

The Utility of Quantitative EEG in Detecting Delayed Cerebral Ischemia After Aneurysmal Subarachnoid Hemorrhage

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Summary: In this review, we discuss the utility of quantitative EEG parameters for the detection of delayed cerebral ischemia (DCI) after aneurysmal subarachnoid hemorrhage in the context of the complex pathophysiology of DCI and the limitations of current diagnostic methods. Because of the multifactorial pathophysiology of DCI, methodologies solely assessing blood vessel narrowing (vasospasm) are insufficient to detect all DCI. Quantitative EEG has facilitated the exploration of EEG as a diagnostic modality of DCI. Multiple quantitative EEG parameters such as alpha power, relative alpha variability, and alpha/delta ratio show reliable detection of DCI in multiple studies. Recent studies on

epileptiform abnormalities suggest that their potential for the detection of DCI. Quantitative EEG is a promising, continuous, noninvasive, monitoring modality of DCI implementable in daily practice. Future work should validate these parameters in larger populations, facilitated by the development of automated detection algorithms and multimodal data integration.

Key Words: Quantitative electroencephalography, EEG, Delayed cerebral ischemia, Subarachnoid hemorrhage, Transcranial Doppler, Vasospasm.

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Aneurysmal subarachnoid hemorrhage (SAH) accounts for only 3% of all stroke types but carries high morbidity and mortality.¹ Delayed cerebral ischemia (DCI) occurs in 33% to 50% of SAH patients with the peak incidence between 3 to 14 days after ictus.^{2–4} Delayed cerebral ischemia increases the risk of poor long-term outcomes, including decreased instrumental activities of daily living, cognitive deficits, and reduced quality of life.⁴ Delayed cerebral ischemia is preventable with timely intervention only if it is detected before clinical deterioration or radiographic infarction. Although frequent clinical examinations are important for detecting new neurological deficits indicating ischemia, their utility is limited in high-grade SAH patients who have the highest risk of DCI. Furthermore, SAH is associated with multiple complications, such as rebleeding, seizures, and hydrocephalus, which can confound clinical examinations. Hence, much effort has focused on discovering accurate tests and parameters to predict impending DCI. Sonographic or radiographic modalities, which have varying degrees of accuracy, display changes in blood vessel caliber or blood flow and are the accepted standard of care measures for DCI surveillance. However, these studies can only be performed once or twice a day at best. Given the need for a diagnostic modality with the ability to provide real-time, noninvasive monitoring for DCI, continuous EEG (cEEG) has emerged as a valuable tool in assessing risk of impending DCI.

DEFINITION OF DCI

Historically, several terms have been used to describe DCI, including delayed ischemic neurological deficits, symptomatic vasospasm, secondary cerebral ischemia, and cerebral infarction. To address confusion generated from these various terms and inconsistency in clinical study definitions, a multidisciplinary expert group proposed a unified definition of DCI as cerebral infarction identified on CT or MRI or proven at autopsy after exclusion of procedure-related infarctions or the new occurrence of focal neurological impairment or a decrease of at least two points on the Glasgow Coma Scale, with or without radiological findings that cannot be attributed to other causes by means of clinical assessment, CT, or MRI scanning of the brain and appropriate laboratory studies.⁵ This definition combines both clinical and radiographic criteria for DCI, thereby capturing the full breadth of patients who experience this complication. To provide clarity in our terminology for this review, we will be using the term “DCI” as defined here, whereas any reference to observations limited to blood vessel narrowing assessed by radiographic or sonographic imaging will be referred to as “vasospasm.”

PATHOPHYSIOLOGY OF DCI

The exact pathophysiology of DCI remains incompletely understood, contributing to the varied descriptions of DCI above. Conventionally, vasospasm was believed to be the sole cause of DCI, but accruing evidence suggests that DCI is secondary to other phenomena such as cortical spreading depolarization (CSD), impaired cerebral autoregulation, microcirculatory dysfunction, microthrombosis, and neuroinflammation.^{6–9}

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Vasospasm

In 1949, Robertson¹⁰ first suggested temporary vasospasm as the cause of infarction in an area of the brain remote from the ruptured aneurysm, an observation which has since been supported by both radiographic and sonographic evidence of vasospasm after SAH.^{11–15} Current diagnostics and therapeutic strategies, such as endovascular treatment, are largely targeted at reducing vasospasm to reduce DCI and poor functional outcome.¹⁶

However, the causal link between vasospasm and DCI has been questioned because of observations that DCI can occur without vasospasm and not all patients with vasospasm develop DCI.^{17–19} Failed treatment trials also call into question this relationship, such as recent trial failures of clazosentan, an endothelin-receptor antagonist, which induced significant reduction of moderate-to-severe vasospasm from 66% to 23% without changing the incidence of DCI ($P = 0.315$).^{20,21} This conflicting data allude to more complex mechanisms of DCI not ascribed to vasospasm alone.

Cortical Spreading Depolarization

Cortical spreading depolarization is a wave of depolarization spreading across the cortex propagating over minutes.²² This phenomenon has received more recent attention as a potential contributory mechanism of DCI because its presence has been observed in cases of DCI without vasospasm.²³ Drier et al.²⁴ used electrocorticography to assess the presence of CSD in 18 SAH patients and noted that DCI occurred in a time-locked fashion to CSD in 13 patients. Also, CSD is proposed to cause DCI via increased metabolic demand during the CSD at an unsustainable level in the injured brain state of SAH, thereby directly causing neuronal injury and death.^{25,26} Simultaneously, persistent CSD triggered by insults to the brain, such as SAH, can induce vasoconstriction in contradiction to the normal response of vasodilation upon increased metabolism, which precipitates ischemia and accelerates the vicious cycle of prolonged CSD causing flow-metabolism uncoupling and energy failure, making it difficult to recover from CSD to the normal state.^{27,28} Moreover, the persistent excitation results in increased extracellular glutamate and the subsequent activation of NMDA-receptors, which can lead to excitotoxic injury in energy-compromised neurons.²⁹ The trigger for CSD after SAH remains unclear. However, theories about relative ischemia and decreased extracellular nitric oxide levels suggest that in some cases, there is a potential interplay by which vasospasm may induce CSD and increase the risk of DCI.^{30,31} Although CSD is typically detected using electrocorticography, cEEG could prove useful. One study of CSD in traumatic brain injury patients with simultaneous electrocorticography and cEEG recording found that spreading depolarizations induced a detachable spread of depression on the order of minutes to hours.³² However, scalp EEG is limited because it is generally only sensitive to clustered spreading depolarizations.³³ Future research is needed to better characterize scalp EEG signatures of CSD after SAH.

Impaired Cerebral Autoregulation and Microcirculatory Dysfunction

Cerebral autoregulation is a mechanism to regulate regional cerebral blood flow (CBF) with cerebral vasoconstriction and

vasodilation to maintain constant cerebral perfusion pressure under different physiologic conditions. Impaired cerebral autoregulation has been observed in SAH and may contribute to the development of DCI.^{34,35} Patients who deviated from autoregulation-based blood pressure targets had worse functional outcomes at 90 days compared with those who did not, suggesting that the disruption of cerebral autoregulation contributes to postbleed complications.³⁶ Previous studies showed that vasospasm itself does not always result in reduced regional CBF.³⁷ It was postulated that impaired cerebral autoregulation in microvasculature distal to the restricted segments of vasospasm plays a crucial role in failure to preserve regional CBF, leading to the development of DCI.^{7,38} Some studies proposed that an independent process of microvascular spasm and dysfunction, which is perpetuated by CSD in SAH with or without proximal vasospasm may cause cerebral infarction.^{39,40} One study found that patients who develop DCI and vasospasm have distinct autoregulation patterns from those who develop only DCI, implying that impaired autoregulation of cerebral blood flow might be an independent pathological process that can lead to DCI.⁴¹

Impaired regional CBF was investigated in relation to microcirculatory dysfunction. Although transcranial Doppler (TCD) or conventional angiogram can visualize large cerebral vessels, they are poor at detecting changes in microcirculation. Abnormal measures of microcirculatory function were observed in DCI irrespective of vasospasm.⁴² This impaired microcirculation in DCI is believed to be related to endothelial dysfunction in SAH causing microthrombi, which can lead to infarction.^{42–45}

Neuroinflammation

Recently, inflammation-based mechanisms of DCI have gained attention. One study implicated the role of matricellular proteins (MCPs) periostin, osteopontin, and galectin-3 in DCI; machine learning models incorporating plasma levels of these MCPs achieved approximately 90% prediction accuracy for DCI.⁴⁶ As components of the extracellular matrix, MCPs affect vascular permeability and cell death, thereby contributing to other dysfunctional processes such as microcirculatory dysfunction and neuroinflammation.⁴⁶ Overall, these results indicate that MCPs may comprise part of DCI pathology.

Several inflammatory biomarkers are elevated after SAH in patients who develop DCI.^{30,47,48} For example, the sulfonylurea receptor 1–transient receptor potential melastatin 4 channel is upregulated after SAH, and inhibition of this receptor in rats reduces neuroinflammation and cognitive impairment after SAH.^{49,50} Some inflammatory biomarkers, such as soluble growth stimulation expressed gene 2, can independently predict DCI.^{51,52} Notably, stimulation expressed gene 2 is linked to new epileptiform abnormalities (EAs) after SAH, making cEEG a useful tool to detect inflammation and predict DCI.⁵³ Inflammation can also interact with thrombosis to create a positive feedback loop wherein a pro-inflammatory state can induce the formation of microthrombi and vice versa.⁵⁴ Altogether, these results suggest an inflammatory pathology underlying DCI although they do little to elucidate the precise mechanism.

The above evidence suggests that DCI has multifactorial pathophysiology (Fig. 1).⁵⁵ Therefore, diagnostic tools designed

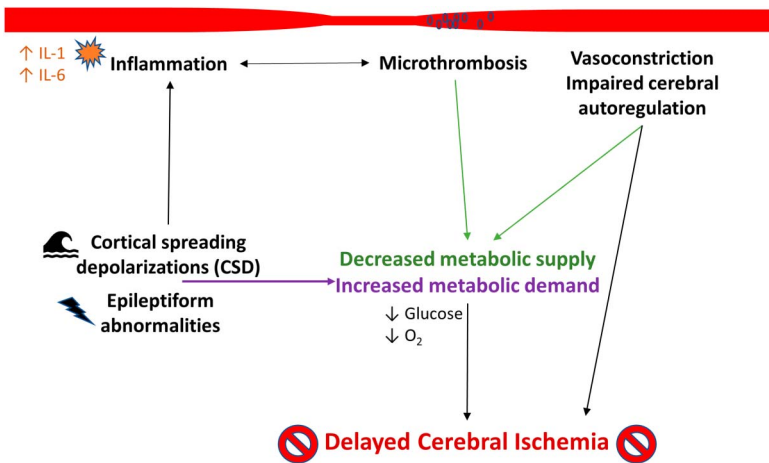


FIG. 1. Multifactorial pathophysiology of delayed cerebral ischemia. After aneurysmal subarachnoid hemorrhage, delayed cerebral ischemia can occur as a result of multifactorial pathophysiology. Vasospasm, impaired cerebral autoregulation and microemboli, which can form as a result of a proinflammatory, hypercoagulable state after aneurysm rupture, contribute to decreased metabolic supply. Cortical spreading depressions and epileptiform abnormalities can lead to an increase in metabolic demand. This metabolic supply-demand mismatch can ultimately lead to the development of delayed cerebral ischemia.

to detect vasospasm alone are insufficient to capture all cases of DCI, necessitating the development of novel diagnostic methods that directly assess known DCI contributors.

TCD FOR MONITORING VASOSPASM

Despite the emergence of other mechanisms of DCI, vasospasm is still the best understood mechanism contributing to DCI, and its detection and treatment are critical in reducing the devastating consequences of DCI. Thus, multiple modalities are used to screen for vasospasm including TCD, CT, MR angiography, CT perfusion, and catheter-based digital subtraction angiography. Although digital subtraction angiography remains the gold standard for detecting vasospasm,⁵⁶ TCD is the most commonly used diagnostic tool for monitoring vasospasm as recommended in 2012 by the American Heart Association and American Stroke Association. Support for using TCDs is based on class IIa/level B evidence because it provides a rapid, noninvasive, and portable modality without radiation exposure.⁵⁷

TCD Parameters

Introduced in 1982, TCD detects differences in frequency between emitted ultrasonic waves and the reflected echoes, which are proportional to the velocity of a moving object.⁵⁸ Assuming that CBF is laminar and constant, according to the continuity equation, the velocity of blood flow and the area of the blood vessel are in inverse relationship, and thus, the increased speed of blood flow can reflect a narrowed blood vessel diameter such as seen in vasospasm.^{59,60} Several different parameters of TCD are used for monitoring vasospasm, including mean flow velocity (MFV), pulsatility index, and the Lindegaard ratio. Mean flow velocity is measured in the bilateral middle, anterior, and posterior cerebral arteries, internal carotid arteries as well as the basilar artery; its increased value can be a surrogate marker of vascular narrowing.⁶¹ Pulsatility index is calculated with peak systolic velocity and end-diastolic velocity to assess distal vascular resistance, and a low value can reflect dilated arteries distal to the narrowed segment of vasospasm.⁶² The caveat in assessing the

diameter of the blood vessel with velocity is the assumption of constant CBF; in case of hyperemia, MFV can be elevated without changes of the diameter. Lindegaard ratio, a ratio of MFVs in middle cerebral artery and internal carotid artery, helps to differentiate between hemodynamic changes and narrowed blood vessels in the setting of high velocity; Lindegaard ratio of <3 indicates hyperdynamic status, whereas Lindegaard ratio of >3 is more likely to represent vasospasm.^{61,63}

Limitations of TCD

Transcranial Doppler does not detect vasospasm equally for all blood vessels and is known for low sensitivity in detecting anterior cerebral artery or posterior cerebral artery vasospasm.⁶¹ Even for middle cerebral artery vasospasm, accuracy fluctuates depending on the parameter threshold; only for the range of MFV of ≤ 120 or ≥ 200 cm/second did it show reliable predictive values.^{64,65} Although Lindegaard ratio is used to differentiate hyperemia and vasospasm, it is common that both states coexist, and its interpretation can be affected by various clinical factors such as blood pressure.⁶⁶ Additionally, TCD is highly dependent on the manual skills of the operator to insonate the maximal velocity signals. Anatomical variations of patients' bony anatomy can limit insonation because of poor acoustic windows.⁶⁷ Most importantly, even at the most resource-rich hospitals, TCDs are often done only once or twice a day (with guidelines recommending only every other day monitoring), thereby limiting assessment of vasospasm to the time of day performed. With these limitations and the increased recognition that vasospasm is only one of the contributors to DCI, there is broad interest in exploring other tools, which circumvent these limitations.

EEG AND CEREBRAL ISCHEMIA

Since the advent of scalp EEG, multiple studies have tried to identify unique patterns that reflect cerebral ischemia. Normal human CBF is estimated to be > 50 to 54 mL per 100 g of brain tissue per minute.⁶⁸ Early research observed the correlation between EEG changes and cerebral ischemia upon clamping the

carotid artery during carotid endarterectomy.^{69,70} These studies noted abnormal EEG activity at CBF of <17 to 18 mL/100 g/minute and isoelectricity with a further decrease of CBF to <10 to 12 mL per 100g/minute. As CBF progresses from normal to the range of anoxia, EEG showed a spectrum of gradual changes including emergence of delta activity and suppression of fast alpha and beta activities depending on the duration of the insult^{70,71} (Fig. 2). Subsequent studies using positron emission topography and MRI revealed that the CBF threshold for permanent infarction was around 8 mL/100g per minute albeit dependent on the duration of decreased CBF.^{72,73} Therefore, based on the observed EEG alterations during carotid endarterectomy, gradual predominance of slow activities along with disappearance of fast activities reliably indicates early cerebral ischemia.

Emergence of Quantitative EEG

Although several studies reliably show notable EEG patterns associated with cerebral ischemia, it is challenging to use EEG for prolonged periods in real time. Furthermore, interpretation requires specific training, and subtle changes can be missed with visual inspection alone.⁷⁴ Therefore, quantitative EEG (qEEG) has been pursued as a time-saving method by which to process and display various trends calculated from the EEG signal. Dietsch first attempted to perform qEEG with Fourier analysis in 1932, but it was not until the widespread use of digital EEG and the invention of the fast Fourier transformation in 1965 that raw EEG data could be compressed into a density spectral array.⁷⁵ Since then, multiple qEEG parameters have been developed, such as spectrograms, asymmetry, and power band assessments.

EEG and DCI

Reports of EEG changes in relation to DCI after SAH were first published in the 1970s.^{76,77} The emergence of qEEG and the advances of commercial software facilitate our ability to define features of EEG associated with DCI (Table 1).

THE EEG/qEEG PARAMETERS RELATED TO DCI

qEEG Absolute Power Parameters

Total Power

Innovative work in the early 1990s showed that total power, a summation of all frequency band powers (1–30 Hz in this study), was well-correlated (100% sensitivity) with clinical and radiographic changes in all grades of SAH; a decrease in total power confirmed cerebral ischemia.⁷⁸ Subsequent studies have not replicated these findings, although differing research methodologies, including varying number of electrodes and SAH severity, may have impacted the results.^{79,80}

Alpha Power

In addition to total power, power of the alpha frequency band (variably defined as 8–12, 8–12.5, or 8–13 Hz) has been explored in multiple studies.^{79,80,81} In one study, a decrease in alpha power was the strongest predictor of vasospasm (optimal cutoff 40%, area under the curve [AUC] = 0.66; Se = 89%; Sp = 77%).⁸² Similarly, Rots et al.⁸⁰ showed a decrease in alpha power as a distinct EEG feature in DCI ($P = 0.008$). Others have confirmed these associations and have gone on to show that a decrease in daily alpha power can precede clinical deterioration by more than 24 hours among assessed parameters, including focal slowing, decreasing alpha/delta ratio, and EAs.⁸³

Delta and Theta Power/Focal Slowing

Early observations of increased slowing associated with progressive cerebral ischemia increased attention to these parameters in DCI. Parkes and James⁸⁴ evaluated slowing on raw EEG and noted a significant increase in theta power with vasospasm ($P < 0.02$). However, a later study reported a *reduction* in theta power similar to alpha power decreases observed in DCI patients.⁸² Although the utility of theta power in DCI prediction is unclear, delta power, and especially alpha/delta ratio as discussed below,

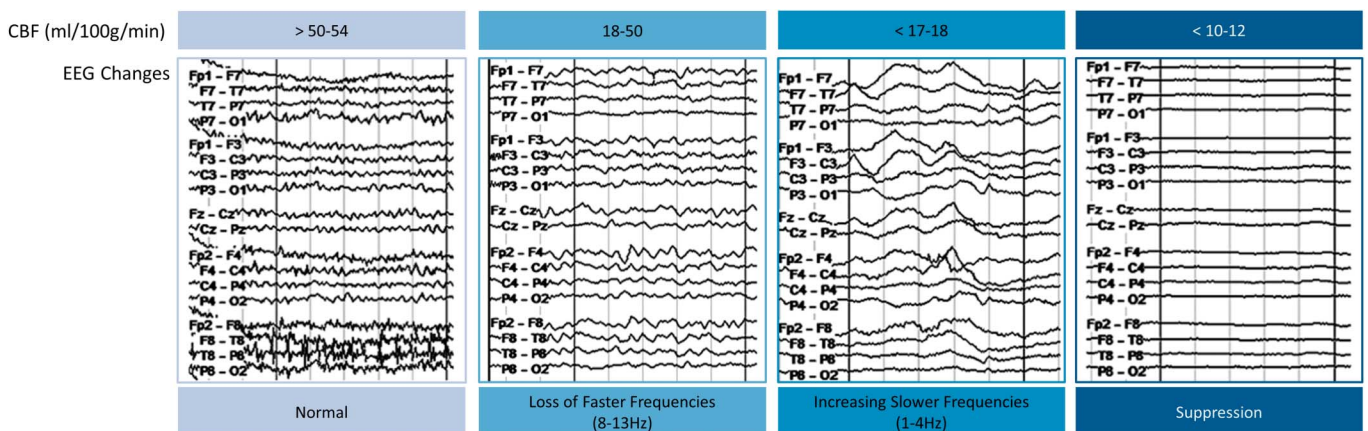


FIG. 2. The changes of EEG activities in relation to the cerebral blood flow (CBF, mL/100 g/minute). As CBF decreases from the normal threshold of 50 to 54 mL/100 g/minute, fast activities are lost, whereas slow activities become more prominent. If CBF is reduced below 10 to 12 mL/100 g/minute, EEG becomes nearly isoelectric.

TABLE 1. Summary of Original Studies on the Features of Raw EEG or qEEG

	Study Type	No. of Vasospasm or DCI/Total N	SAH Grade	EEG Methods	EEG/qEEG Features
Parkes and James ⁸⁴	Prospective	6/13 angiographic or clinical	All	8-channel raw EEG	Increases in the percent time of theta and delta activity
Rivierez et al. ⁹⁴	Retrospective	104/151 angiographic	Fisher 1-3	8-channel raw EEG	Prognostic values of localized delta wave, delta diffuse wave, "axial bursts"
Labar et al. ⁷⁸	Prospective	8/11 clinical or radiographic	H-H 1-4	2-channel qEEG	Decreases in the total power
Vespa et al. ⁸⁴	Prospective	19/32 angiographic or sonographic	All	8 electrodes, 10-20 system, qEEG	Decreases in RAV
Claassen et al. ⁷⁹	Prospective	9/34 angiographic, clinical, or radiographic	H-H 4-5	F3-C3 and F4-C4, or Fp1-F3 and Fp2-F4, or F7-T3 and F8-T4 for the anterior circulation, P3-O1 and P4-O2, or T5-O1 and T6-O2 for the posterior circulation	Decreases in the delta/total power ratio
Rathakrishnan et al. ⁸¹	Prospective	8/12 clinical or radiographic	All H-H, mFS 3-4	20 electrodes, 10-20 system, qEEG; analysis restricted to anterior quadrants	Composite alpha index
Gollwitzer et al. ⁸²	Prospective	6/12 clinical or radiographic	All	10 electrodes, 10-20 system, qEEG	Decreases in the alpha and theta powers
Rots et al. ⁸⁰	Prospective	11/21 clinical or radiographic	All	8 electrodes, 10-20 system, qEEG	Decreases in either ADR, alpha power, alpha variability, combination of ADR and alpha variability
Kim et al. ⁸⁸	Retrospective	53/124 clinical or radiographic	H-H 4-5, Fisher 3	10-20 system, qEEG	Late onset of any type of IICAs except GRDA
Rosenthal et al. ⁸³	Prospective	52/103 clinical or radiographic	H-H 4-5, mFS 3-4	10-20 system, qEEG	Worsening focal slowing, ADR, or RAV
Balança et al. ⁸⁷	Retrospective	9/15 radiographic	H-H or WFNS 4-5	10-20 system, qEEG	Decreases in A/T/D

ADR, alpha/delta ratio; A/T/D, alpha-theta/delta ratio; DCI, delayed cerebral ischemia; GRDA, generalized rhythmic delta activity; IIC, ictal-interictal continuum; mFS, modified Fisher scale; qEEG, quantitative EEG; RAV, relative alpha variability; SAH, subarachnoid hemorrhage; WFNS, World Federation of Neurosurgical Societies grading.

show a strong correlation with DCI ($P = 0.003$).⁷⁹ A recent study combining delta and theta powers in the definition of focal slowing showed a positive trend of focal slowing on DCI prediction, but this did not reach statistical significance.⁸³ Thus, although there is some suggestion that *absolute* measures of low frequency bands are associated with DCI, their utility is mixed, emphasizing the potential importance of assessing relative changes in the power of each frequency band.

qEEG Relative Power Parameters

Relative Alpha Variability

Relative alpha variability (RAV), defined as the percentage of 6 to 14 Hz over the total 1 to 20 Hz frequency, is another qEEG feature found to change preceding or concomitant to vasospasm after SAH.⁸⁵ In this first study, all patients who were found to develop vasospasm on TCD or angiogram (19 out of 32) showed decreased RAV around the time of vasospasm. Moreover, for 10 of 19 patients, it was detected more than two days before vasospasm. Similarly, Rots et al.⁸⁰ showed that decrease in RAV (8–12.5/1–30 Hz) strongly predicted DCI up to 7 hours before clinical or radiographic changes occurred, especially involving all eight studied patients with the cutoff value of 38%. This close association was upheld in a study performed exclusively for high-grade SAH patients ($P = 0.004$).⁷⁹ In a recent study assessing the diagnostic accuracy of EEG for the detection of DCI, a decrease in RAV was found to have the lowest false-positive rate of 2% and highest odds ratio (36.7 [4.70–286.11]; $P < 0.01$) among assessed parameters, including focal slowing, decreasing alpha/delta ratio, and EAs.⁸³

Alpha/Delta Ratio

Alpha/delta ratio (ADR) is one of the most common parameters assessed for the early detection of DCI combining the observations of a decrease in alpha and an increase in delta power as a reflection of DCI. A prior study shows the strongest association of ADR both globally and in affected territories with DCI (AUC = 0.83; $P < 0.0001$) for multiple EEG measures, including those mentioned in the preceding sections.⁷⁹ Subsequent studies with different methodologies support the correlation between a decrease in ADR and DCI but with varying sensitivity.^{80,82,83} A recent meta-analysis of five studies shows moderate correlation of ADR with DCI (AUC = 0.84; Se = 0.83; Sp = 0.74).⁸⁶ An example of ADR reduction during DCI is illustrated in Fig. 3.

Alpha-Theta/Delta Ratio

Most recently, alpha-theta/delta ratio was evaluated as an indicator of DCI in high-grade SAH.⁸⁷ The potential relation of alpha-theta/delta ratio with DCI was postulated from the previous reports on the association of decreases in ADR and theta power with DCI.^{79,82} In a small study by Balança et al.,⁸⁷ a transient decrease in alpha-theta/delta ratio was noted even in patients without DCI. However, prolonged decrease for the minimum of 3.7 and 1.4 hours with cutoff values of 30 and 50%, respectively, showed the best prediction for DCI (AUC = 0.94; Se = 1; Sp = 0.83). Moreover, in six of nine patients with confirmed cerebral

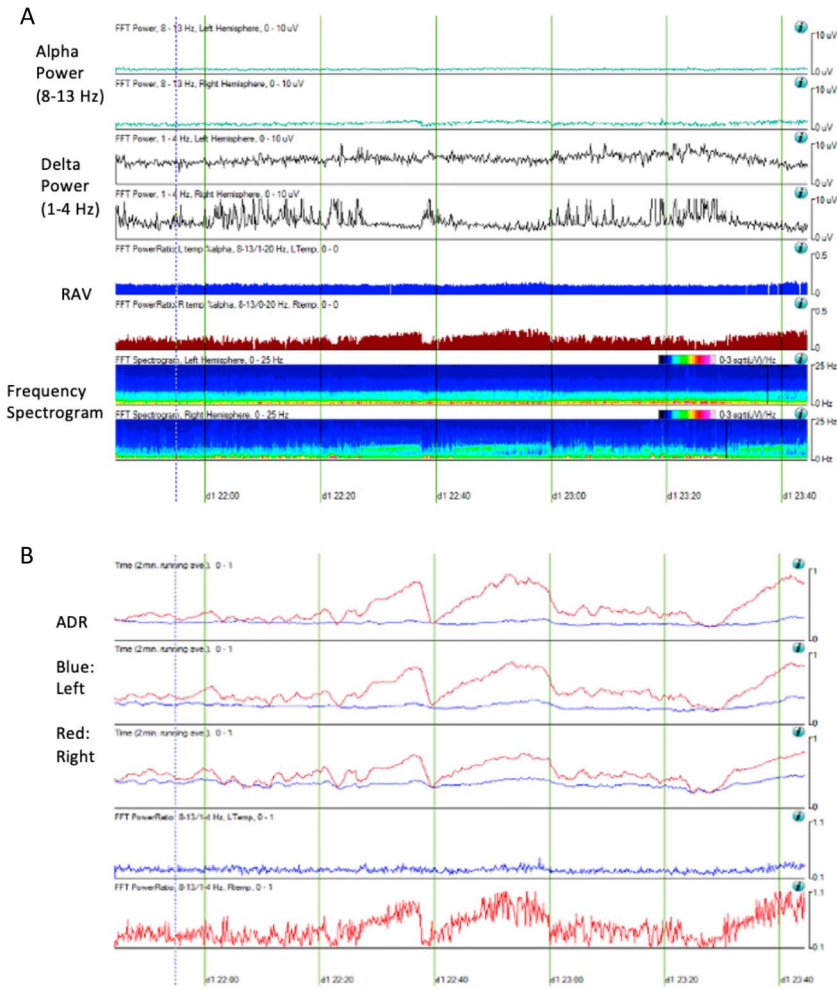


FIG. 3. Quantitative EEG parameters of a 57-year-old woman at the time of delayed cerebral ischemia who presented with subarachnoid hemorrhage of Hunt Hess grade 3 and modified Fisher scale 3. She developed vasospasm in the left middle meningeal artery on postbleed day 3. The trends displayed above were generated via Persyst software version 13 (Persyst Development Corporation, Prescott, AZ). Alpha power is decreased in the left hemisphere compared with the right hemisphere, whereas delta power is increased in the left hemisphere. The left temporal lobe shows poor relative alpha variability (RAV), but the right temporal lobe maintains good RAV (A). Alpha/delta ratio (ADR) is decreased in the left temporal lobe compared with the right temporal lobe (B).

infarction, a decrease in alpha-theta/delta ratio was noted in the in the same region of infarction at least one day earlier.

Other

Epileptiform Abnormalities

Most studies to date have focused on changes in background activity, but more recently investigators have begun to explore the relationship between DCI and EAs, including seizure, sporadic epileptiform discharge, and periodic/rhythmic activity.⁸⁸ All abnormal activities except seizure and generalized rhythmic delta activity showed statistically higher cumulative incidence in the DCI group compared with the non-DCI group for each abnormal activity. Seizure was also found to occur more frequently in patients with DCI, but presumably, it did not reach statistical significance because of the small number, 7 of 124 combining both groups. The study further investigated the temporal association of EAs with DCI. Most abnormalities occurred before the development of DCI, thereby suggesting the potential of EAs to predict DCI. In exploring the predictive value of all types of EAs, except seizure, new or increasing EAs were a strong predictor of impending DCI

(63.5%).⁸³ The presence of *either* EA or abnormal background activity were even more predictive of DCI (96.2% vs. 19.6%; DCI vs. no DCI; odds ratio = 102.5; 95% confidence interval = 21.3–494; $P < 0.01$).⁸³

Combination of Multiple Parameters

Some groups assessed the composite measures of the suggested parameters as a marker for DCI. Rots et al.⁸⁰ confirmed the findings of the prior studies using the ADR and RAV to predict DCI (AUC = 0.90 and 0.73, respectively). The receiver operating characteristic curve of these two parameters combined resulted in better performance (AUC = 0.92). Another study assessed the product of mean alpha power and its SD (composite alpha index).⁸¹ This study showed that changes in composite alpha index were responsive to intravenous milrinone, a phosphodiesterase 3 inhibitor. Composite alpha index increased with milrinone initiation and maintenance, whereas a decrease was observed during weaning and discontinuation. Rosenthal et al.⁸³ reported that combining new focal slowing, decreased ADR, and decreased RAV predicted DCI in 63.5% of cases. These studies suggest that multiparameter qEEG may improve predictive power of DCI.⁸³

DISCUSSION

Quantitative EEG is a valuable modality for monitoring DCI because it addresses the limitations of conventional tools, such as TCD or digital subtraction angiography. It provides noninvasive, real-time, continuous assessment of brain activity and requires a relatively shortened time for review compared with raw EEG assessment. With increasing availability of software capable of calculating these qEEG features in real time, there is great clinical potential for the timely treatment of DCI using this technology. It may even be used as a screening tool to specifically enroll patients with high-risk qEEG features in clinical trials testing novel therapies to mitigate and prevent DCI.³³

However, there are still gaps limiting its widespread utilization. Although the above studies show the value of various qEEG parameters in predicting DCI, many of these studies use a limited number of patients with various definitions of DCI. Thus, these features must be validated as reliable markers on a larger scale under the unified definition of DCI. Moreover, the accuracy of the parameters has yet to be studied based on the location of ischemia or the involved vascular territories.

Constructing a DCI management algorithm with qEEG for daily clinical practice renders significant logistical challenges even if the qEEG parameters indicating DCI are validated. The interpretation of those parameters still necessitates real-time individual inspection in the context of the changes in raw EEG by neurophysiologists specially trained for reviewing qEEG and the recorded parameters. Therefore, an automated detection alarm system using these qEEG parameters should be developed for the widespread use of qEEG, sparing a continuous review of qEEG by an expert but still enabling real-time detection of DCI. However, these measures can be confounded by other concurrent pathologic states, such as high intracranial pressure, hydrocephalus, surgery, or medications and thus must be contextualized. Furthermore, because of the prevalence of artifacts in the intensive care unit, automated calculation of these qEEG features without a priori selection of artifact-free segments of data or manual review by trained neurophysiologists is challenging for fully automated DCI detection algorithms.⁸⁹ This limitation was demonstrated in a study attempting to automate an algorithm for DCI detection using ADR and RAV qEEG parameters.⁹⁰ They found suboptimal sensitivity and specificity with significant drop-offs in either parameter depending on the chosen threshold of ADR or RAV changes. Thus, further work needs to be done to improve automated calculations in combination with artifact reduction algorithms. Designing a multi-feature algorithm based on all qEEG features mentioned above including the incorporation of epileptiform activity is the next step in optimizing a DCI prediction algorithm that can be clinically implemented.

A multimodal approach, incorporating TCDs along with qEEG features may improve upon the performance of either diagnostic tool alone. Although TCD was used as a modality to confirm vasospasm in a few previous studies, the predictive value of combining TCD and qEEG for DCI detection has not been studied. Newer technologies, such as near-infrared spectroscopy, may serve as another modality by which to improve DCI prediction. Near-infrared spectroscopy is another noninvasive,

real-time, bedside modality for monitoring regional cerebral ischemia. It uses a characteristic of oxyhemoglobin and deoxyhemoglobin absorbing a specific spectrum of light wavelengths for the detection of tissue oxygenation and has been used mainly in vascular and cardiac surgeries.⁹¹ Its use is technically limited to the frontal areas of the brain and is a technology not yet widely available at many institutions with controversy on its utility and unestablished protocols. However, a few small studies have shown that near-infrared spectroscopy may serve as a useful tool in DCI detection.^{92,93} Thus, incorporating TCD and newer monitoring modalities, such as near-infrared spectroscopy, with qEEG may improve DCI prediction.

Ultimately, qEEG is a promising modality implementable in daily practice allowing real-time, noninvasive monitoring with global coverage across the brain. It simultaneously has the potential benefit of cost and time efficiency, especially with the future development of automated systems, which could facilitate prompt detection and early intervention on DCI. Clinical trials testing novel interventions specifically targeted at those with high-risk EEG signatures can then be developed to improve patient outcomes in SAH.

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