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Complex Neurovascular Reactivity in Patients with Focal Epilepsy

Gulnur Tekgöl Uzuner, MD, Assist. Prof. of Neurology

Eskisehir Osmangazi University, Faculty of Medicine, Department of Neurology, Eskisehir, TURKEY
E-mail: uzunergulnur@gmail.com

Nevzat Uzuner, MD, Prof. of Neurology
Eskisehir Osmangazi University, Faculty of Medicine, Department of Neurology, Eskisehir, TURKEY
E-mail: nevzatuzuner@gmail.com

Corresponding author:
Nevzat Uzuner, MD, Prof. of Neurology
Eskisehir Osmangazi University, Faculty of Medicine, Department of Neurology, Meselik, 26480 Eskisehir, TURKEY
Tel: +90 222 2392979/3650
E-mail: nevzatuzuner@gmail.com

Abstract: Background: Complex neurovascular activation by transcranial Doppler (TCD) is not presented at the moment in drug-responsive patients with focal epilepsy. The objective of this study is to assess the neurovascular activation to complex visual stimulation of drug-responsive patients with focal epilepsy during interictal period. **Methods**: Twenty-five patients with focal epilepsy and 25 healthy subjects were screened for this study in our Neurosonology Laboratory. We performed transtemporal TCD recordings from the P2-segments of both posterior cerebral arteries (PCA) simultaneously during complex visual stimulation at least ten days after last epileptic attack. The individual reactivity was defined as a relative increase of the blood flow velocities as a percentage change of the baseline values. **Results**: Most of the patients have an epileptic focus in the temporal lobe documented by the EEG. The Doppler data of the epileptic sides and non-epileptic sides were analyzed separately. The complex visual reactivity was significantly higher at the epileptic side in the patients (52.5%) from those of the controls (36.8%) (p=0.002). **Discussion**: In contrast to the earlier reports of the studies which were found diminished neurovascular reactivity to simple or complex visual stimulation using TCD, our study showed the temporal and occipital region of the patients with focal epilepsy have hyperactive neurovascular units at the epileptic side during the interictal period when comparing with the healthy subjects. Although to emphasize the importance of investigating neurovascular coupling in epilepsy, further studies are needed.
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Keywords: Epilepsy; vascular reactivity; transcranial Doppler; ultrasound; neurovascular coupling.

Introduction

The increased metabolic demands of cerebral activation result in the dilation of arterioles and a corresponding rise in the flow velocities of the basal cerebral arteries [Aaslid, 1987]. TCD sonography provides information about blood flow velocity changes in individual cerebral arteries as a representation of cerebral blood flow to visual or motor stimulation [Aaslid, 1987; Uzuner et al., 2000]. Besides, TCD method can provide excellent temporal information about the dynamics of the response [Daffertshofer & Hennerici, 1995]. Continuously recording of blood flow velocities at PCA during visual stimulation tasks show the relation between metabolic demand and neuronal activation. This phenomenon is called as neurovascular coupling, and it gives information about the neuronal activation of the visual cerebral cortex as well as the reactivity of cerebral cortical vessels or both [Uzuner et al., 2002].

There are limited data about the neurovascular relationship that have been evaluated by TCD in patients with focal epilepsy. Unilateral PCA blood flow velocity changes as a response to photic driving were found lower than those of controls in the very early published study [Diehl, 1998]. Later the second study published [Panczel & Pohlmann-Eden, 2004], in which they used the more complex visual stimulation. They found lower reactivity in patients with focal epilepsy. However, their patients have intractable focal epilepsy.

Simple visual stimulation like photic stimulation can be inhibited by the antiepileptic drugs, and, therefore, the observed reactivity might be found lower than the expected in the earlier report of the functional TCD study. Thus, we used complex visual stimulation to activate the larger area of the temporal and occipital lobes perfused by PCA. The objective of this study is to assess the neurovascular activation to complex visual stimulation of the drug responsive patients with focal epilepsy during the interictal period.

Materials and Methods

This study was done in the Department of Neurology of Eskisehir Osmangazi University between September 2012 and August 2014. Twenty-five patients with focal epilepsy and 25 healthy people served as controls were enrolled in the study. A detailed medical history and history of epilepsy has been questioned in all subjects. A physical examination and complete neurological examination were done in all subjects including ultrasound examination of extracerebral arteries. Laboratory investigation and radiological examination were also done in patients when necessary. None of the patients has visible an abnormality on the cerebral magnetic resonance imaging (MRI). The epileptic side was described when an epileptic focus documented by EEG and allocated to the epileptic side or left side. Diagnosis of focal epilepsy was done according to the clinical appearance and the EEG results.

All enrolled patients were studied during the seizure-free period with Transcranial Doppler, and all patients were receiving their antiepileptic treatment at the time of TCD recording. We excluded one patient because of inadequate PCA insonation through the temporal bone window. The data of the remaining patients (12 female and 12 male; mean age 33.9±15.8 years) and controls (7 female and 18 male; mean age 28.4±7.7 years) were included the analysis. A two-tailed t-test for the parametric variables and the chi-square test for the non-parametric variables were applied for statistical analysis, and $p<0.05$ was accepted as the statistical significance. This study was approved by the Ethical Committee of Eskisehir Osmangazi University (Number: 2012/172 and date: 17th August 2012). All the participants gave their informed written consent according to the Declaration of Helsinki.

The test was performed in a quiet room, and subjects lay comfortably. We performed transtemporal TCD recordings with a Multi-Dop X4 (DWL, Sipplingen, Germany), using 2 MHz transducers from the both PCAs simultaneously during visual stimulation as eyes open and watching color images for 20 s (‘on’ phase) followed by 20 s with closed eyes (‘off’ phase). Ten cycles were performed and averaged. A detailed description of the complex visual stimulation was found elsewhere [Wolf et al., 2009].

The standard for successful the P2 segment of PCA recording was a clear-cut increase in flow velocity during the period when the subjects had their eyes opened as opposed to the time when their eyes were closed [Sturzenegger, Newell & Aaslid, 1996]. An acoustic signal initiated stimulus on and off phases. Fast Fourier transformation was used to calculate a time-averaged mean flow velocity for each cycle (Figure 1).

Calculations were performed off-line, and individual reactivity was defined as a relative increase of blood flow velocities as a percentage change of baseline values [BFv=100(Vs-Vr)/Vr]. Where Vs indicates maximum velocity at stimulation (eyes open and stimulus on); Vr, minimum velocity at rest (eyes closed and stimulus off). They are calculated by the special software of this system that allows trigger-related BFv averaging over an adjustable period of stimulus on compared with an adjustable period of stimulus off [Sturzenegger, Newell & Aaslid, 1996], following the procedure as shown in figure 2.

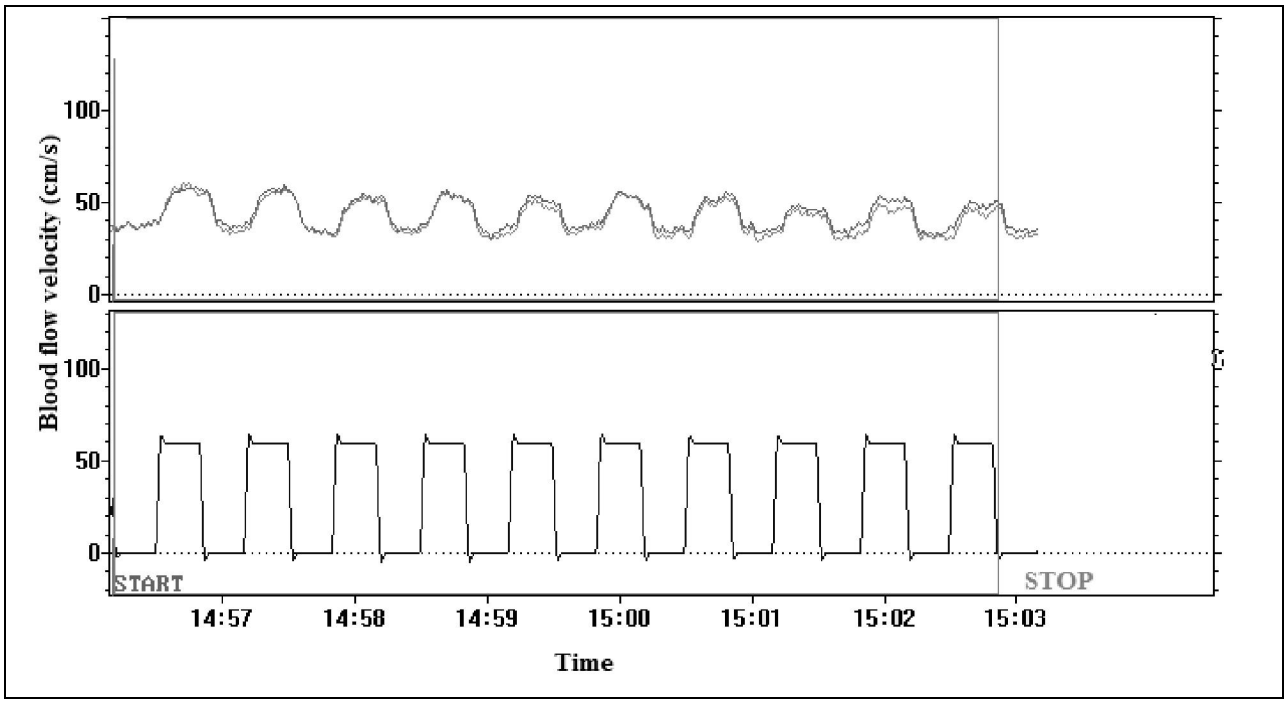

Figure 1. Continuous recordings of blood flow velocities concurrently in the both PCA during 10 cycles. Each cycle consists of a sequence of rest (20 seconds), followed by the bilateral stimulus on (20 seconds) represented in the lower curve. Opening the eyes induced a regular increase of the velocities.

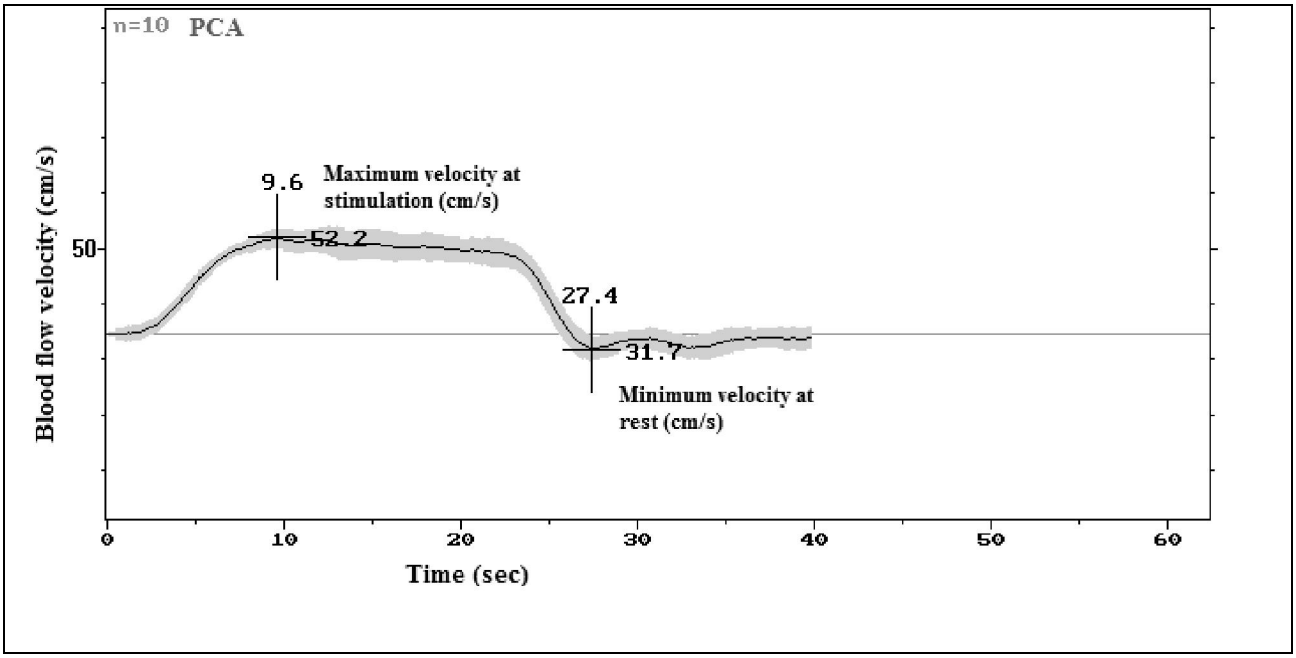

Figure 2. The figure shows the averaged responses of 10 cycles recorded in the P2 segment of the PCA during stimulus on and the rest period in a subject (mean value, the shaded areas indicate ± 2SEM). The maximum and minimum values were calculated as a single value at stimulation and rest, respectively.

Results

Doppler data of the subjects were presented in Table 1. Briefly, the visual stimulation provided a significant blood flow velocity increase on both sides ($p<0.001$) in all the subjects.

Table 1: Doppler data of the subjects

	Controls (n=25)	Epileptic patients (n=24)	P value
Non-epileptic side or right side			
Velocity at stimulation (cm/s)	46.0 ± 06.7	47.6 ± 11.2	0.55
Velocity at rest (cm/s)	33.8 ± 04.8	33.9 ± 07.2	0.55
Reactivity (%)	36.5 ± 12.5	40.1 ± 15.1	0.94
Epileptic side or left side			
Velocity at stimulation (cm/s)	45.9 ± 06.2	47.8 ± 10.4	0.46
Velocity at rest (cm/s)	33.7 ± 04.1	31.5 ± 06.5	0.16
Reactivity (%)	36.8 ± 14.7	52.5 ± 18.3	0.002*

Values are mean ± standard deviation; independent samples test was used between groups.

The velocities at stimulation were found slightly higher in the patients from that of controls on the non-epileptic side or right side. Although, the velocities at rest was quite similar. As a consequence, neurovascular reactivity was not significantly different in the patients (40.1±15.1) from that of controls (36.5±12.5). Conversely, the reactivity to visual stimulation was slightly higher in the patients on the epileptic side or left side (52.5 ± 18.3) from those of the controls (36.8 ± 14.7) ($p=0.002$).

Discussion

Normal brain activity is subject to a continuous resource of oxygen and glucose through cerebral blood flow (CBF). The local brain activity has to be supplemented by an associated increase in regional CBF. The fast CBF changes are paralleled by changes in both oxygenation and blood volume rather than the glucose usage [Malonek et al., 1997]. Besides the neuronal activation, the glial activation plays a considerable role in the neurovascular coupling; particularly during visual stimulation [Metea & Newman 2006; Petzold & Murthy, 2011]. Endothelial cells and pericytes are also involved in the neurovascular coupling [Peppiatt et al., 2006]. Even so, the exact coupling mechanism of the neurovascular unit is not yet fully understood. TCD provides information about blood flow velocity changes in cerebral arteries to appropriate neuronal stimulation tasks. Besides, TCD sonography allows for the real-time analysis of the flow velocities in the large cerebral arteries, and the velocity changes after a vasodilatory stimulus such as acetazolamide, CO_2, or apnea [Vernieri, 1999]. Hypoxia caused by breath holding results in an autoregulatory vasodilatation and an increase in CBF to the cortex [Johnston, 2003]. The increased CBF can be evaluated by the TCD, and can deliver data concerning the vascular reactivity [Markus & Harrison, 1992]. When considering that the diameter of the basal cerebral arteries is relatively constant during the hypoxia, the blood flow velocity changes related to the capillary vascular organization are mainly responsible for the cerebral vascular autoregulation [Cole, 1993]. Recently, increased cerebrovascular reactivity using a breath-holding test in patients with epilepsy was published [Bek, 2010]. Although, the authors concluded that the increased vasoreactivity might be the result of an adaptive mechanism that protects the brain from hypoxic challenges due to seizure apnea rather than the abnormality.

In the present study, the blood flow velocities in the stimulation period on the patients were slightly higher than those of the control subjects. In contrast, blood flow velocities obtained on the patients during rest period fairly lower than those of controls only at the epileptic side. Our study was not planned to define the perfusion deficits in the epileptic patients. However, the lower cerebral blood flow velocities during the rest period may represent cerebral hypoperfusion within the examined vessels area at the epileptic side. Nevertheless, this difference did not reach a significant level. Because of the blood flow velocity obtained during rest period lower than those of controls in our study, the amplified reactivity in patients seems to be related to the preserved vasodilator ability of the vessels. Also, more recently the significant increase in activated N-methyl-D-aspartate (NMDA) receptor availability was shown in patients

with focal epilepsy. They suggest that increased NMDA activation in patients with chronic focal epilepsy extends beyond the presumed epileptogenic zone [McGinnity, 2015]. Increased NMDA activation may be partly responsible the increased neurovascular reactivity.

Our results seem different earlier studies. The selected visual stimulation procedure and the patient population likely make this difference. One of these studies has the patients with intractable epilepsy. Instead, our patients were under control with appropriate antiepileptic drugs, and none of our patients has a visible gross pathology at the cerebral imaging. Another study used the photic stimulation for assessing the neurovascular reactivity. Because of the simple visual stimulation like photic stimulation may be inhibited by antiepileptic drugs, we prefer to use the complex visual stimulus to activate the larger area to avoid the inhibitor effect of the antiepileptic drugs.

Our results suggest the presence of the hyperactive neurovascular unit in the temporal and occipital region at the epileptic side in patients with focal epilepsy during the interictal period. We, however, did not study the effect of the drug management of the patients with the neurovascular reactivity. The presence of the hyperactive neurovascular units may call attention to being careful against unprovoked or provoked seizures.

Conclusions:

Advancing our understanding of the process of neurovascular coupling is important, in particular, to enable development of novel treatments for brain conditions in which neurovascular coupling is broken. In spite of the difficulties of the experimental design using transcranial Doppler in the PCA after visual stimulation, to emphasize the importance of investigating neurovascular coupling in epilepsy, especially to demonstrate a link between seizures and neurovascular integrity further studies are needed.

Authors' contributions:

Gulnur Tekgol Uzuner designed the experiments, contributed analysis tools, wrote the manuscript, and prepared the tables.

Nevzat Uzuner conceived the experiments, performed the experiments, contributed analysis tools, prepared the figures, and reviewed drafts of the paper.

Conflict of interest disclosure: There is no conflict of interest.

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