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ORIGINAL COMMUNICATION

Cerebral vasomotor reactivity in epilepsy patients

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Abstract Vasomotor reactivity, which can be defined as the cerebral vasculature response to hypoxia, is not well known in epilepsy patients. We aimed to evaluate cerebrovascular reserve in idiopathic generalized epilepsy patients using transcranial Doppler ultrasonography (TCD). The study included 20 patients and 20 healthy volunteers. Diagnosis of epilepsy was based on the observation of seizure in the video electroencephalography unit. Cerebrovascular reactivity was evaluated by means of the breath-holding index. Insonation depth and basal velocity were symmetrical and not significantly different between the two groups ($p > 0.05$). The breath-holding index ranged from 0.62 to 4.45 (mean 2.13 ± 0.83) in the epilepsy patients and 0.57 to 2.55 (mean 1.60 ± 0.46) in the control group ($p < 0.05$). Breath-holding index values showed that cerebrovascular reserve in epilepsy patients was increased, as compared to healthy individuals. Cerebrovascular reserve was increased in epilepsy patients; this should not be accepted as an abnormality, but might have been the result of an adaptive mechanism that protects the brain from hypoxic challenges due to seizure apnea.

Keywords Idiopathic generalized epilepsy · Neurovascular coupling · Transcranial Doppler ultrasonography · Cerebral blood flow velocity · Cerebral hemodynamics

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Introduction

A generalized tonic-clonic seizure (GTCS) is the most dramatic type of seizure. It is a symptom of many idiopathic, cryptogenic, or symptomatic epilepsies. Apnea is the typical feature in the tonic and clonic phases. Recovery begins with the cessation of clonic contractions, and respiration is restored with deep inspiration [1]. Either muscle contraction or central mechanisms are responsible for the apnea observed in GTCS.

Transcranial Doppler ultrasonography (TCD) is a non-invasive technique used to assess sudden changes in cerebral blood flow velocity (CBFV) in the basal cerebral arteries [2]. It is particularly useful for monitoring instant changes. It is assumed that flow changes during breath-holding are due to altered resistance caused by changes in diameter of the small vessels distal to the M1 segment and even distal to the M2 segment of the middle cerebral artery (MCA), and that the large vessels primarily serve as conductance channels without a diameter change [3–5]. These observed changes in the flow are indicative of cerebrovascular reserve of the cerebral vasculature in response to hypoxia [6].

The breath-holding maneuver mimics the apnea period observed in GTCS. In the present study, we aimed to collect data on cerebrovascular reserve in idiopathic generalized epilepsy (IGE) patients in response to hypoxia induced with breath-holding.

Methods

Patients

We examined 20 patients (all male; mean age 21.0 ± 1.0 years) with IGE and 20 healthy volunteers (all

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male; mean age 20.6 ± 0.8 years). All subjects provided informed consent prior to examination. The study was approved by the local ethics committee. Diagnosis of epilepsy was based on the observation of seizure in the video electroencephalography (EEG) unit, according to the International League against Epilepsy (ILAE) [7]. All of the patients had experienced seizures for more than 3 years, but were drug naive. Moreover, none of the patients were receiving antiepileptic treatment at the time of admission and TCD recording. Rigid exclusion criteria were established to avoid any bias due to concomitant diseases or drug therapy that could affect TCD recording. None of the subjects had hypertension, diabetes mellitus, obesity, congestive heart failure, chronic obstructive lung disease, cerebrovascular disease (any history of transient ischemic attack or stroke), carotid artery disease, or hematological disease; all were non-smokers. Magnetic resonance angiography was performed in all and confirmed that none of the subjects had any variation in the circle of Willis, or any intracranial stenosis, arteriovenous malformation, or aneurysm. Cerebral magnetic resonance imaging and neurological examinations were normal in all. All participants chosen were men of similar age because age and sex differences might influence TCD results [8].

Transcranial Doppler study

Subjects were invited to our sonography laboratory in the morning (0800) postprandial after 8 h of night sleep. The studies were performed using a DWL Multi-Dop X4 TCD instrument with patients in the supine position. Pulsed-wave Doppler probes (2 MHz) were fixed over each transtemporal window with a probe holder and fixator. The optimal signal for the MCA was obtained at a depth of 45–55 mm on both sides. Software included with the DWL instrument facilitated continuous recording of the mean velocity in arteries insonated during baseline and breath-holding challenges. Baseline was defined as a stable velocity during the last 3 min of an initial 10 min resting trial, after fixation of both probes. The breath-holding challenge was performed so as to activate vasomotor reactivity in the cerebral vasculature; three sets of breath-holding were performed. The subjects were instructed to hold their breath for 30 s with 5-min intervals of rest. Velocity measurements were made offline. The breath-holding maneuver was performed without any side effects, but the procedure had to be explained repeatedly to some patients in order for us to achieve the desired level of cooperation.

Cerebrovascular reactivity was evaluated by means of the breath-holding index (BHI). The BHI is obtained by dividing the percentage of increase in mean flow velocity that occurs during breath-holding by the length of time (30 s was standardized in this study) subjects held their breath after normal inspiration (mean flow velocity at the end of breath-holding − mean flow velocity at rest/mean flow velocity at rest × 100/seconds of breath holding) [4, 9].

Statistical analysis

Data were analyzed using SPSS v.15.0 statistical software. All measurements were evaluated using the t test. Quantitative data are presented as mean ±standard deviation, and p values <0.05 were considered significant.

Results

Two patients and one control subject were excluded because of inadequate temporal insonation. Data collected from 18 patients and 19 control subjects were evaluated.

Basal velocity obtained bilaterally from a depth of 49.44 ± 4.05 mm (49.44 ± 4.10 mm on the right side and 49.44 ± 4.10 mm on the left side) in the patient group was 51.84 ± 12.99 cm/s (51.47 ± 13.20 cm/s on the right side and 52.20 ± 13.16 cm/s on the left side) and from a depth of 49.58 ± 3.61 mm (49.26 ± 3.65 mm on the right side and 49.89 ± 3.63 mm on the left side) in the control group was 56.07 ± 12.48 cm/s (56.16 ± 13.68 cm/s on the right side and 55.98 ± 11.54 cm/s on the left side). Insonation depth and basal velocity were symmetrical and did not significantly differ between the groups ($p > 0.05$). Basal velocity in both groups was within our laboratory's normal range [10].

Although basal velocity did not differ between the groups, the BHI index ranged from 0.62 to 4.45 (mean 2.13 ± 0.83) among the epilepsy patients and from 0.57 to 2.55 (mean 1.60 ± 0.46) in the control group ($p < 0.05$). Detailed data are given in the tables. Breath-holding index values show that cerebrovascular reserve in the epilepsy patients was higher than in the controls.

Discussion

The ILAE glossary defines GTCS (formerly known as grand mal seizure) as bilateral symmetrical tonic contraction, followed by bilateral clonic contractions of somatic muscles, usually associated with autonomic phenomena [11]. During the tonic phase, there is sustained contraction of all skeletal muscles. Tonic contraction of the diaphragm and chest wall muscles appears to be responsible for the cyanosis that results from inadequate alveolar ventilation. The tonic phase may be brief (1–3 s) or as long as 20 s. The clonic phase is characterized by continuously

repetitive, massive, symmetrical, and synchronous flexor clonic convulsions, which last from 30 s to 1–2 min. Recovery begins with cessation of clonic contractions, and respiration is restored with deep inspiration [1].

Ictal apnea during epileptic seizures may be due to contraction of the diaphragm muscles and other muscles involved in breathing, or reduced central breathing drive [12]. On the other hand, partial seizures without respiratory muscle contraction that manifest with apnea have been reported [13]. Although several cortical-subcortical regions were suggested to be responsible for central apnea, the exact region responsible for ictal epileptic apnea is not well defined [12].

Cerebral hypoxia and ischemia seem to play a crucial role in self-regulatory seizure cessation, based on various animal models. Failure of seizure inhibition leads to seizure prolongation and status epilepticus. Prolonged GTCS was reported with self-induced breath-holding. During cerebral hypoxia, metabolic requirements lower the seizure threshold, a phenomenon widely known to trigger absence seizures [14]. Transient ictal oxygen desaturation is observed in 35–60% of patients with partial seizures and in 10–25% of patients with generalized convulsions [15]. Recent studies report that the nadir of oxygen desaturation coincides with seizure cessation, confirming at least a correlation between hypoxia and seizure cessation [15, 16].

Nevertheless, apnea causes transient hypoxia in the cerebral cortex. Hypoxia is a well-known precipitating factor that lowers the seizure threshold and causes cortical damage. As soon as the seizure stops, hypoxia should be surpassed in order to minimize the hazardous effects of hypoxia, which can lead to ischemia and even cortical infarct. Intact vasomotor reactivity and evaluation of cerebrovascular capacity in epilepsy patients might be helpful in this regard.

Transcranial Doppler sonography has proved to be a suitable non-invasive technique for measuring CBFV in the large cerebral arteries [2]. Under physiological conditions changes in neuronal activity, CBF, and metabolism are closely related. As blood flow and metabolism are closely coupled, increased perfusion might result from increased metabolic demand due to neuronal activation. The opposite of this may also be true, as a decrease in perfusion might result in a net decrease in metabolism due to inhibition [17]. This increase in perfusion is directly related to CBFV changes in the proximal portion of the cerebral arteries and can be easily measured with TCD [18].

Among the non-invasive and low-cost methods for assessing cerebral hemodynamics, TCD plays a fundamental role. With TCD it is possible to measure cerebral artery blood flow velocity (CBFV) and hence to analyze variations in CBF. The vasodilation capacity of the cerebral arterioles can be evaluated indirectly from the blood flow velocity in the major cerebral arteries. Vasodilatory stimulus-carbon dioxide inhalation, acetazolamide injection, and breath-holding are used to evaluate this capacity, which is defined as cerebrovascular reserve or vasomotor reactivity [6].

The present study aimed to investigate cerebrovascular reserve in epilepsy patients. We observed a significant difference in BHI values between the patients and controls, indicating that the epilepsy patients had an increase in cerebrovascular reserve in response to hypoxic challenges. Basal CBFV values were similar in both groups, which shows that while at rest cerebrovascular dynamics did not differ between the patients and the healthy controls. The breath-holding maneuver provided 30-s hypoxia, and the cerebral blood flow increase was more prominent in the patient group, which is indicative of the capacity of the arterioles to vasodilate.

A decrease in cerebral vasomotor reactivity has been reported in numerous clinical conditions, including Alzheimer's disease [19], stroke and carotid artery disease [20], and even in depression [21] and erectile dysfunction [22]. Restoration of vasomotor reactivity has also been reported [23–26]. To the best of our knowledge, increased cerebrovascular reactivity has been reported only in migraine patients and was considered an abnormality [22]. The present study is the first to evaluate vasomotor reactivity in epilepsy patients.

What mechanism is responsible for increased cerebrovascular capacity in epilepsy, and is it abnormal? The epileptic brain is accustomed to transient hypoxia, as apnea is observed during each GTCS. Increased CBFV after apnea could be the result of an adaptive mechanism that minimizes the hypoxic damage. As we know, nitric oxide (NO) has an important role in cerebrovascular blood flow. Recent studies show that basal NO release is important for controlling human CBF, but not cerebrovascular reactivity [27]. In young healthy humans, pharmacological blockade of NO synthesis did not affect increases in cerebral blood flow with hypoxia and hypercapnia, suggesting that NO is not required for cerebrovascular responses to hypoxia and hypercapnia [28]. These data suggest that inhibition of tonic production of NO does not appear to alter dynamic cerebral autoregulation in humans [29]. In the present study basal CBF velocity did not differ between the groups, indicating that NO metabolism in each group was similar and that NO was not responsible for the increased BHI observed in the epilepsy patients (Tables 1, 2).

Another hypothesis involves adenosine. Increased adenosine concentrations can be observed during diffuse anoxia-ischemia and under conditions of extreme metabolic stress, such as that which occurs during prolonged seizures or during traumatic brain injury, resulting in a micromolar surge in adenosine levels [30]. Moreover,

Table 1 Detailed data of blood flow velocities recorded from bilateral middle cerebral arteries (MCA) and breath-holding indices (BHI) recorded from bilateral MCA in three challenges of the control group

Subject no.	Right MCA mean basal blood flow velocity (cm/s)	Left MCA mean basal blood flow velocity (cm/s)	Right MCA BHI 1	Left MCA BHI 1	Right MCA BHI 2	Left MCA BHI 2	Right MCA BHI 3	Left MCA BHI 3
1	70.0	69.7	1.10	0.97	0.57	1.26	0.86	0.68
2	49.8	52.9	1.95	2.09	1.69	1.83	1.55	1.77
3	53.9	51.6	1.99	1.38	1.86	0.99	1.92	1.25
4	52.3	49.9	1.13	0.67	1.00	0.67	1.00	0.67
5	62.9	81.0	2.50	1.98	2.44	1.93	2.55	1.93
6	37.1	33.6	1.70	1.33	2.33	1.43	1.88	1.23
7	41.5	42.6	2.21	1.60	1.81	1.28	2.13	1.52
8	67.6	50.1	1.84	1.72	1.70	1.46	1.70	1.72
9	49.6	45.4	1.30	1.07	1.30	1.07	1.30	1.15
10	42.4	51.7	1.62	1.50	1.93	1.82	2.01	1.57
11	55.7	49.2	1.63	1.75	1.75	1.82	1.69	1.75
12	75.9	60.3	1.85	1.86	1.76	2.14	1.50	1.70
13	48.3	55.3	2.05	2.33	2.19	1.73	2.53	1.73
14	36.1	54.5	1.47	1.19	1.75	1.56	1.38	1.13
15	55.2	67.1	2.46	2.08	2.10	1.68	2.22	1.93
16	54.1	55.9	1.90	1.56	1.97	1.62	2.15	2.03
17	68.0	54.9	1.13	1.10	0.78	0.80	0.83	0.80
18	56.8	60.5	1.19	1.29	1.19	1.29	1.24	1.18
19	89.8	77.4	1.53	2.01	1.60	2.18	1.60	2.18

Table 2 Detailed data of blood flow velocities recorded from bilateral middle cerebral arteries (MCA) and breath-holding indices (BHI) recorded from bilateral MCA in three challenges of the epilepsy group

Patient no.	Right MCA mean basal blood flow velocity (cm/s)	Left MCA mean basal blood flow velocity (cm/s)	Right MCA BHI 1	Left MCA BHI 1	Right MCA BHI 2	Left MCA BHI 2	Right MCA BHI 3	Left MCA BHI 3
1	77.1	57.2	1.55	1.62	1.34	1.39	1.34	1.33
2	46.7	60.0	2.16	1.89	4.30	3.89	2.16	2.06
3	57.3	43.8	2.25	2.53	1.32	1.23	1.73	1.54
4	49.2	44.4	3.04	2.75	3.37	3.05	3.37	3.05
5	82.5	86.2	1.60	1.31	1.60	1.27	1.84	1.50
6	52.2	57.2	2.54	2.26	1.33	1.33	1.84	1.50
7	40.9	49.0	1.56	2.04	1.80	2.04	2.21	2.18
8	44.7	38.2	1.96	2.60	1.59	2.16	1.29	1.90
9	56.0	58.5	2.20	2.36	2.44	3.05	1.85	1.91
10	56.9	56.0	1.94	1.79	1.47	1.37	2.17	1.85
11	43.4	38.9	3.35	2.66	3.81	3.26	2.35	2.07
12	31.2	36.4	3.61	3.26	2.54	3.72	2.86	4.45
13	46.9	46.2	1.78	1.50	2.49	1.93	4.41	3.81
14	41.9	35.0	1.12	1.52	1.04	1.62	1.20	1.43
15	60.3	72.6	0.92	0.98	0.65	0.75	0.65	0.62
16	38.4	61.8	1.53	1.57	1.96	1.90	1.96	1.84
17	39.7	49.7	2.71	2.30	2.80	2.23	2.46	2.23
18	61.2	48.5	2.60	2.71	2.60	2.78	2.77	3.13

adenosine levels remain elevated above basal values during the postictal refractory period [31]. Adenosine acts as an endogenous antiepileptic regulator in the brain [32]. The release of the endogenous anticonvulsant adenosine is a physiological consequence of seizures and a mechanism of seizure termination [30]. Likewise, therapeutic adenosine

augmentation is an effective strategy for the suppression of seizures. This seizure-induced rise in adenosine was considered to be sufficient to terminate ongoing seizure activity.

Adenosine can be released directly from astrocytes [33]. Under physiological conditions, extra- and intracellular levels of adenosine are rapidly equilibrated via distinct families of nucleoside transporters [34]. As neuron-centered pharmacotherapy fails in about 30% of patients, researchers have focused on neuron-glial interactions. A single astrocyte can sense the activity and integrate the function of hundreds of neurons within its domain. In addition, each astrocyte extends at least one process with end-feet surrounding the blood vessels of the microvasculature. As such, astrocytes are uniquely located to adjust regional CBF to regional energy metabolism. Astrocytes play a key role in regulating the extracellular availability of endogenous anticonvulsant adenosine. Adenosine, in particular, plays a prominent role in seizure regulation and is reported to be elevated in patients following seizures, leading to the conclusion that adenosine released during a seizure mediates seizure arrest and postictal refractoriness [34].

Adenosine released at the start of a seizure might be responsible for vasodilation in the arterioles, which manifests as increased vasomotor reactivity to hypoxia in epilepsy patients. Hypoxia experienced in normal subjects also activates adenosine release, as we know anoxia triggers the mechanism, but extra- and intracellular levels of adenosine are rapidly equilibrated via distinct families of nucleoside transporters under physiological conditions. In an epileptic brain, this equilibration sequence might be slower.

Some limitations of the present study should be addressed. All the participants were male. Using sex-matched groups of patients and healthy controls would have eliminated confounding due to sex differences and would have been more representative. We limited the study groups to males, as in our previous study, because sex differences could influence TCD results [4, 8].

In conclusion, the results of the present study suggest that cerebrovascular reserve increases in epilepsy patients. Basal CBF velocity did not differ between the groups, indicating that NO metabolism in each group was similar and that NO was not responsible for the observed increase in cerebrovascular reserve. Although adenosine levels were not evaluated in this study, we propose an answer to the question, "what increases cerebrovascular capacity in epilepsy, and is it abnormal?" Taken together, data provided by the present study and previous studies might indicate that adenosine plays a role in mediating seizure arrest and postictal refractoriness. Adenosine might be responsible for increasing cerebrovascular reserve. Increased cerebrovascular reserve should not be accepted as an abnormality, as it is in migraine patients, but might be the result of an adaptive mechanism that protects the brain from hypoxic challenges due to seizure apnea. Additional research with adenosine antagonists and/or agonists should be conducted to elucidate precisely the role of adenosine in cerebrovascular hemodynamics and sudden unexplained death in epilepsy patients, to which patients without an increase in cerebrovascular reserve might be more susceptible.

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