KEY MESSAGES

1. Both intracranial electroencephalography and detection of wavelet-transformed high-frequency oscillations (HFOs) may be beneficial in surgery for patients with focal epilepsy.

2. Detection of wavelet-transformed HFOs may increase the percentage of patients eligible for resective surgery by 5% to 6.5%, compared with intracranial electroencephalography alone.

3. Detection of wavelet HFOs may improve surgical outcome by 17% to 18%, compared with intracranial electroencephalography alone, and by 30% if no intracranial electroencephalography is used.

4. High-frequency oscillations that are detected at the onset of seizure help determine seizure outcome.

5. Cortical areas that demonstrate hyperexcitability may be associated with HFOs.

Introduction

Epilepsy is a neurological disease that places a heavy burden on society. Approximately 68,000 patients in Hong Kong have some form of seizure disorder, and one-third of these patients have seizures that are refractory to medical treatment. Surgery may provide a cure in due course, but identification of seizure focus is necessary for success. In patients with a clear and resectable structural lesion, surgery may proceed after video electroencephalography, magnetic resonance imaging, and clinical psychological testing. Nonetheless, some patients do not appear to have a resectable lesion according to these methods.

High-frequency oscillations (HFOs) refer to electrographic activity of 80 to 500 Hz. It is hypothesised that HFOs can be biomarkers for epilepsy. Wavelet transformation may accurately depict HFOs. We propose that detection of wavelet-transformed HFOs of a seizure may help determine the seizure-onset zone that is essential for epilepsy surgery.

Methods

A total of 128 patients with refractory epilepsy underwent resective surgery in our hospitals between July 2013 and June 2015. Of these patients, 15 women and 19 men (mean age, 34 years) gave informed consent to undergo intracranial electroencephalography. These patients underwent implantation of grid or strip electrodes with a range of configurations to delineate seizure foci. Episodes of stereotypic seizure with clinical manifestations were recorded in 3-minute epochs, adopting bipolar montage and good technical quality. Each epoch covered the entire seizure and centred on a quarter of its own length from the onset of seizure. Electroencephalographic findings for each seizure were first analysed visually by a neurologist, followed by offline export of data for wavelet analysis. The number of scales that corresponded to the range of 80 to 500 Hz was used. The algorithm was generated using a MATLAB platform. The mother wavelet used was biorthogonal 6.8. The density of HFOs was calculated by a peak-to-trough power ratio of 50 to 70. If the ratio fell below 10, the electrode position might not have represented the seizure onset zone.

A previous cohort served as a pilot control group in which the percentage of patients eligible for resective surgery was 70% and the rate of good surgical outcome was 57%. During the recording procedures, conventional frequency ictal patterns,
hyperexcitability, and radiological lesion were also recorded.

An ancillary study included the technical aspect of electroencephalographic data. Hyperexcitability was defined as the appearance of after-discharges or clinical seizures following electrical stimulation (50 Hz, biphasic, pulse width of 0.5 ms, 5 s, 5 mA). The mean proportion of HFOs among resected channels was compared with that of the conventional frequency ictal pattern, hyperexcitability, and radiological lesion.

**Results and Discussion**

The proportion of patients who were eligible for resective surgery was 76.5% following review of wavelet-transformed HFOs and 75% following visual analysis of HFOs. Thus, an increase of 5% to 6.5% was expected when wavelet-transformed HFOs were analysed. The proportion of patients who attained good surgical outcome with accurate identification of seizure-onset zone was 71.4% following review of wavelet-transformed HFOs, compared with 75% following visual analysis of HFOs. This represented an increase of 17% to 18% when compared with no visual analysis of HFOs, and an increase of 30% when compared with no intracranial electroencephalography.

By testing for HFOs, we demonstrated a safe and fast methodology to determine the laterality of onset for patients with bilateral mesial temporal sclerosis (Fig 1). In patients in whom electrographic signals were sampled in the greater curvature of a neocortical surface, the number of channels involved initially may have been so extensive that rapid identification of foci was not feasible. Our mathematical representation identified the distinctive region with HFOs and added strength to information not visible to the naked eye (Fig 2). In addition, our analysis showed additional evolution of discharges throughout the seizure epoch that was not uniform. Fast activity was evident at the very first moment of the seizure, followed by a decrease in power towards the mid-portion. As the seizure epoch concluded, spectral power was regained, culminating in final, abrupt cessation of seizure. This phenomenon was not observable by visual analysis of HFOs. Hyperexcitability co-occurred with HFOs, conventional frequency ictal patterns, and radiological lesions (Fig 3).

Combining two or more modalities may improve selection of candidates for surgery. Our data suggest that when both wavelet-transformed HFOs and hyperexcitability are used, sensitivity can be maintained at 100% (95% confidence interval [CI]=0.52-1) and specificity may be increased from 66.7% (95% CI=0.31-0.91) to 75% (95% CI=0.36-0.96), compared with wavelet-transformed HFOs alone.
Our study demonstrated that by testing for wavelet-transformed HFOs, patients who would otherwise be denied surgery may receive a potential cure. Our study has used an effective research platform in electroencephalography whose results concur with those of other studies.\textsuperscript{4,5} We are interested in ictal HFOs because they have been revealed during intracranial recordings. Identifying the moment of seizure provides researchers with the strongest evidence of localisation and lateralisation. Surgery improves seizure outcome and is feasible in refractory epilepsy, and patient quality of life can be improved. This project may improve public awareness and institutional priority and in turn, benefit patients with epilepsy.

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**Ethical Approval**

Informed consent was obtained from each participant.

**Declaration**

The authors have no conflicts of interest to disclose.

**References**