Original article

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Ictal cerebral haemodynamic characteristics during typical absence seizures, compared to focal seizures with brief alteration of awareness

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ABSTRACT – *Aims*. To investigate ictal cerebral haemodynamic characteristics during spontaneous typical absence seizures (TAS) and hyperventilation-evoked absence seizures in paediatric patients, relative to brief complex partial seizures (BCPS).
Methods. All children diagnosed with seizures using real-time transcranial doppler ultrasonography (TCD) and sleep-deprived video-EEG (vEEG) from 2015 to 2017 in our hospital were included. The seizures were diagnosed based on the video and EEG findings. Mean cerebral blood flow velocity ($CBFV_m$) of the unilateral middle cerebral artery was measured using TCD. TCD and vEEG data were integrated for a synchronous assessment of $CBFV_m$ changes and epileptic status. Baseline and peak $CBFV_m$ for TAS and BCPS were compared by T-test.
Results. Six children (two boys and four girls) with TAS and two girls with BCPS were enrolled. A total of 15 spontaneous TAS, 14 hyperventilation-evoked absence seizures, and six BCPS were recorded using real-time TCD-vEEG monitoring. During spontaneous TAS, whether awake or asleep, the $CBFV_m$ decreased by 20-40% compared to baseline. During hyperventilation-evoked absence seizures and BCPS, the $CBFV_m$ increased by 50-150% and 20-30% over baseline levels, respectively.
Conclusions. The haemodynamic characteristics during TAS and BCPS are distinct, and thus our results may provide a new method to diagnose typical absence seizures using dynamic $CBFV_m$ curves. Ictal cerebral haemodynamic characteristics during spontaneous typical absence seizures and hyperventilation-evoked absence seizures may reflect different pathophysiological mechanisms and networks compared with BCPS.

Key words: cerebral haemodynamics, typical absence seizures, hyperventilation-evoked absence seizures, paediatric, cerebral blood flow velocity

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Neuronal activity has a high metabolic demand, which is closely associated with cerebral blood supply. Previous studies have demonstrated that alterations in neuronal activity may lead to abnormal cerebral blood flow (CBF) and/or metabolism (Iadecola, 2004). Meanwhile, epileptic seizures can increase CBF to respond to the high metabolic demands due to elevated neuronal activity (Kovács *et al*., 2012). In the literature, multiple neuroimaging modalities have been applied to evaluate cerebral haemodynamics and metabolism. Although positron emission tomography (PET) is valuable for identifying hypometabolic cerebral regions between ictal phases of epilepsy, its application during ictal phases is limited due to the short half-life of positron emitting isotopes (Simone *et al*., 1998). Single photon emission computed tomography (SPECT) can be used in ictal phases, while the radioactivity of isotopes should be minimized (Simone *et al*., 1998). Transcranial doppler ultrasonography (TCD) is a non-invasive technique to assess instantaneous haemodynamic changes in large arteries, and it is the optimal method for assessing cerebral blood flow velocity (CBFV) in ictal phases.

The correlation between cerebral haemodynamics and neuronal activity is called "neurovascular coupling" (Iadecola, 2004). In the last few years, many experimental and clinical studies have been conducted on neurovascular coupling. Real-time TCD-video EEG (vEEG) has been used as the first choice to assess instantaneous haemodynamic changes as well as neurovascular coupling in patients with epilepsy (Rosengarten *et al*., 2012; Merceron *et al*., 2014).

Absence seizures refer to a sudden paroxysmal loss of consciousness, related to bursts of bilateral, synchronous 3-3.5-Hz spike-and-wave discharges recorded on EEG (Proposal for revised classification of epilepsies and epileptic syndromes, 1989). Ictal cerebral haemodynamic changes in childhood absence epilepsy (CAE) and juvenile absence epilepsy (JAE) remain controversial (Sanada *et al*., 1988; Nehlig *et al*., 1996; Simone *et al*., 2002; Bek *et al*., 2010). Additionally, although absence seizures can be evoked by hyperventilation, the ictal cerebral haemodynamic characteristics in childhood hyperventilation-evoked absence seizures have not yet been reported. Brief complex partial seizures (BCPS) are clinically indistinguishable from absence seizures. In this study, we investigated ictal cerebral haemodynamic characteristics during typical absence seizures, hyperventilation-evoked absence seizures, and BCPS in paediatric patients. This study aimed to explore how hyperventilation causes absence seizures and the differences between absence seizures and BCPS.

Materials and methods

Subjects

All children diagnosed with seizures using real-time transcranial doppler ultrasonography (TCD) and sleep-deprived vEEG from 2015 to 2017 in our hospital were included. The inclusion criteria were:

– (1) normal spectrum and symmetric CBF velocity (CBFV) during TCD examination in the awake stage;

– (2) no probe shedding due to seizures during the examinations;

– and (3) guardians of the children had approved the examinations and signed an informed consent.

Cases with intense seizures were excluded. Ultimately, six children (two boys and four girls) with typical absence seizures and two girls with BCPS were enrolled. The diagnosis was made according to the classification of the International League against Epilepsy (Proposal for revised classification of epilepsies and epileptic syndromes, 1989). The previous medical history was unremarkable and there were no intellectual or neurological abnormalities in any of the children. The children were not treated previously with antiepileptic drugs. None of these children had neuroradiological abnormalities.

This study was approved by the local ethics committee.

Real-time TCD-vEEG monitoring

According to the method previously described (Peng *et al*., 2016), absence seizures were recorded by digital EEG polygraphy (NicoletOne EEG, Natus, USA). Nineteen collodion-applied scalp electrodes were placed according to the 10-20 system (Electrocap, ECI, OH, USA). Simultaneously, systolic CBFV (Vs), diastolic CBFV (Vd), and mean CBFV (CBFVm) of the unilateral middle cerebral artery (MCA) were measured at a depth of 48-60 cm using TCD (Doppler-box, DWL, Heidelberg, Germany). Vm was calculated based on the following formula: $Vm = (Vs+Vd\times2)/3$. We chose Vm to delineate the dynamic curve. Signals were obtained with a 2-MHz probe, which was subsequently fixed to the temporal window by a helmet. Spectral data were recorded, and the dynamic CBFVm curve was acquired during real-time vEEG monitoring. TCD and vEEG data were integrated for a synchronous assessment of CBFVm changes and epileptic status. The baseline interictal CBFVm was measured at one minute before seizure onset. Compared to baseline CBFVm, a >10% variation was identified as a significant change, as described previously (Yao *et al*., 2015).

The seizures were diagnosed based on the video combined with EEG findings. vEEG recordings were

not stopped after the first seizure. The 3-3.5-Hz spike-and-wave discharges with no clinical symptoms were excluded. Seizures were diagnosed as absence seizures or complex partial seizures according to the Commission on Classification and Terminology of the International League Against Epilepsy (ILAE) (1989).

Data analysis

The baseline and peak CBFVm during each absence seizure were analysed. All baseline CBFVm and the peak CBFVm of each patient were averaged. CBVFm changes were calculated as the mean, as "(peak CBFVm-baseline CBFVm)/baseline CBFVm".

Results

The age of the enrolled patients ranged from six years to 12 years. Detailed demographic data and haemodynamic parameters are summarized in *table 1*. A total of 15 spontaneous typical absence seizures, 14 hyperventilation-evoked absence seizures, and six BCPS were recorded utilizing real-time TCD-vEEG monitoring.

All absence seizures started with 3-3.5-Hz generalized synchronous spike-and -slow-wave discharges (gSWD), lasting from 8 to 20 seconds. Postictal confusion lasted for 2-3 seconds with slow waves.

During spontaneous typical absence seizures, whether awake or asleep, the CBFVm decreased by 20-40% when compared to baseline CBFVm. At the end of the absence seizure episode, the CBFVm recovered gradually to the interictal level within an average time of 15 seconds (range: 8-20 seconds) after the termination of gSWD (*figure 1*).

During hyperventilation-evoked absence seizures, the CBFVm increased by 50-150% when compared to the baseline level (*figure 2*). In healthy children, TCD-vEEG revealed that hyperventilation led to a significant reduction in CBFVm (Diehl *et al.*, 2010). Notably, the CBFVm was still lower than the baseline level in interictal phases and similar to the CBFVm during spontaneous typical absence seizures (*figure 2*).

During BCPS, the CBFVm increased by 20-30% over the baseline level. Approximately 1-2 seconds after the seizure episode, the CBFVm recovered gradually to the interictal level (*figure 3*).

The dynamic CBFVm curve throughout vEEG monitoring clearly delineated all seizures (*figures 1, 2, 3*). The dynamic CBFVm curve is superior to EEG in the identification of seizures.

Table 1. Detailed demographic data and hemodynamic parameters.

Patient	Age (years)	MRI	Gender	Diagnosis	Side of MCA	Spontaneous seizures (times)	Baseline $CBFV_m$ during spontaneous seizures	Peak $CBFV_m$ during spontaneous seizures	Change (%)	Evoked seizures (times)	Baseline $CBFV_m$ during hyperventilation	Peak $CBFV_m$ during evoked seizures	Change (%)
1	6	N	Male	TAS	Left	5	120	74	-38	No	-	-	-
2	10	N	Female	BCPS	Right	1	115	150	23	No	-	-	-
3	12	N	Female	BCPS	Right	7	90	128	30	No	-	-	-
4	8	N	Female	TAS	Left	No	-	-	-	3	20	50	150
5	7	N	Male	TAS	Left	3	90	70	-22	10	35	80	129
6	8	N	Female	TAS	Right	5	100	62	-38	No	-	-	-
7	6	N	Female	TAS	Right	3	145	110	-24	No	-	-	-
8	7	N	Female	TAS	Right	3	105	75	-29	3	55	85	55

N: normal; TAS: typical absence seizures; BCPS: brief complex partial seizures; MCA: middle cerebral artery; CBFVm: mean cerebral blood flow velocity

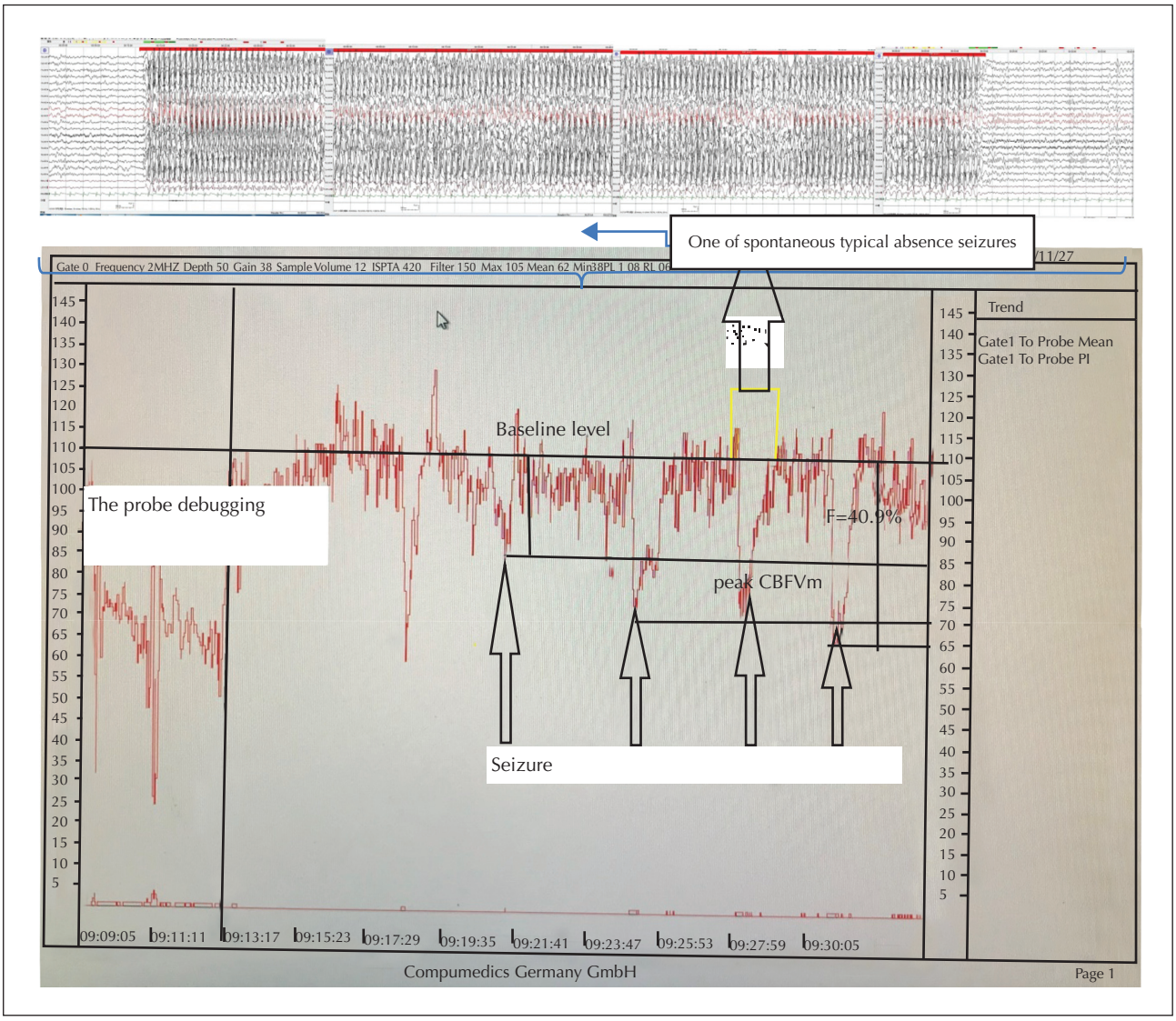

Figure 1. TCD-vEEG monitoring during spontaneous typical absence seizures showing CBFVm reduced by 20-40% when compared to baseline level.

Discussion

In the current study, we found that CBFVm decreased during typical absence seizures but increased during BCPS. It has been widely accepted that CBF is closely correlated to neuronal activity; neuronal activation increases metabolic demand, and as a result, CBF and corresponding perfusion increase. The CBFVm changes may indicate a neurovascular coupling mechanism (Iadecola, 2004). In the literature, TCD has been used to evaluate cerebral haemodynamics in patients with CAE (Sanada *et al*., 1988; Nehlig *et al*., 1996; Simone *et al*., 2002,), JAE (Bek *et al*., 2010), gSWDs (Diehl *et al*., 2010), partial seizures (Yao *et al*., 2015), and electrically induced generalized seizures (Vollmerhaase *et al*., 1998). Real-time TCD-vEEG monitoring is an appropriate technique to investigate CBF changes during seizure activity; this method is characterized by high temporal resolution and poor spatial resolution. Generally, during gSWD, CBF initially increases and subsequently decreases, which reflects neuronal activation. The decrease in CBF is attributable to the hyperventilation-induced hypocapnia (Peng *et al*., 2016).

The pathophysiology of absence seizures differs from that of partial seizures. It has been proposed that both the cortex and the thalamus are involved in the generation of typical absence seizures, and the thalamocortical system is mostly considered an oscillating network generating neurophysiological rhythms

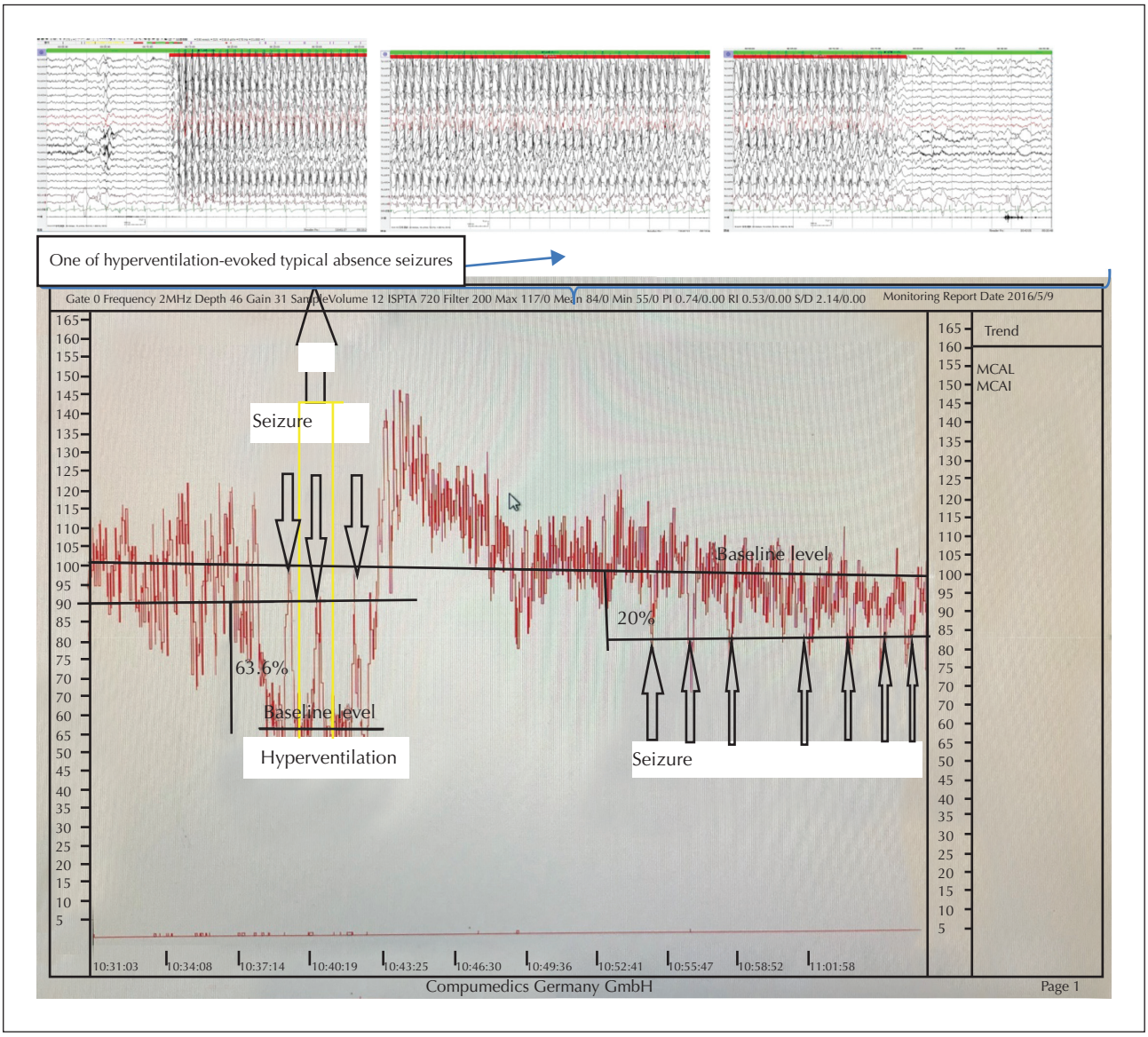

Figure 2. TCD-vEEG monitoring during hyperventilation-evoked absence seizures showing CBVFm increased by 50-150% when compared to baseline level.

(Meeren *et al*., 2005). Meanwhile, the findings that ethosuximide (an agent effective for absence seizures) specifically affects low-threshold calcium channels in thalamic neurons also support the role of thalamus neuronal activity in the generation of absence seizures (Coulter *et al*., 2010). Prevett *et al*. demonstrated an increase in CBF in the left thalamus using PET (Prevett *et al*., 1995). However, in our study, specific CBFV changes in the thalamus could not be detected by TCD due to the limited spatial resolution. Nonetheless, the peak level of CBF during hyperventilation-evoked absence seizures was still similar to the baseline level of CBFV during spontaneous typical absence seizures. We speculate that the redistribution of CBF during absence seizures, including the increase in CBF in the thalamus and the decrease in CBF in the cortex (reflecting excitation of thalamic neurons and inhibition of cortical neuronal activity), may represent metabolic recruitment of thalamocortical loops. It is well known that the thalamus is more tolerant of hypoxia than the cortex. During hyperventilation, the excitability of thalamic neurons exists but cortical neuronal activity is inhibited, and thus we posit that typical absence seizures are more apt to be evoked by hyperventilation. Further, in focal epileptogenic lesions, the overexcitation of cortical neurons increases metabolic demand and results in an increase in cortical CBF (Kovács *et al*., 2012).

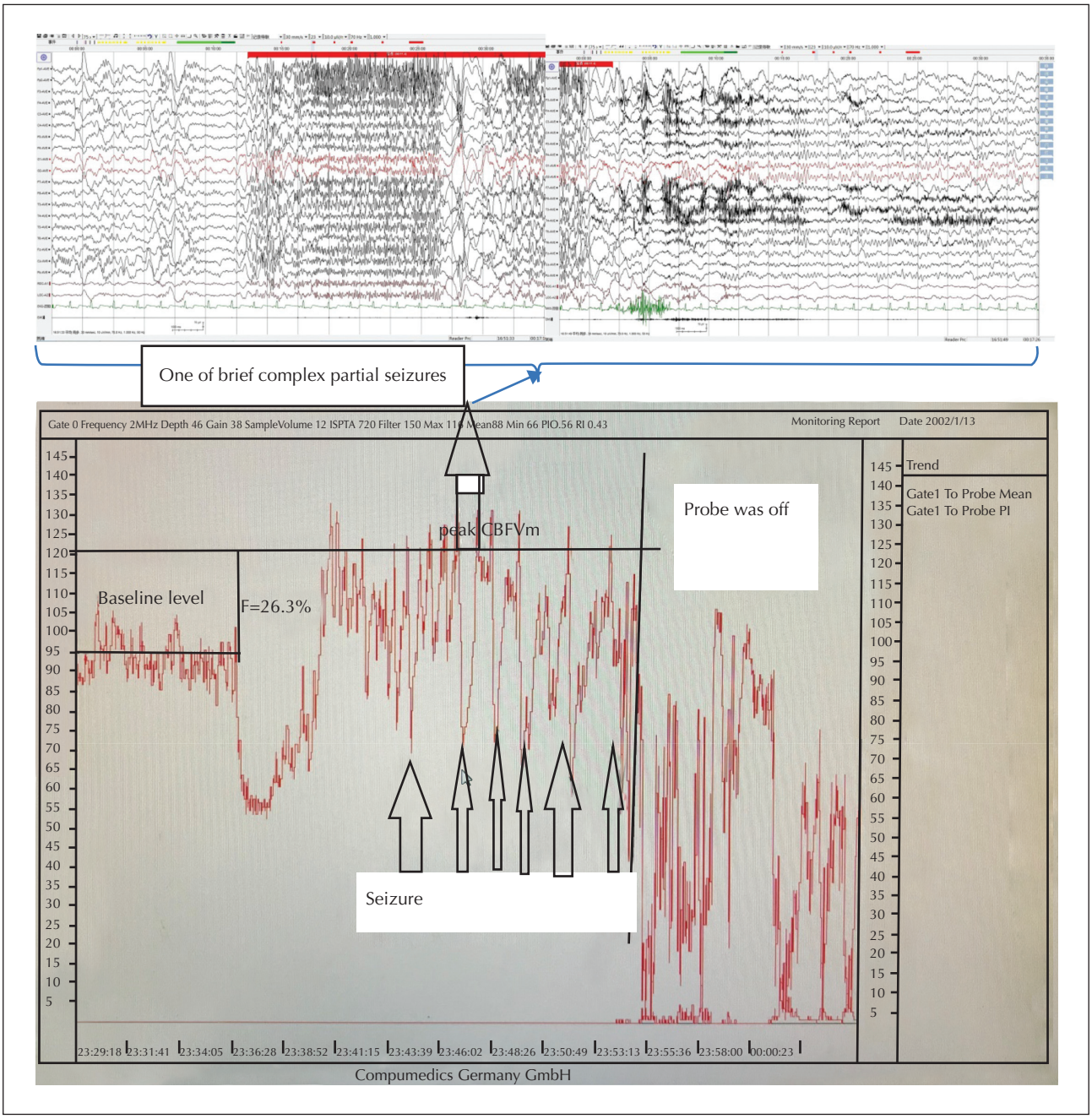

Figure 3. TCD-vEEG monitoring during brief complex partial (focal with alteration of awareness) seizures showing CBVFm increased by 20-30% compared to baseline level.

In our study, real-time TCD-vEEG revealed a decrease in CBF during all spontaneous absence seizures. Nehlig *et al*. observed a decrease in CBF in both cortical capillaries and the middle cerebral artery during absence seizures (Nehlig *et al*., 1996). Bek and colleagues also noted a similar phenomenon in patients with JAE (Bek *et al*., 2010). Additionally, we found an increase in CBF during hyperventilation-evoked absence seizures. This interesting finding may explain why hyperventilation causes absence seizures. According to our previous study (Peng *et al*., 2016), hyperventilation can lead to a significant reduction of arterial carbon dioxide partial pressure ($PaCO_2$), which may result in a decrease in CBF. Hyperventilation leads to hypocapnia and a resultant decrease in CBF to the cortex. This results in inhibition of cortical neurons and an override by thalamo-cortical loop oscillation. The increased CBF in the present

study may be due to a compensation to alleviate hypocapnia when hyperventilation ceased abruptly. The definitive mechanism of hyperventilation-evoked absence seizures remains unclear. We speculate that hyperventilation-related hypoperfusion may increase the risk of absence seizures.

BCPS can mimic absence seizures in clinical symptoms. EEG features can facilitate diagnosis. Based on this study, the dynamic curve of CBF could be used as a tool for an alternative diagnostic approach for the identification of absence seizures.

Given the above, we suggest that TCD-vEEG monitoring is a promising, appropriate, and inexpensive technique for the evaluation of neurovascular coupling in epilepsy. To the best of our knowledge, this is the first study comparing ictal cerebral haemodynamic characteristics during typical absence seizures and BCPS in paediatric patients.

There are several limitations to our study. Only eight cases were included which precluded any relevant statistical analysis. However, all our cases with TAS showed consistent ictal cerebral haemodynamic characteristics. Nevertheless, the number of cases with BCPS was limited, and thus the ictal cerebral haemodynamic characteristics of BCPS require further investigation. CBF changes were only detected in the unilateral MCA, as bilateral fixing of the probe was challenging to perform in paediatric patients. However, a previous study on partial seizures found a rapid increase in CBF in the bilateral MCA, which was more exaggerated on the onset side (Yao *et al*., 2015). CBF changes in bilateral arteries during absence seizures, therefore the CBF measurement of the unilateral MCA should not affect the trend in ictal cerebral haemodynamic changes. TCD-vEEG monitoring has poor spatial resolution, and thus we did not investigate CBF distribution or regional metabolic changes. In recent years, functional magnetic resonance imaging (fMRI) has been used to locate epileptic foci and analyse ictal connectivity. In future studies, we intend to combine TCD-vEEG monitoring and fMRI techniques.

Conclusions

The haemodynamic features during typical absence seizures and BCPS are different. Thus, the dynamic CBFVm curve provides a new method to diagnose typical absence seizures. Ictal cerebral haemodynamic characteristics during spontaneous typical absence seizures and hyperventilation-evoked absence seizures may be related to dysfunction of thalamocortical networks, reflecting different pathophysiological mechanisms and networks relative to BCPS. □

Key points

- Our study indicates that the haemodynamic characteristics during TAS and BCPS are distinct: during spontaneous TAS, whether awake or asleep, the CBFVm decreased compared to baseline, while during BCPS, the CBFVm increased over baseline levels.
- In our study, real-time TCD-vEEG revealed a decrease in CBF during all spontaneous absence seizures, and an increase in CBF during hyperventilation-evoked absence seizures. This interesting finding may explain why hyperventilation causes absence seizures.
- Based on this study, the dynamic curve of CBF could be used as a tool for an alternative diagnostic approach for the identification of absence seizures.

Disclosures.
None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) Absence seizures are clearly identified using vEEG; what is the value of the dynamic curve of CBF?

(2) How do you explain the difference between the haemodynamic characteristics during TAS and BCPS?

(3) Why are absence seizures easily induced during hyperventilation?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".