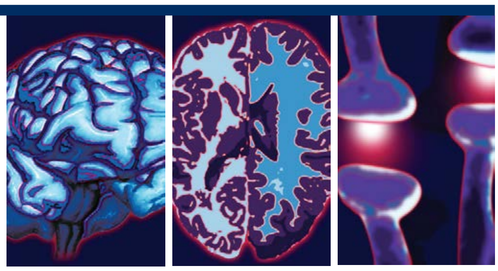

The Prognostic Value of Quantitative Electroencephalography Combined with Transcranial Doppler in Patients with Ischemic Stroke in Neurological Intensive Care Units

Xiaoming Yin, Ying Chen, Xiaonan Song†, Yingqi Xing†

Abstract

Introduction: We investigated whether quantitative electroencephalography (QEEG) and transcranial Doppler (TCD) have prognostic value in determining functional outcomes six months following ischemic stroke.

Methods: We performed TCD monitoring on middle cerebral artery (MCA) blood flow, QEEG, and the National Institutes of Health Stroke Scale (NIHSS) on 22 patients presenting with severe acute supratentorial ischemic stroke 24–72 h post-stroke. The MCA waveforms in the ischemic hemisphere (MIH) were graded as follows: 0, absent; 1, blunted; 2, stenotic; and 3, normal. Patient follow-ups were conducted after six months, and patient outcomes were assessed using the modified Rankin scale (mRS). Finally, we compared the NIHSS, area of infarction, MIH grades, and QEEG parameters between survivors and deceased patients.

Results: The risk of death was highest in patients with MIH grade 0 (80%). Relative delta power was significantly correlated with mRS score at month 6 (Spearman's rho = 0.829, P < 0.01). In the receiver operating characteristic (ROC) analysis, death was predicted by relative delta power with an overall accuracy of 86.36%. The best combination for prediction of mortality was obtained by the combination of MIH with relative delta power with an area-under the curve of 1. The moderate disability group was predicted by relative theta power with an overall accuracy of 92.86%.

Conclusions: QEEG and TCD may have prognostic value in determining functional outcomes in patients with acute supratentorial infarction.

Keywords

Quantitative electroencephalography, Transcranial doppler, Stroke, Intensive care units

Background

Stroke is one of the leading causes of adult-onset disability and death worldwide [1-4]. In the acute stage of cerebral ischemia, however, it may be difficult to predict whether patients with severe neurological deficits will recover, remain permanently disabled, or die. Nevertheless, it is very important to assess the outcome of cerebral stroke in order to provide optimal support to the patients and their relatives, and as a guideline in the choice of early treatment and rehabilitation actions.

Department of Neurology, The First Norman Bethune Hospital of Jilin University, Changchun, Jilin, China 130021

†Author for correspondence: Xiaonan Song, Department of Neurology, The First Norman Bethune Hospital of Jilin University, Changchun, Jilin, China 130021, Tel: 86-15844047846; Fax: 86-431-88782378; email: xingyq@sina.com

†Author for correspondence: Yingqi Xing, Department of Neurology, The First Norman Bethune Hospital of Jilin University, Changchun, Jilin, China 130021

The anatomical location and severity of a stroke have been found to be strong predictors of post-stroke disability; however, functional recovery is not always related to the extent of the initial damage [5], but rather to the recovery of cerebral blood flow and synaptic plasticity between neurons [6,7]. Neural activity is closely related to regional cerebral blood flow both spatially and temporally, which is termed neurovascular coupling (NVC) [8]. Cerebral ischemia could lead to attenuation of NVC, and NVC dysfunction may disrupt regional cerebral blood flow and metabolic regulation [8,9]. The transcranial Doppler (TCD) method is a noninvasive method for monitoring blood flow that reflects the alterations of the hemodynamic state [10]. Research has demonstrated that TCD can be used to determine the prognosis of patients with stroke [11-15]. Electroencephalography (EEG) measures the brain's electrical activity, mainly from excitatory and inhibitory postsynaptic currents in dendrites of cortical pyramidal cells, and has been a widely used electrophysiological tool for prognostication [7,16]. However, EEG analysis can be challenging for untrained personnel and is prone to subjectivity. Quantitative EEG (QEEG) provides a compressed and simplified view of the raw EEG signals, potentially allowing for evaluation by non-neurophysiologists [17] and has been attracting increasing attention [2,4,5,7,18-24].

The application of QEEG combined with TCD could simultaneously measure neural activity and cerebral blood flow. However, research on the application of QEEG combined with TCD to predict the prognosis of patients with acute ischemic stroke is lacking. Given the high morbidity and mortality of patients with cerebral ischemia in neurological intensive care units (NICU), it seems particularly important to develop a method that could be used to predict patient outcomes. In this study, we explored the ability of combined QEEG and TCD to predict functional outcome in terms of disability, dependency, and death six months following an ischemic stroke.

Methods

■ Patients

Consecutive patients who experienced an acute ischemic stroke and were treated in the NICU at the First Hospital of Jilin University between July 2015 and March 2016 were included. All patients or their family members (in cases of disturbed consciousness) provided informed consent to participate in the study. The study was approved by the Ethics Committee of the First Hospital of Jilin University.

The inclusion criteria were as follows: (1) aged over 18 years, (2) clinical and neuroimaging-based diagnosis of supratentorial ischemic stroke, and (3) presented to the hospital within 72 h of the last known time the patient did not have a neurological deficit. Patients were excluded in the following cases: (1) cerebral hemorrhage; (2) stroke was confirmed to be the result of a brain tumor, brain trauma, or blood disease; (3) history of stroke; (4) presence of liver, kidney, hematopoietic, endocrine, bone and joint, psychiatric, or other serious diseases; (5) presence of seizures; (6) diagnosed with lacunar stroke, stroke of other determined source, or embolic stroke of undetermined source.

All patients underwent baseline examinations, including a medical history, physical examination, routine blood biochemistry and blood count, carotid Duplex, TCD, chest CT, and initial brain CT. All patients received a follow-up brain CT or magnetic resonance imaging (MRI) to measure the biggest infarction area. EEG and TCD were simultaneously performed within 24–72 h after the last time the patient was known to be without a neurological deficit. All patients received standardized medical treatment. The Modified Rankin scale (mRS) was implemented to assess the degree of disability six months after the cerebral infarction.

■ TCD examination

Both the intracranial and extracranial arteries were assessed using TCD (EMS-9A, Delica, China) and carotid Duplex (Philips, Andover, MA, USA) to determine the baseline state of the arteries [25,26]. Then, TCD examinations were performed with a 2-MHz probe (EMS-9A, Delica, China) to detect two-sided MCA through the temporal window at a 45–62 mm depth before QEEG monitoring. A stroke neurologist performed the TCD study, and immediately interpreted the results. According to the residual flow, MIH could be classified into one of the following 4 grades: "Grade 0, absent," absent flow signals, equivalent to Thrombolysis in Brain Ischemia (TIBI) grades 0 or 1 developed by Andrew et al.; [10] "Grade 1, blunted," flattened systolic flow acceleration of variable duration and decreased mean flow velocities (MFV) by > 30% compared to the control side, equivalent to TIBI grades 2 or 3; "Grade 2, stenotic," an MFV >80 cm/s and a velocity difference of >30% compared to the control side or, if both sides were affected and with a velocity difference of <30%, MFV > 80 cm/s and a signal of turbulence, equivalent to TIBI grade 4; "Grade 3, Normal," <30% mean velocity difference and similar waveform shapes compared to the control side, equivalent to TIBI grade 5 [10].

QEEG acquisition and analysis

EEG was recorded using NSD-8100 (Delica China) for up to 20 min, according to the international 10-20 system with 19 Ag/AgCl electrodes (Fp1, Fp2, F3, F4, C3, C4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, and Pz). Electrode impedance was maintained below 10 kΩ. EEG was recorded for at least 20 min in every patient in an eyes-closed state. After data filtering (high pass 0.3 Hz, low pass 30 Hz) and visual artifact rejection, the first 60 s of the artifact-free raw EEG were analyzed. Quantitative EEG refers to any computational method that uses mathematical and analytical algorithms to transform and compress raw EEG signals, usually into numerical values, ratios, percentages, or graphical representations. Moreover, the widest application parameter of QEEG is the spectral power. Spectral power was calculated using Fast Fourier Transform for each electrode of EEG over the 1–30 Hz range, and the relative power of the delta (1–3 Hz, RD), theta (4–7 Hz, RT), alpha (8–13 Hz, RA), and beta (14–20 Hz, RB) frequency bands over all channels were used to calculate the global delta/alpha ratio (DAR) and (delta + theta)/(alpha + beta) ratio (DTABR).

Statistical analysis

Data analysis was performed using Microsoft Excel (version 2016) and SPSS (version 17.0). Cross tabulations using the χ^2 test and Mann–Whitney U test were used to compare MIH grades between survivors and deceased patients. Spearman's rank-order correlation was used to compute the correlation coefficients between QEEG measures, NIHSS scores, area of ischemia, MIH, and mRS scores. Age at stroke onset, NIHSS score, area of ischemia, and QEEG parameters were considered as continuous variables, and stroke outcome measures were dichotomized for analysis. Between-group comparisons were performed using the Mann–Whitney U test. The respective capacities of the preliminary thresholds to accurately classify participants as deceased or having survived and as having moderate disability or severe disability were then analyzed using receiver operating characteristic (ROC) techniques. Classifier specificity and sensitivity values were calculated for each preliminary threshold. The general predictive value of the combination of the QEEG and MIH measures was determined based on the area under the ROC curve (AUC). The significance level was set at P<0.05.

Results

Twenty-two patients (17 male, mean age 59 ± 12.56, range 41–80 years) were recruited **(Table 1)**. The median NIHSS score was 17.5 (range 9–37). Patients were divided into three groups according to mRS score: the mild disability group (mRS = 3), severe disability group (mRS = 4 or mRS = 5), and death group. Eight patients (36.36%) died, five patients (22.73%) survived with severe disability, and nine patients (40.91%) survived with mild disability.

TCD and carotid duplex examination

TCD examination could not be performed on four patients (18.2%) due to an insufficient temporal bone window. Eleven patients (50%) had an occlusion in the internal carotid artery (ICA) ipsilateral to the ischemic hemisphere. Five patients had occlusive disease in the MCA, three patients had stenosis, and two patients had occlusion. Only two patients had no artery occlusions, both of whom survived.

Amongst the five patients with MIH flow grade 0, four patients (80%) died and one survived with mild disability. Of the eight patients with MIH grade 1, one patient (12.5%) died. There were significant differences in the mortality rate between patients with MIH grades 0 and grade 1 (Fisher's exact test, P<0.05). Of the three patients with MIH grade 2, one patient had severe stenosis at both-sides of the MCA and died. Both patients with MIH grade 3 survived.

Correlation analyses

The outcomes of the correlation analyses are summarized in **Table 2**. There was a significant correlation between mRS and NIHSS score, area of infarction, relative alpha power, relative theta power, relative delta power, DAR, and DTABR respectively. Relative delta power had the high correlation with mRS (rho = 0.829, P < 0.01), followed by infarction area (rho = 0.773, P<0.05), and delta/alpha ratio (rho = 0.712, P<0.01). However, no statistically significant correlations were found between MIH and QEEG measures **(Table 3)**.

Table 1: Characteristics of patients.

Age	59 ± 12.56
Gender (%)	
male	77
female	23
Hemispheric Side (%)	
right	54.55
left	45.45
mRS (%)	
3	40.91
4	13.64
5	9.09
6	36.36
NIHSS (median)	17.5
Area (mm²)	4464.55 ± 1700.57

mRS: modified Rankin scale; NIHSS: National Institutes of Health Stroke Scale; Area: area of infarction.

Table 2: Spearman correlation between clinical variables and prognosis.

	Spearman's rho	*P*
NIHSS	0.455	< 0.05
AREA	0.773	< 0.05
RD	0.829	< 0.01
RT	-0.708	< 0.01
RA	-0.596	< 0.01
RB	0.135	NS
DAR	0.712	< 0.01
DTABR	0.48	< 0.05
MIH	-0.222	0.375

AREA: area of infarction; NIHSS: National Institutes of Health Stroke Scale; RD: relative delta power; RT: relative theta power; RA: relative alpha power; RB: relative beta power; DAR: delta/alpha ratio; DTABR: (delta +theta)/(alpha +beta) ratio; MIH: middle cerebral artery waveforms in the ischemic hemisphere; NS: not statistically significant.

Table 3: Spearman's rho correlation coefficients between quantitative EEG indices and middle cerebral artery waveforms in the ischemic hemisphere.

	Spearman's rho	*P*
RD	-0.053	NS
RT	-0.044	NS
RA	0.113	NS
RB	0.190	NS
DAR	-0.124	NS
DTABR	-0.291	NS

RD: relative delta power; RT: relative theta power; RA: relative alpha power; RB: relative beta power; DAR: delta/alpha ratio; DTABR: (delta +theta)/(alpha +beta) ratio; NS: not statistically significant.

■ Discriminatory parameters for death

The area of infarction, NIHSS score, relative delta power, DAR, and DTABR were significantly higher in the deceased group; relative alpha power and relative theta power were higher in the survival group. There was no significant between-group difference in relative beta power. MIH grades were lower in non-survivors than in survivors (P<0.05).

ROC curve analysis was performed on area of infarction, NIHSS score, relative delta power, DAR, and DTABR. The outcomes of ROC analyses of classifier performance on these thresholds are summarized in **Table 4**. In brief, relative delta power demonstrated optimal classifier performance in all QEEG measures, as indicated by an area under the ROC curve (AUC) value of 0.929 (P<0.01), second only to the ischemic area (P<0.01). Death was predicted by relative delta power with an overall accuracy of 86.36%. The next most accurate classifier indices according to their respective AUC values were DAR (0.875, P<0.01) and DTABR (0.821, P<0.05), while the poorest classifier was NIHSS score. The combination of MIH and QEEG measures had a better predictive value than QEEG measures alone. Moreover, the best combinations for prediction of mortality was obtained by the combination of MIH with relative delta power with an area-under the curve of 1, as well as the combination of MIH with the ischemic area.

■ Discriminatory parameters for 6-month functional outcomes of survivors

Comparing age, NIHSS score, infarction area, and QEEG parameters between patients with mild disability and patients with severe disability, we found significant differences in age, relative delta power, relative theta power and the DAR (P<0.05). However, no significant between-group differences were found in NIHSS score, infarction area, relative alpha power, relative beta power, or DTABR. Mild disability was predicted from relative theta power with an AUC of 0.911 (P<0.05), with an overall accuracy of 92.86%. Relative delta power with the best predictive value reached an area-under the curve of 0.956 (P<0.01). Relative alpha power was not significantly predictive of mild disability (P = 0.096, **Table 5**).

Discussion

The course of acute ischemia stroke is capricious, and the results of treatment are variable. However, concerns have been raised about survival and quality of life, especially in patients with severe stroke. With regard to these concerns, it would be useful to establish parameters that may help to predict the potential for functional outcome as early as possible after stroke, preferably during the acute and subacute phases, i.e., while the patient is still being treated in the intensive care unit. TCD reflects changes in cerebral blood flow and metabolism within seconds, which can be directly reflected in the neuronal rhythms detected by real-time EEG [27]. Moreover, EEG is a non-invasive, bedside-available tool, which can continuously monitor brain function and is used in a growing number of neurological intensive care units. However, visual EEG analysis can be difficult for untrained personnel, and is prone to subjectivity and subsequent delays to intervention.

By applying a Fourier transformation, QEEG transforms and compresses raw EEG signals to generate numerical values, ratios, or percentages to graphically display arrays or trends, and to set thresholds for alarms. QEEG can aid in the interpretation of a large volume of data generated by EEG monitoring, potentially allowing for evaluation by non-neurophysiologists. A variety of QEEG measures have been used clinically to quantify slowing or attenuation of faster frequencies in the EEG. Specifically, the calculation of power within different frequency bands (i.e., delta, theta, alpha, and beta) and ratios or percentages of power in specific frequency bands. QEEG is being used for numerous clinical indications for brain monitoring in critically ill patients that include seizure detection, monitoring depth of sedation, ischemia detection, vasospasm/DCI detection, and prognosis after cardiac arrest [17,28].

In the present study, no significant correlations were observed between MIH and QEEG parameters, which is the opposite of the expected outcome. It has been known that adequate blood supply of neurons does not only depend on the patency of the cerebral vessels and collateral systems, but also on compensative mechanisms in the microcirculation [29]. The MIH classification developed in this study only reflected blood flow of large intracranial artery. Impaired neurovascular coupling was found in patients with large intracranial artery stenosis, or small vessel disease, or cerebral ischemia, meaning impaired microcirculation regulation, which caused local cerebral blood flow not in accordance with the underlying neuronal activity [9,29]. The elected patients in this study all had experienced severe cerebral infarction, and most had large intracranial artery stenosis or occlusion.

The outcomes of patients with acute ischemic stroke were heterogeneous and included complete recovery as well as death. This study confirmed the value of QEEG and TCD in determining the prognosis of patients with cerebral infarction.

Table 4: Outcomes of ROC analyses for NIHSS, area of infarction, and respective QEEG indices.

	Threshold	Sensitivity	Specificity	AUC	*P*
NIHSS	30	0.625	0.929	0.759	0.048
AREA	4240	1	0.786	0.937	0.001
RD	68.30	1	0.786	0.929	0.001
DAR	5.25	1	0.714	0.875	0.004
DTABR	3.80	1	0.571	0.821	0.014

ROC: receiver operator characteristic, NIHSS: National Institutes of Health Stroke Scale; AREA: area of infarction; RA: relative alpha power; RT: relative theta power; RD: relative delta power; DAR: delta/alpha ratio; DTABR: (delta +theta)/(alpha +beta) ratio.

Table 5: Outcomes of receiver operator characteristic analyses in survival.

	Threshold	Sensitivity	Specificity	AUC	*P*
RD	67.366	1	0.8	0.956	0.006
RT	10.79	1	0.800	0.911	0.014
RA	14.39	0.556	1.000	0.778	0.096
NIHSS	17.5	0.778	0.600	0.611	0.505
AREA	4475	1	0.600	0.644	0.386

RD: relative delta power; RT: relative theta power; RA: relative alpha power; NIHSS: National Institutes of Health Stroke Scale; AREA: area of infarction;

Our results showed that QEEG measurements correlate with mRS scores, and the combinations of QEEG and TCD may have the best predictive value for mortality, providing a new method to predict outcome in patients with ischemic infarction.

One of our notable results was the positive association between relative delta power and mRS scores, suggesting that delta activity is one of the strongest predictors of functional outcome, which supported findings suggesting that increase of delta activity indicates a poor prognosis. On the contrary, the negative correlation between relative alpha power and mRS scores and between relative theta power and mRS scores indicates that the preservation of alpha and theta activity may lead to a good prognosis, which is in accordance with previous observations [7,22].

The present study findings indicate that relative delta power is an optimal measure to estimate the prognosis and predict a patient's functional outcome, followed by the area of ischemia. This is in line with previous findings that that delta power was the best predictor for long-term outcomes [19,20]. However, analyzing QEEG measures for 154 patients with suspected ischemic stroke, Sheorajpanday et al. proposed that the DTABR was superior to other power spectrum measures to predict the outcome of patients [2,23]. The different results may be attributed to the studied sample and/or the time at which QEEG was performed. The selected sample consisted of patients with supratentorial ischemic stroke in NICUs with no previous history of stroke. Sheorajpanday et al., on the other hand, selected patients with a wider range of damage, including anterior circulation ischemia, posterior circulation ischemia, and lacunar ischemia, and did not take history of stroke into account. Additionally, we measured QEEG 24–72 h after stoke onset, whereas Sheorajpanday et al. measured QEEG from 6 h to 7 d post-stroke. These differences could account for the contrasting results, and further study is required to elucidate these points.

The current findings could help clinicians to identify which patients require more aggressive treatment measures, especially considering that the values of relative delta power, the DAR, the DTABR, NIHSS, and area of ischemia are higher and the MIH grade is lower in non-survivors compared to survivors. The capacity of relative delta power, DTABR, and DAR to predict death is stronger than the capacity of the NIHSS. The NIHSS has limited practical applications because its assessments of language function or level of consciousness are often not possible to apply to aphasic or comatose patients,[19] while QEEG and TCD are highly accurate and objective evaluation methods. Relative delta power was determined to be the optimal index of all QEEG parameters to predict death; the mortality rate in the group with MIH grade 0 was 80%.

None of the previous studies have investigated the ability of the combination of QEEG and TCD to predict death. We found that the combination with the best predictive value was composed of relative delta power and MIH. This combination with the highest predictive value reached an area-under the curve of 1. In addition, the study indicated that the respective combinations of other QEEG parameters and MIH showed better prognostic value than the QEEG parameters alone.

Moderate disability was predicted from relative theta power with an AUC of 0.911 ($P < 0.05$). Relative alpha power was not significantly predictive of moderate disability. A possible explanation for these findings may be that alpha and theta power decreases are related to the tissue at risk, penumbra, and edema [20,30-32]. These cerebral injuries are reversible, and their recovery signifies residual nerve cells and neural networks, i.e., greater retention of neurological function, which plays an important role in patients with a good prognosis. Thus, relative theta power plays a key role in the prognosis of surviving patients.

Limitations

There are several limitations to our study that should be noted. First, the small number of patients limits the statistical power of our results. Despite this, the results of this study support the hypothesis that QEEG and TCD are reliable predictors of functional outcomes. However, verification of these results in larger cohorts is needed to determine the clinical utility of this approach. Second, the selected QEEG monitoring time window of this study was 24–72 h post-stroke and the application of QEEG on other time windows is not yet clear. This is because the patients' condition tends to stabilize 24 h following a stroke, but is unstable in the first 24 h. Thus, the next step will be to explore the value of QEEG in different monitoring time windows post stroke. Third, due to inadequate bony windows, the MIH grade could not be determined for all patients, which may have led to a biased blood flow score for prognostic prediction.

Conclusion

In summary, the current results indicate that QEEG and TCD can objectively assess brain function in patients with ischemic stroke and predict functional prognosis and mortality. Further studies incorporating larger samples are warranted to confirm these findings.

Acknowledgments

We would like to thank all patients for their participation. We would also like to thank the staff of the NICU of the First Hospital of Jilin University for helping with QEEG monitoring and TCD.

Competing Interests

None of the members of the writing committee have conflicts of interest in respect to this manuscript.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article

References

1. Romano JG, Sacco RL. Decade in review-stroke: progress in acute ischaemic stroke treatment and prevention. *Nature. Reviews. Neurology* 11(1), 619-621 (2015).
2. Sheorajpanday RV, Nagels G, Weeren AJ, *et al.* Additional value of quantitative EEG in acute anterior circulation syndrome of presumed ischemic origin. *Clin. Neurophysiol* 121(1), 1719-1725 (2010).
3. Forti P, Maioli F, Procaccianti G, *et al.* Independent predictors of ischemic stroke in the elderly: prospective data from a stroke unit. *Neurology* 80(1), 29-38 (2013).
4. Sheorajpanday RV, Nagels G, Weeren AJ, *et al.*Quantitative EEG in ischemic stroke: correlation with functional status after 6 months. *Clin. Neurophysiol* 122(1), 874-883 (2011).
5. Simis M, Doruk D, Imamura M, *et al.* Neurophysiologic predictors of motor function in stroke. *Restor. Neurol. Neurosci* 34(1), 45-54 (2015).
6. Sheorajpanday RV, Nagels G, Weeren AJ, *et al.* Quantitative EEG in ischemic stroke: correlation with infarct volume and functional status in posterior circulation and lacunar syndromes. *Clin. Neurophysiol* 122(1), 884-890 (2011).
7. Finnigan S, van Putten MJ. EEG in ischaemic stroke: quantitative EEG can uniquely inform (sub-)acute prognoses and clinical management. *Clin. Neurophysiol* 124(1), 10-19 (2013).
8. Guhathakurta D, Dutta A. Computational Pipeline for NIRS-EEG Joint Imaging of tDCS-Evoked Cerebral Responses-An Application in Ischemic Stroke. *Front. Neurosci* 10(1), 261 (2016).
9. Povlsen GK, Longden TA, Bonev AD, *et al.* Uncoupling of neurovascular communication after transient global cerebral ischemia is caused by impaired parenchymal smooth muscle Kir channel function. *J. Cereb. Blood. Flow. Metab* 36(1), 1195-1201 (2016).
10. Demchuk AM, Burgin WS, Christou I, *et al.* Thrombolysis in brain ischemia (TIBI) transcranial Doppler flow grades predict clinical severity, early recovery, and mortality in patients treated with intravenous tissue plasminogen activator. *Stroke* 32(1), 89-93 (2001).
11. Marti-Fabregas J, Belvis R, Guardia E, *et al.* Prognostic value of Pulsatility Index in acute intracerebral hemorrhage. *Neurology* 61(1), 1051-1056 (2003).
12. Stolz E, Cioli F, Allendoerfer J, *et al.* Can early neurosonology predict outcome in acute stroke?: a metaanalysis of prognostic clinical effect sizes related to the vascular status. *Stroke* 39(1), 3255-3261 (2008).
13. Wijnhoud AD, Koudstaal PJ, Dippel DW. The prognostic value of pulsatility index, flow velocity, and their ratio, measured with TCD ultrasound, in patients with a recent TIA or ischemic stroke. *Acta. Neurologica. Scandinavica* 124(1), 238-244 (2011).
14. Baracchini C, Manara R, Ermani M, *et al.* The quest for early predictors of stroke evolution: can TCD be a guiding light? *Stroke* 31(1), 2942-2947 (2000).
15. Aoki J, Raber LN, Katzan IL, *et al.* Post-intervention TCD examination may be useful to predict outcome in acute ischemic stroke patients with successful intra-arterial intervention. *J. Neurol. Sci* 334(1), 26-29 (2013).
16. Deng R, Koenig MA, Young LM, *et al.* Early Quantitative Gamma-Band EEG Marker is Associated with Outcomes after Cardiac Arrest and Targeted Temperature Management. *Neurocritical. Care* 23(1), 262-273 (2015).
17. Swisher CB, Sinha SR. Utilization of Quantitative EEG Trends for Critical Care Continuous EEG Monitoring: A Survey of Neurophysiologists. *J. Clin. Neurophysiol* 33(1), 538-544 (2016).
18. Cillessen JP, van Huffelen AC, Kappelle LJ, *et al.* Electroencephalography improves the prediction of functional outcome in the acute stage of cerebral ischemia. *Stroke* 25(1), 1968-1972 (1994).
19. Cuspineda E, Machado C, Aubert E, *et al.* Predicting outcome in acute stroke: a comparison between QEEG and the Canadian Neurological Scale. *Clinical. EEG. (electroencephalography)* 34(1), 1-4 (2003).
20. Cuspineda E, Machado C, Galan L, *et al.* QEEG prognostic value in acute stroke. *Clin. EEG. Neurosci* 38(1), 155-160 (2007).
21. Finnigan SP, Rose SE, Walsh M, *et al.* Correlation of quantitative EEG in acute ischemic stroke with 30-day NIHSS score: comparison with diffusion and perfusion MRI. *Stroke* 35(1), 899-903 (2004).
22. Finnigan SP, Walsh M, Rose SE, *et al.* Quantitative EEG indices of sub-acute ischaemic stroke correlate with clinical outcomes. *Clin. Neurophysiol* 118(1), 2525-2532 (2007).
23. Sheorajpanday RV, Nagels G, Weeren AJ, *et al.* Reproducibility and clinical relevance of quantitative EEG parameters in cerebral ischemia: a basic approach. *Clin. Neurophysiol* 120(1), 845-855 (2009).
24. Leon-Carrion J, Martin-Rodriguez JF, Damas-Lopez J, *et al.* Delta-alpha ratio correlates with level of recovery after neurorehabilitation in patients with acquired brain injury. *Clin. Neurophysiol* 120(1), 1039-1045 (2009).
25. Zanette EM, Fieschi C, Bozzao L, *et al.* Comparison of cerebral angiography and transcranial Doppler sonography in acute stroke. *Stroke* 20(1), 899-903 (1989).
26. Wong KS, Li H, Chan YL, *et al.* Use of transcranial Doppler ultrasound to predict outcome in patients with intracranial large-artery occlusive disease. *Stroke* 31(1), 2641-2647 (2000).
27. O'Gorman RL, Poil SS, Brandeis D, *et al.* Coupling between resting cerebral perfusion and EEG. *Brain. Topography* 26(1), 442-457 (2013).
28. Finnigan S, Wong A, Read S. Defining abnormal slow EEG activity in acute ischaemic stroke: Delta/alpha ratio as an optimal QEEG index. *Clin. Neurophysiol* 127(1), 1452-1459 (2016).
29. Lin WH, Hao Q, Rosengarten B, *et al.* Impaired neurovascular coupling in ischaemic stroke patients with large or small vessel disease. *Eur. J. Neurol* 18(1), 731-736 (2011).
30. Machado C, Cuspineda E, Valdes P, *et al.* Assessing acute middle cerebral artery ischemic stroke by quantitative electric tomography. *Clin. EEG. Neurosci* 35(1), 116-124 (2004).
31. Fernandez-Bouzas A, Harmony T, Bosch J, *et al.* Sources of abnormal EEG activity in the presence of brain lesions. *Clinical. EEG. (electroencephalography)* 30(1), 46-52 (1999).
32. Gollwitzer S, Groemer T, Rampp S, *et al.* Early prediction of delayed cerebral ischemia in subarachnoid hemorrhage based on quantitative EEG: A prospective study in adults. *Clin. Neurophysiol* 126(1), 1514-1523 (2015).