challenge of treating refractory epilepsy with surgery begins with the exploration of the epileptogenic zone, defined as "the minimal area of cortex that must be resected to produce seizure freedom" (Luders et al., 1993). This apparent basis for presurgical evaluation has fueled research on multimodal investigations that identify or define the electrographic details to which epileptogenic zones conform. In 1954, Penfield and Jasper had already used the concepts of interictal corticography to establish the limits of the epileptogenic zone. By 1962, Talairach and Bancaud introduced the technique of stereo-electroencephalography to study ictal events and advance knowledge of the epileptogenic zone. Today, high-frequency oscillations (HFOs) are added to the armamentarium and hailed as a new biomarker to signify epileptogenesis. We have a far greater number of tools with which to investigate patients with refractory epilepsy compared to what was available in the era of Penfield and Jasper, who meticulously adopted cortical stimulation to reproduce aura and other ictal manifestations. The concept of hyperexcitability was a hallmark of epilepsy from the days of the forerunners in epilepsy research, but it can still be applied today in presurgical evaluation in the setting of intracranial electrode implantation.

HFOs in the range of 80–500 Hz have been identified and classified (Buzsaki et al., 1992) for operational reasons, and their utility in seizure-onset identification has been demonstrated in animal models of epilepsy (Bragin et al., 1999, 2003), and later in intracranial microelectrodes from hippocampal and entorhinal cortices of patients with epilepsy (Bragin et al., 2005; Staba et al., 2002, 2004) and those with neocortical epilepsy (Weiss et al., 2013). These results were replicable with intracranial macroelectrodes (Jirsch et al., 2006; Urrestarazu et al., 2007). We are interested in the analysis of ictal HFOs, as the literature on this aspect of HFO is relatively limited. The traditional method of determining an intracranial seizure-onset zone using conventional frequency ictal patterns (CFIP) suffers from a number of drawbacks: (1) difficulty in deciphering which of the onset patterns may assume superior significance, (2) proximity in time sequence between similar onset patterns of adjacent channels, and (3) problems encountered with rapid spread of discharges. Fujiwara and researchers also pointed out the following: (4) the surface findings of grid electrodes may not indicate what may be happening in deeper cortical sources near the bottom of the sulci, (5) the depth electrode is often impractical and only feasible for a small area of enquiry, (6) epileptogenic areas with a tangential orientation either have undetectable amplitudes or are too widespread, and (7) electrodes may have been placed in such a way that the visual analysis of ictal patterns could be misleading (Fujiwara et al., 2012).

In a study of patients with temporal lobe epilepsy using intracranial EEG, the spatial and time-related properties of HFOs were explored. A spatial correlation of HFO with a seizure-onset zone was observed, and the researchers found the presence of 100–200 Hz HFOs at least 8 s before seizure (Khosravani et al., 2009). In a pediatric study of nine children with neocortical epilepsy, both wide-band (250 Hz) and narrow-band (68–164 Hz) HFOs were registered. In those patients achieving seizure freedom, more electrodes recorded HFOs inside the resection margin than outside, both before and after clinical seizure onset (Ochi et al., 2007). A study of six patients with neocortical epilepsy showed that ictal HFOs, manifested as frequencies $\geqslant$70 Hz with sustained evolution, had a higher peak frequency and more spatially restricted appearance, and they were 10 times more likely to be resected than ictal HFOs without evolution (Modur et al., 2011). In a study that examined intracranial EEG patterns and radiological lesions, HFOs were significantly associated with the developing patterns at seizure onset, regardless of the patterns themselves (Perucca et al., 2014).

The relationship between hyperexcitability and HFOs was explored in one study, which examined *interictal HFO* and electrical stimulation of areas using intracranial macroelectrodes. The EEG segments consisted of 5 min of slow-wave sleep in patients with intracranial implantation. Interictal HFO rates were negatively correlated with thresholds for response to electrical stimulation, lending support to the notion that HFO and hyperexcitability may share a similar mechanistic platform (Jacobs et al., 2010a,b).

We hypothesize the following points in our current study:

(1) Among patients who attain satisfactory surgical outcomes, a higher proportion of the resected channels demonstrate significant ictal HFOs. A test of significance will be carried out with CFIP, hyperexcitability, and radiological lesion using the surgical outcome.
(2) Ictal HFOs are associated significantly with CFIP, hyperexcitability, and radiological lesion using all available channels.
(3) The sensitivity and specificity of using ictal HFOs together with hyperexcitability in determining surgical outcome may be superior to ictal HFOs, CFIP, hyperexcitability, or radiological lesion alone.

2. Methods

We prospectively evaluated 262 patients with refractory epilepsy at a university-affiliated hospital during the period between 2007 and 2012. Eighty patients were eligible for direct resective surgery, and another 55 patients had sufficient information to localize or lateralize a potential area of resection based on MRI, surface video EEG, clinical psychological testing, positron emission tomography (PET), single photon emission computed tomography (SPECT), or Wada test, i.e. a testable hypothesis formulated for implantation of an intracranial electrode. The inclusion criteria were as follows: (1) age $\geqslant$18 and (2) refractory epilepsy with an implantation hypothesis. A typical implantation schedule would consist of grid electrodes to sample the neocortical areas and depth electrodes to sample the mesial temporal regions. The exclusion criteria were as follows: (1) inability to provide written informed consent and (2) lack of ictal episodes being captured during intracranial monitoring. Fifteen patients underwent intracranial EEG when the technical placement of electrodes could be resolved and financed. At the time of recruitment for the study, intracranial EEG was not a fundable item under the Hospital Authority of Hong Kong, so patients required additional financial support to undergo this part of their treatment. The patient characteristics are given in Table 1. We used the Nicolet® machine (Viasys, Santa Ana, CA, USA) for video electroencephalographic monitoring with a minimum sampling rate of 1024 Hz. The intracranial electrodes used met the standard for impedance and stability with platinum contacts of 4.0-mm diameter and 2.3-mm exposure (Ad-Tech, Irving, TX, USA). The ictal recordings from intracranial EEG were analyzed by visual analysis of CFIP, and the final plan for resection was made during a joint epilepsy surgery meeting (HL, XZ, DC, WP, and KW), after consideration of both electrographic information and the results of functional mapping. Inpatient intracranial EEG monitoring may last between 7 and 14 days. Off-line analysis of ictal recordings was carried out using a Matlab-based platform by an independent assessor blinded to the clinical information (SL). In the wake of 2011, we considered ictal HFOs as part of the evidence in the discussion leading up to resective surgery. A minimum follow-up period of 1 year is required for all patients to determine their surgical outcome. Surgical outcome was determined using the Engel classification for epilepsy surgery (Engel, 1993).