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The Ambiguous Nature of Fast Ripples in Epilepsy Surgery

Removing High-Frequency Oscillations: A Prospective Multicenter Study on Seizure Outcome

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Objective: To evaluate the use of interictal high-frequency oscillations (HFOs) in epilepsy surgery for prediction of postsurgical seizure outcome in a prospective multicenter trial. Methods: We hypothesized that a seizure-free outcome could be expected in patients in whom the surgical planning included the majority of HFO-generating brain tissue, while a poor seizure outcome could be expected in patients in whom only a few such areas were planned to be resected. Fifty-two patients were included from 3 tertiary epilepsy centers during a 1-year period. Ripples (80-250 Hz) and fast ripples (250-500 Hz) were automatically detected during slow-wave sleep with chronic intracranial EEG in 2 centers and acute intraoperative electrocorticography in 1 patient. Results: There was a correlation between the removal of HFO-generating regions and seizure-free outcome at the group level for all patients. No correlation was found, however, for the center-specific analysis, and an individual prognostication of seizure outcome was true in only 36 (67%) patients. Moreover, some patients became seizure-free without removal of the majority of HFO-generating tissue. The investigation of influencing factors, including comparisons of visual and automatic analysis, using a threshold analysis for areas with high HFO activity, and excluding contacts bordering the resection, did not result in improved prognostication. Conclusions: On an individual patient level, a prediction of outcome was not possible in all patients. This may be due to the analysis techniques used. Alternatively, HFOs may be less specific for epileptic tissue than earlier studies have indicated.

Commentary

The study of high-frequency oscillations (HFOs) in epilepsy continues to evolve since they were first described over 20 years ago.[1] Incorporation of high-frequency activity into intracranial EEG interpretation can help determine the extent of the seizure-onset zone (SOZ). High-frequency oscillations are spontaneous fast oscillatory EEG events in the frequency range between 80 and 500 Hz and are classified as ripples (ranging from 80 to 250 Hz) and fast ripples (>250 Hz). Ripples are considered a normal expression of normal physiological behavior (thought to reflect summated excitatory postsynaptic potentials), while fast ripples (summated action potentials from synchronously bursting neurons) are proposed to be biomarkers of epileptogenic areas, with the caveat that some cognitive processes are associated with fast ripple band activity.[2] Pathological HFOs in the range of 250 to 500 Hz delineate the SOZ independently with better specificity, albeit with less sensitivity, than spikes.[3,4] Fast ripples may co-occur with spikes yet these 2 types of interictal abnormalities seem to have different pathophysiological implications: ripples are more tightly liked to seizures as they increase preictally and with reductions in AED levels, while spikes are more prominent postictally. Fast ripples have been reported to occur in a variety of epileptic conditions including localization-related epilepsy, genetic epilepsies, and infantile spasms.[5] In addition, other measures of high-frequency interictal activity, such as high γ (80-150 Hz) activity phase-locked to low-frequency EEG discharges might provide additional information on the extent of the SOZ.[6]

Retrospective studies, with small sample sizes, suggest that removal of *interictal* HFO-generating tissue correlates, on a group level, with post-resection seizure freedom. These studies include mixed patient groups (pediatric and adults) with different pathologies and different techniques for spatial sampling, sleep versus awake sampling, time of analysis with relation to the occurrence of seizure activity, and/or changes in anticonvulsant medications.[7] In an intraoperative ECoG study, the rate of presurgically measured HFOs did not predict seizure outcome but the rate measured after resection did.[8] Despite these preliminary reports, a Cochrane review concluded that the evidence for effective use of *ictal* HFOs for epilepsy surgery decision-making is rather poor.[9] Given that analysis methods are time-consuming and complicated, measuring HFOs has not

been used routinely in the presurgical evaluation of surgical candidates.

In the above-cited study, Jacobs et al present the results of a prospective, 3 center trial of 52 medically refractory patients to predict the postoperative seizure outcome in a group of patients with various types of pathologies. For ethical reasons, resections were not tailored to the HFO's results. Epilepsy surgery was performed after intracranial EEG, and patients were followed for a minimum of 12 months and had postsurgical magnetic resonance imaging (MRI) to confirm the extent of the resection. Ripples and fast ripples were automatically detected in 10 minutes of EEG data that were recorded either chronically with grid or depth electrodes or acutely intraoperatively. Comparisons to postsurgical MRI determined the proportion of HFO-generating tissue that was resected. Spearman rank correlation was used to determine the relationship between the resected area containing HFOs and postoperative Engel outcome classifications. Greater removal of HFO-generating tissue was associated with better outcomes in the whole-cohort analysis but only in a small majority of individuals.

The discrepancy in the predictive value of using HFOs to guide the surgical resection is probably affected by the pathological substrate,[10] the location of the epileptogenic zone (medial temporal vs neocortical), and the methodology used to localize and quantify HFOs (specifically whether chronic or acute intraoperative sampling is performed).

Only adequately powered and differently designed prospective trials, such as the ongoing intraoperative ECoG Dutch HFO trial, will answer the question of whether interictal HFOs are true and better markers for the epileptogenic zone than interictal spikes.[11]

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