

REVIEW

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High-frequency oscillations detected by electroencephalography as biomarkers to evaluate treatment outcome, mirror pathological severity and predict susceptibility to epilepsy

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Abstract

High-frequency oscillations (HFOs) in the electroencephalography (EEG) have been extensively investigated as a potential biomarker of epileptogenic zones. The understanding of the role of HFOs in epilepsy has been advanced considerably over the past decade, and the use of scalp EEG facilitates recordings of HFOs. HFOs were initially applied in large scale in epilepsy surgery and are now being utilized in other applications. In this review, we summarize applications of HFOs in 3 subtopics: (1) HFOs as biomarkers to evaluate epilepsy treatment outcome; (2) HFOs as biomarkers to measure seizure propensity; (3) HFOs as biomarkers to reflect the pathological severity of epilepsy. Nevertheless, knowledge regarding the above clinical applications of HFOs remains limited at present. Further validation through prospective studies is required for its reliable application in the clinical management of individual epileptic patients.

Keywords: High-frequency oscillations, Epilepsy, Electroencephalography, Treatment outcome, Seizure prediction, Pathology

Background

Epilepsy is a chronic neurological disorder characterized by recurrent episodes of spontaneous seizures, affecting nearly 1–2% of the population of the world [1]. Despite the overall favorable prognosis, only a few patients can achieve seizure freedom and epilepsy is still a high risk factor for premature death in the general population. Different clinical approaches including assessment of epilepsy treatment outcome, understanding of seizure susceptibility, and reflection of the severity of pathological injury collectively guide the selection of early intervention in epileptic patients. However, currently there

is a lack of biomarker that can be explicitly used for measuring epilepsy severity and activity. Thus, new biomarkers with defined pathophysiological predictions are urgently needed in clinical practice.

In the past decades, high-frequency oscillations (HFOs), i.e., brain electrical activities at frequencies above 80 Hz, have received much attention. In 1989, Huang and White recorded for the first time high-frequency activities (100–800 Hz) in a metrazol-induced epileptic rat model via subcutaneous needle electrodes [2]. Subsequently, Fisher et al. recorded high-frequency activities in five epileptic patients in 1992 using subdural grid electroencephalography (EEG) [3]. In-depth studies on the relationship between HFOs and epilepsy began in 1999, when recordings using microelectrodes in epileptic rat models and epileptic patients further investigated

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the mechanisms of HFOs and its relationship with the probable epileptogenic zone (EZ) [4]. Although currently there is no established standard of HFOs, it is generally accepted that HFOs are “spontaneous EEG events (> 80 Hz), having at least four oscillations with sinusoidal-like morphology in the filtered signal (>80Hz) with a root mean square amplitude increase of more than 5 times the standard deviation compared to background brain activity” [5]. There are three categories of HFOs based on frequency: ripples (R, 80–250 Hz), fast ripples (FR, 250–500 Hz), and very high-frequency oscillations (> 500 Hz) [6, 7]. HFOs can be detected by scalp electrodes as well as various other intracranial electrodes including microelectrodes with a surface of 0.0013–0.0016 mm² and macroelectrodes with a surface of 0.5–10.0 mm².

With subsequent maturity of the technology and more extensive studies in this area, HFOs in EEG are now considered as a potential marker of EZ or seizure onset zone (SOZ) [5, 8]. HFOs are not only detected interictally but can also apparently increase during the preictal or ictal periods [9, 10]. Since invasive intracranial EEG (iEEG) can overcome many physical limits of scalp EEG by recording signals directly from the brain tissue, most insightful findings of HFOs were derived from iEEG in patients with refractory epilepsy, as part of the preoperative evaluation [11]. The electrode contact of iEEG can either be on the cortical surface (electrocorticography, ECoG) or within the cortex and hippocampus. HFOs from ECoG are thought to be novel biomarkers for the localization of epileptic generator [12]. ECoG only detects EEG signals from gyrus surfaces, whereas stereo-electroencephalography (SEEG) is an invasive surgical procedure that enables more accurate neuroelectrophysiological monitoring of deep brain structures [13, 14]. HFOs detected by SEEG are used to identify brain areas from which epileptic seizures originate and enables pre-surgical evaluation [15, 16]. Nevertheless, the scope of iEEG application is greatly limited due to the risks and cost associated with the invasive surgery. In contrast, scalp EEG is widely accepted due to the safety and cost-effectiveness in monitoring the scalp activity of the brain. The recording of HFOs with technical development has unexpectedly revealed high frequencies in the ictal state on scalp EEG recordings [17, 18]. More recent studies have proposed that the scalp EEG can detect both ripples and FR [19–21]. Studies have shown that although having small cortical generators, low amplitudes (10–20 μV when measured on the brain surface) and submillimeter and millimeter-scale areas, HFOs are detectable on the scalp with a high signal-to-noise ratio [22, 23]. One additional key issue is that a higher spatial sampling density is necessary for both extracranial and intracranial HFO recordings [24–26]. Nonetheless, there are still

challenges for detection of scalp HFOs: simultaneous recordings of scalp and intracranial HFOs demonstrated that only 0.1% of intracranial HFOs are visible on scalp EEG recordings [22]. Over the last decade, the clinical applications of HFOs to evaluate epilepsy activity and severity have been investigated [27, 28]. In this review, we discuss the epileptic applications of HFOs by EEG, such as in assessment of treatment outcome, prediction of epileptic seizure and susceptibility to epilepsy, and reflection of pathological severity.

HFOs as a biomarker to evaluate treatment outcome of epilepsy

Evaluating the epilepsy treatment outcome could predict the likelihood of seizure occurrence, and thereby facilitates setting early appropriate interventions to reduce the magnitude and/or frequency of seizures and prevent poor outcomes. Numerous clinical studies and animal experiments using scalp EEG and iEEG have found a strong relationship between HFOs and treatment outcome epilepsy. A study performed simultaneous scalp EEG and iEEG recordings in epilepsy patients and concluded that the widespread HFOs are linked to a poor post-surgical outcome [29]. Evaluation of HFOs before severe seizure attacks enables timely clinical intervention, thereby reducing the seizure recurrence and improving therapy outcomes.

As for pharmacotherapy, either monotherapy (such as levetiracetam, lacosamide and vigabatrin) or mixed anti-epileptic drug (AED) can reduce HFOs [30–33]. In line with this, a study has reported that HFOs increase with reduction of mixed AEDs as do the seizures, while the spikes are relatively stable [34]. This suggests that HFOs are useful biomarkers for disease activity and more strongly linked to seizures than spikes.

As for surgery, surgical resection of HFO-generating areas led to favorable postoperative seizure freedom [35–37]. Wu et al. have reported that intra-operative FR detected in 80% of pediatric epilepsy cases is correlated with the outcome of epilepsy surgery, and complete removal of FR-containing cortex led to postoperative seizure freedom in pediatric patients with mostly extratemporal lesions [38]. Another prospective study in pediatric epilepsy patients showed that incomplete resection of FR-containing cortex predicts postoperative seizures [39]. A retrospective observational study of 123 patients who underwent focal cortical resection indicated that the coupling between high-frequency activities (HFA) and the following slow waves during interictal recording may be a potential predictor for postoperative seizure outcome [40]. Patients with drug-resistant neocortical epilepsy are often faced with greater barriers to localizing epileptogenic focus and making therapeutic plans than those

with mesial temporal lobe epilepsy (MTLE) [41]. By retrospectively analyzing ECoG recorded from 54 refractory focal epilepsy patients, van 't Klooster and coworkers identified that the specificity of the FR for outcome prediction is better than spikes, and that the post-resection FR may be the strongest predictor for recurrent seizures, especially in patients with a neocortical lesion [42]. In neocortical epilepsy, the resection of brain regions with higher HFO rates in either an interictal [3, 43] or an ictal phase [44, 45] results in post-surgical seizure-free outcomes. The potential value of interictal HFOs deserves special attention, as there is no need to record seizures, which is a time- and labor-consuming process that may increase the risk of complications following secondary generalization after lowering or withdrawal of AEDs.

Secondary epilepsy deriving from multiple clinical disorders with probably different underlying epileptogenic processes, is also related with HFOs in outcomes. Taking tuberous sclerosis complex (TSC) as an example, over 50% of patients with TSC suffer from refractory epilepsy, and epilepsy surgery is frequently used for TSC treatment [46]. TSC is a multisystemic neurocutaneous genetic condition with autosomal dominant inheritance [47]. A study has identified that resection of ictal HFOs can contribute to good surgical outcomes in children with refractory epilepsy secondary to TSC [48].

West syndrome is a severe form of early-onset infantile epilepsy with a high incidence and poor prognosis [49]. The progression and management of West syndrome has been hampered by the lack of reliable prognostic biomarkers until the report of its associations with HFOs both on scalp EEG and iEEG [11, 17, 50, 51]. Kobayashi et al. observed that the scalp HFO rate reduces after the adrenocorticotrophic hormone (ACTH) treatment in infants with hypsarrhythmia and West syndrome [52]. A retrospective study in children with West syndrome undergoing short-term drug treatment found that HFOs coupled to 2–3 Hz slow-wave activity increases the seizure incidence in non-refractory epileptic children, compared to those who were refractory [20]. This study also indicated that the HFO rate reduces with drug treatment but shows no difference between responders and non-responders. Iwatani et al. reported that the ictal HFOs on scalp EEG seen during spasms contribute to the identification of EZ in symptomatic West syndrome. In addition, the regions of the maximum augmentation of HFOs at 80–150 Hz are consistent with the neuroimaging findings in 4 children with symptomatic West syndrome, and two of them underwent resection of the area containing HFOs and thus achieved Engel class I [53]. Taken together, for West syndrome, the reduction of HFOs is significantly related to the improvement of treatment outcome, regardless of the medical or surgical

intervention. Similar findings have been obtained in a spectrum of pediatric disorders from benign childhood epilepsy with centrotemporal spikes (BECTS) to atypical benign partial epilepsy (ABPE), and to epilepsy with continuous spike-waves during slow-wave sleep (CSWS). A high ratio of ripples per spike has been confirmed in epilepsy with CSWS [21] and the percentage reduction of HFOs after corticosteroids therapy is indicative of a good prognosis [54, 55]. In ABPE, HFOs mirror disease severity and are observed to be more sensitive to methylprednisolone treatment than spikes [56]. Kobayashi et al. proposed that spike-related HFOs in idiopathic partial epilepsy (IPE), including a patient with epilepsy evolving from BECTS to ABPE with CSWS, may indicate whether or not the spikes have a propensity for aggravation [57]. Shibata et al. analyzed spike-associated HFA and its association with spike foci in the EEG of patients with BECTS and Panayiotopoulos syndrome (PS) and found that the proportion of spike-associated HFA was higher in BECTS than in PS [58].

Intractable epilepsy shows a negative impact on the cognitive functioning of children [59, 60]. To investigate the correlation between the number of HFOs and the cognitive outcome, a retrospective study was conducted to analyze the pre-resection ECoG and post-resection ECoG in 20 children with focal refractory epilepsy who received epilepsy surgery [61]. The result showed that HFOs could be used as a biomarker for prediction of cognitive outcome after epilepsy surgery. Similarly, in chronic temporal lobe epilepsy animal models, removal of the FR-generating areas led to the amelioration of cognitive deficits [62]. This evidence supports the predictive potential of HFOs for the cognitive outcome of epilepsy surgery.

In addition, a large number of studies has shown that HFOs correlate with the effect of antiepileptic treatment. It seems that HFOs respond to antiepileptic treatment in a stable and nonspecific manner regardless of the type of treatment. However, a study concluded that tailoring epilepsy surgery can be guided by FRs, but careful assessment of the ECoG is also required, as FR in functionally eloquent areas might not be pathologic [42]. Two meta-analyses based on the existing studies even suggested that the evidence for HFOs as a predictor of surgical outcome is rather weak [63, 64]. In a recent study, the pre-resection of FR-generating regions is not predictive of surgical outcome, while the absence of FR in post-resection ECoG predicted favorable operative outcome [65]. In addition, a prospective multicenter study conducted in chronic SEEG (2 centers) and intra-operative ECoG (1 center) patients showed that prediction is possible at the group rather than the individual level [66]. Consequently, unlike earlier studies, this study inferred that HFOs may

be less specific for epileptic tissues. So far, it remains unclear whether HFOs can be utilized to guide treatment or predict the clinical success or failure of therapy, which necessitates the need for more large-scale and longer follow-up studies to assess the reliability of HFOs as a biomarker for outcome prediction.

HFOs as a biomarker to predict seizures and susceptibility to epilepsy

An effective non-invasive biomarker for seizures could identify patients potentially prone to various threats including genetic predisposition and environmental factors [67]. It has been documented that HFOs play a critical role in the prediction of seizures [68].

HFOs could reflect a predisposition to epileptic seizures in animal models. Bragin et al. observed the occurrence of late spontaneous seizures from weeks to months after the detection of FR in three kainic acid-treated rats, and found that all the chronic epileptic rats with HFOs developed recurrent spontaneous seizures. The initial HFO activity was detected after status epilepticus where the first spontaneous seizure occurred, and as time passed, seizure frequency increased [69]. Subsequently, they recorded HFOs a lateral fluid percussion injury model within 2 weeks from the trauma and found that the intracranially recorded HFOs are linked with spontaneous seizure [70]. Besides, they defined a novel pattern of paroxysmal EEG activity as “repetitive HFOs and spikes”, which was proved to predict susceptibility to post-traumatic epilepsy [70, 71]. Levesque et al. found that the interictal spikes with FR in CA3 region are the best predictors for seizure occurrence in status epilepticus rats [30]. Overall, these findings suggest that seizure prediction is possible with the use of HFOs in animal models.

Studies have shown that HFOs occur before clinical spasticity and that clinical epileptic seizures may be triggered by HFOs [50]. In a prospective cohort of children with a first unprovoked seizure, HFOs can predict the development of chronic epilepsy, whereas epileptic spikes fail to determine if the patients would develop epilepsy [72]. Worrell et al. found that an increase in HFA within 20 min before the onset of neocortical seizure predict 62% of seizures in patients with neocortical epilepsy [73]. Subsequently, accumulating evidence has indicated variable changes in the HFO rate prior to seizure onset in focal epilepsy [74–77]. In addition, in pediatric drug-resistant focal epilepsy, the scalp HFO rate is correlated with seizure frequency and thus epilepsy severity, but not with spike rates, in the individual patient; and the higher the HFO rate, the higher the seizure frequency [78, 79]. These studies provide evidence of identifying periods of

increased seizure onset probability and clarifying mechanisms of seizure generation in epilepsy.

Focal cortical dysplasia (FCD) is a localized malformation of brain cortical development that causes epilepsy in nearly 30% of patients, and HFOs are generally found in FCD [80]. The HFO rate is higher in patients with FCD type II lesions than in those with type I lesions. The type II lesions are more likely to cause epilepsy with an earlier seizure onset and a greater seizure frequency [81]. Sato et al. analyzed the correlation between spike-related HFOs and post-spike slow-wave power in SOZ during both interictal and preictal periods in 10 pediatric patients with FCD type II. Their results suggest that the relative power reduction of post-spike slow waves to spike-related HFOs correlates with seizure initiation, therefore may contribute to seizure prediction [82].

The duration of medication in BECTS is difficult to determine in the clinical setting since long-term exposure to anticonvulsants may cause side effects such as attention deficits, aggressiveness, nervousness, and sleep disorders [83, 84], while no-treatment or premature discontinuation of treatment could induce seizures, injury or death [85]. Although spikes are being studied as a predictor for seizure attack in BECTS, they can remain detectable even years after the last seizure [50, 86]. A prospective study attempted to test spike ripples as a reliable biomarker to predict seizure risk and they ultimately found that ripples co-occurring with epileptiform discharges predict seizure risk in BECTS better than spikes, regardless of the medication status [87]. Another study showed that the absence of ripples on top of rolandic spikes predicts a likelihood of children to develop benign rolandic epilepsy rather than atypical rolandic epilepsy [79]. Such results provide further evidence for spike ripples as a noninvasive biomarker for predicting the seizure risk of BECTS and facilitating therapeutic stratification, medication guidance, and assessment of relapse risk.

To summarize, HFOs could be considered as a tool to predict seizure occurrence and susceptibility to epilepsy. These findings are inspiring and compelling but large-scale prospective trials are still required to understand the effectiveness of HFOs for the prediction of seizures and detection of epilepsy susceptibility.

HFOs as a biomarker to mirror pathological severity

HFOs can also reflect the severity of pathological injury. The pathological alterations linked with neuronal loss and synaptic reorganization may contribute to the generation of FR [88, 89]. Cepeda et al. have reported that enhanced GABAergic synaptic activity is correlated with interictal FR in the epileptic zone and hyperactivity of GABAergic interneurons is

observed in areas with HFOs, suggesting that GABAergic interneurons play a role in the generation of pathological HFOs [90, 91]. The above research all supports the correlation between HFOs and pathology. Generally, radiologically revealed lesions have a predictive value for the surgical outcome [92]. However, for some patients, even in the presence of pathology injury, the general imaging examination including computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) could not reveal any abnormalities, which hinders pre-operative evaluation. Fortunately, studies have determined a strong association between HFOs and radiological lesions such as severe hippocampal damage. HFOs have been recorded ipsilateral to the side of hippocampal sclerosis (HS) in patients with MTLE, and they do not propagate contralaterally in 10 of 11 (91%) patients. Accordingly, the ictal HFOs in the medial temporal lobe are direct electrophysiological evidence for HS [9]. A recent study in a MTLE model further suggested that changes in HFO generation, associated with progressive neuronal loss in the hippocampus, occur as the disease progresses [93]. The rate of interictal HFO has a negative correlation with the electrical stimulus thresholds, supporting the notion that hyperexcitability and HFOs may share common mechanisms [94, 95]. A subsequent study investigated the close relationship between ictal HFOs and hyperexcitability with regard to surgical outcomes. They found that related to cortical hyperexcitability, the proportion of ictal HFOs among resected channels is significantly higher in patients with Engel Class I/II outcomes than in those achieving III/IV outcomes. In addition, a significantly larger percentage of channels with ictal HFOs was found among channels with radiological lesions compared with those without radiological lesions ($P < 0.001$); likewise, the percentage of channels with ictal HFOs is higher among those meeting the condition of hyperexcitability than those that did not ($P < 0.001$) [96]. In addition, for other diseases such as FCD, the HFO rate not only varies with different pathologies but also helps define the extent of pathology in epileptogenic dysplastic tissues [80, 81].

Studies have validated the association between HFOs and epileptic networks [29, 97–100]. Fahoum et al. investigated the brain regions involved in HFOs by combining EEG and functional MRI, and concluded that a higher rate of epileptic ripples is related to a more active pathologic cortical-thalamocortical network [101]. From these findings it becomes evident that HFOs are a good indicator for the severity of pathological injury, which largely broadens its application spectrum.

Challenges in the application of HFOs as a clinical tool

HFOs however have not been widely applied in routine clinical practice [27]. There are several barriers that hinder the use of HFOs in clinical practice. First, the identification of HFOs is challenging. Currently, there is no universal definition of HFOs. Visual inspection of HFOs is still the gold standard, which is a very time-consuming process [102] and prone to subjectivity [103, 104] and poor reproducibility. To address this problem, several groups have developed automated HFO-detection algorithms, many of which have been confirmed with sufficient accuracy and increased processing rate [105]. Second, each channel is analyzed independently, either manually or through automated means [106]. This unbiased approach may induce an increased risk of mistaking non-brain electrical activity for HFOs, known as “false HFOs”. Removing muscle artifacts improves the specificity of HFOs to a certain extent [107, 108]. Third, how to distinguish physiological HFOs from pathological HFOs remains a conundrum [109]. Some studies have indicated that the pathophysiological HFOs are more likely to co-occur with epileptiform spikes, whereas pathological HFOs often occur without spikes or outside SOZ [110]. Besides, the pathophysiological HFOs are found to be coupled with different phases of sleep slow waves: they typically appear before the peak of negative half-waves of the sleep slow waves, while physiological HFOs frequently occur after this peak [111–114]. Moreover, they have different interactions with slow-wave activities: the spectral frequency bands of pathological HFOs are more likely to be higher than physiological HFOs [115]. In spite of the above difficulties, the evidence in support of the role of HFOs in activity and severity of epilepsy is steadily accruing (Table 1).

Conclusions

The present review summarizes current knowledge on the roles of HFOs in the activity and severity of epilepsy. Although pieces of evidence on this topic are still very limited, both iEEG and scalp EEG evidence points to the value of HFOs in assessing treatment outcome, measuring pathological severity and predicting susceptibility to epilepsy. Among these, the contribution of scalp HFOs to epilepsy is informative, but we cannot ignore the existing controversy on the reliability of scalp HFOs. Most of the current research on scalp EEG signals focuses on the international 10–20 system, which has shortcomings such as the low spatial and temporal resolution. With the emergence of dense-array EEG technologies, more accurate electrical source imaging has become available. Moreover, integrating

Table 1 Overview of studies correlating the post-surgical outcome with the removal of HFOs

References	Patients Type	Patient Population	No. of Patients	EEG methodology	HFOs measurement	Correlation
Ochi et al. [44]	Children	Intractable neocortical epilepsy	9	Subdural grids	Ictal R	R
Wu et al. [38]	Children	Drug-resistant epilepsy	24	Subdural grids /strips	Interictal FR	FR
Akiyama et al. [116]	Children	Drug-resistant epilepsy	28	Subdural/depth	Interictal R and FR	R and FR
Nariai et al. [50]	Children	Epileptic spasms	11	Subdural grids	Ictal R and FR	R
van Klink et al. [117]	All	Drug-resistant epilepsy	14	Subdural grids /strips	Interictal R and FR	FR
Cho et al. [43]	All	Drug-resistant epilepsy	15	Subdural/depth	Interictal R and FR	FR
van't Klooster et al. [42]	All	Drug-resistant epilepsy	54	Subdural grids /strips	Interictal FR	FR
Fedele et al. [35]	All	Drug-resistant epilepsy	54	Subdural grids/strips	Interictal R and FR	R and FR
Fedele et al. [118]	All	Drug-resistant focal epilepsy	20	Subdural grids /strips	Interictal R and FR	R and FR
Fedele et al. [36]	All	Drug-resistant epilepsy	9	Subdural grids/strips	Interictal FR	FR
van't Klooster et al. [65]	All	Drug-resistant epilepsy	54	Subdural grids/strips	Interictal R and FR	FR
Cuello-Oderiz et al. [119]	All	Focal cortical dysplasia	21	Depth	Interictal R and FR	R and FR
Boran et al. [25]	All	Drug-resistant epilepsy	22	Subdural grids/strips	Interictal FR	FR

HFOs High-frequency oscillations, EEG Electroencephalogram, R Ripples, FR Fast ripples

multi-modal neuroimaging data is warranted for greater clinical application. In the future, more technical and methodological advances for HFOs analysis and more high-quality prospective cohort studies and randomized controlled trials are needed to draw firmer conclusions in this field.

Abbreviations

ABPE: Atypical benign partial epilepsy; ACTH: Adrenocorticotropic hormone; AED: Anti-epileptic drug; BECTS: Benign childhood epilepsy with centrotemporal spikes; CSWS: Continuous spike-waves during slow-wave sleep; CT: Computed tomography; EEG: Electroencephalography; ECoG: Electrocorticography; EZ: Epileptogenic zone; FCD: Focal cortical dysplasia; FR: Fast ripples; HFA: High-frequency activities; HFOs: High-frequency oscillations; HS: Hippocampal sclerosis; iEEG: Intracranial EEG; IPE: Idiopathic partial epilepsy; MRI: Magnetic resonance imaging; MTL: Mesial temporal lobe epilepsy; PET: Positron emission tomography; PS: Panayiotopoulos syndrome; R: Ripples; SEEG: Stereo-electroencephalography; SOZ: Seizure onset zone; TSC: Tuberous sclerosis complex.

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Authors' contributions

QW conceived, designed, and supervised the study. YQS drafted the manuscript. GPR, JCR, and QW critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Declarations

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Consent for publication

All authors gave consent to publication of this review.

Competing interests

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