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Will a Critical Level of Hyperventilation-Induced Hypocapnia Always Induce an Absence Seizure?

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Summary: We wished to determine if the degree of hypocapnia correlates with increased frequency of absence seizures and if there is a critical pCO_2 at which absence seizures are reliably provoked. Twelve untreated children with newly diagnosed absence epilepsy were continuously monitored by EEG and end-expiratory CO_2 recording during quiet respiration and hyperventilation (to absence seizure or exhaustion) while breathing four gas mixtures: (a) room air, (b) 100% O_2, (c) 4% CO_2 in room air, or (d) 4% CO_2 + 96% O_2). In quiet respiration, a reduction in number of spike and wave bursts and total seconds of spike and wave was noted in children breathing supplemental CO_2 (gases c and d vs. gases a and b), $p < 0.05$. Supplemental O_2 had no effect. Eight subjects had absence seizures elicited with each trial of hyperventilation. All subjects had their own critical pCO_2, ranging from 19 to 28 mmHg. Three children had no seizures, two despite hypocapnia to pCO_2 of 19 and 21 and 1 who achieved a pCO_2 of only 25. In 1, absence seizures were provoked in only six of nine hyperventilation trials to pCO_2 of 17–23. In 67% of subjects, absence seizures were reliably provoked by hypocapnia. Critical pCO_2 varied among children with absence. Determination of whether variation in sensitivity to hypocapnia may be helpful in determining response to antiepileptic drugs (AEDs) or remission of seizures will require further study. **Key Words:** Hypocapnia—Absence seizures—Epilepsy—Hyperventilation.

Hyperventilation produces slowing of the EEG in most patients and is a known precipitant of absence seizures. This technique is often used to confirm the diagnosis of absence epilepsy and to assess seizure control in patients receiving antiepileptic drugs (AEDs). The degree of hypocapnia and the duration of hyperventilation required to induce absence seizures in untreated children has not been studied. We wished to determine if supplemental CO_2 and O_2 correlates with decreased frequency of absence seizures and if there is a consistent critical pCO_2 below which the absence seizure frequency increases.

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METHODS

We identified children with newly diagnosed absence epilepsy prospectively by reviewing EEG records at the Izaak Walton Killam Hospital for Children in Halifax, Nova Scotia. All pediatric EEG records for the province of Nova Scotia are reported in this department. Inclusion criteria included: (a) EEG showing typical 3-Hz generalized spike and wave discharge, (b) clinical confirmation of typical absence epilepsy by a pediatric neurologist, and (c) ability of the child to hyperventilate on request. All children meeting entry criteria between December 1993 and February 1995 were invited to participate in the study, and all patients were studied before initiation of AED treatment.

EEGs were continually recorded during the testing with a 16-channel electroencephalograph. Subjects breathed through a snorkel apparatus that delivered the desired gas during the inspiratory phase of the respiratory cycle and allowed continuous monitoring of end-expiratory CO_2. Serum pH was not assessed since it could not be monitored noninvasively.

TABLE 1. *Does supplemental CO_2 decrease spontaneous spike-wave discharge?*

Subject	No. of spike-wave bursts per hour			No. of seconds of spike-wave per hour		
	No CO_2	CO_2	Δ	No CO_2	CO_2	Δ
1	8	7	1	140	68	72
2	20	0	20	68	0	68
3	34	11	23	284	94	190
4	5	0	5	39	0	39
5	2	0	2	4	0	4
6	0	3	−3	0	39	−39
7	1	0	1	14	0	14
8	1	5	−4	3	34	−31
9	14	0	14	120	0	120
10	7	7	0	25	11	14
11	12	2	10	71	22	49
12	21	16	5	49	46	3
Mean	10.4	4.3	6.2[a]	68.1	26.2	41.9[a]

[a] $p < 0.05$ (Student's t test).

Quiet respiration

Each subject was recorded at rest for a minimum time of 120 s while breathing room air, 100% O_2, 4% CO_2 in room air, and 4% CO_2/96% O_2. Between trials with the various gases, the breathing apparatus was flushed with the new gas, followed by quiet respiration by the subject for 1 min before recording was resumed. The number of bursts and total duration of spike and wave activity were noted for each gas mixture.

To assess whether CO_2 decreased spontaneous spike and wave discharge, the difference in number of bursts and total seconds of spike and wave with supplemental CO_2 (4% CO_2 in room air, 4% CO_2/96% O_2) and with no supplemental CO_2 (room air, 100% O_2) was compared for each patient. To determine if supplemental O_2 decreased spike and wave discharge, we performed similar calculations, comparing gases containing supplemental O_2 (100% O_2, 4% CO_2/96% O_2) and no supplemental O_2 (room air and room air with 4% CO_2).

Hyperventilation

Subjects were then asked to hyperventilate while breathing each gas mixture until an absence seizure occurred or until the child was exhausted. The end-expiratory CO_2 at seizure onset or point of exhaustion was noted for each hyperventilation trial. Critical pCO_2 was defined as the mean level of end-expiratory pCO_2 required to induce an absence seizure. Gases containing supplemental O_2 and CO_2 were used during several hyperventilation trials to ensure that absence seizure induction occurred at a given level of hypocapnia rather than being dependent on effort or duration of hyperventilation since subjects would have to exert greater effort to achieve the same level of hypocapnia while breathing a gas mixture containing supplemental CO_2. Statistical analysis was performed with Epilnfo 6 (1). Student's t test was used to determine if supplemental CO_2 and O_2 were associated with decreased spontaneous spike-wave discharge.

RESULTS

Thirteen patients with newly diagnosed absence seizures were eligible, and 12 of 13 (92%) agreed to participate. There were 9 girls and 3 boys (mean age 9.3 years, range 5.9–12.5 years). Eleven had childhood absence epilepsy and 1 (subject 6) had juvenile absence epilepsy.

Quiet respiration

The total bursts of generalized spike and wave per hour and seconds of spike and wave per hour during quiet respiration are shown with and without supplemental CO_2 (Table 1) and O_2 (Table 2). Supplemental CO_2 significantly decreased both the number of bursts and total seconds of spike and wave discharge ($p < 0.05$), but supplemental oxygen had no effect.

Hyperventilation

Collectively, 103 trials of hyperventilation were conducted in the 12 subjects with the four gas mixtures (mean number of trials per subject 8.6, range 5–14). For trials that were discontinued because of exhaustion, the mean duration of hyperventilation was 163 s (range 120–330 s). Subjects could be divided into three groups based on their response to hyperventilation (Fig. 1).

Group 1

Subjects 1–8 reliably had absence seizures provoked with hyperventilation. Their mean age was 9.9 years (range 5.9–12.5 years). Critical pCO_2 varied among subjects (19–28 mmHg) but was consistent for individual children (±3 mmHg). There was

TABLE 2. *Dose supplemental O_2 decrease spontaneous spike-wave discharge?*

Subject	No. of spike-wave bursts per hour			No. of seconds of spike-wave per hour		
	No O_2	O_2	Δ	No O_2	O_2	Δ
1	3	16	−13	34	280	−246
2	20	0	20	68	0	68
3	23	31	−8	274	115	159
4	1	8	−7	8	63	−55
5	2	0	2	4	0	4
6	3	0	3	39	0	39
7	1	0	1	14	0	14
8	6	0	6	38	0	38
9	6	17	−11	50	139	−89
10	9	6	3	15	22	−7
11	3	12	−9	28	65	−37
12	16	22	−6	42	53	−11
Mean	7.8	9.3	−1.6[a]	51.2	61.4	−10.3[a]

[a] p = NS (Student's t test).

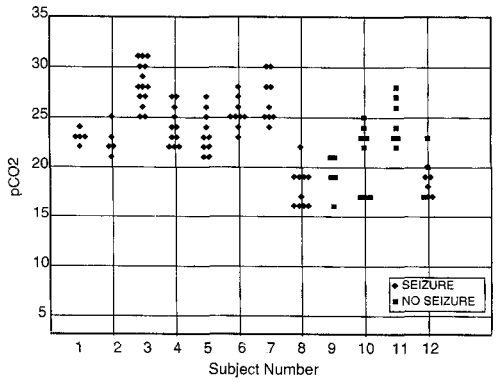

FIG. 1. Response to hyperventilation. Group 1 (subjects 1–8) had reliable provocation of spike-wave discharge with hyperventilation. Group 2 (subjects 9–11) had no provocation of spike-wave discharge with hyperventilation. Group 3 (consisting of 1 subject, subject 12) had occasional provocation of spike-wave discharge with hyperventilation.

no correlation between seizure frequency at rest and mean end-expiratory pCO_2 at seizure onset.

Group 2

Subjects 9–11 had no seizures during multiple hyperventilation trials, although subject 11 may not have achieved a sufficiently low end-tidal CO_2. Their mean age was 10.6 years (range 10.2–10.8 years).

Group 3

Group 3 consisted of subject 12, who showed an intermediate response to hyperventilation, with spike and wave discharge occurring in only six of nine hyperventilation trials. Her age was 10.7 years.

Although younger patients were more likely to show activation of spike and wave discharge with hyperventilation, this finding did not reach statistical significance.

DISCUSSION

Hyperventilation causes EEG slowing in normal subjects that is greatest in younger children and is a well-known activation technique for precipitation of absence seizures (2). Proposed mechanisms for EEG slowing include cerebral hypoxia and neuronal hyperexcitability. Hypocapnic-induced reduction of cerebral blood flow and increased hemoglobin oxygen affinity could cause cerebral tissue hypoxia. However, Kennealy et al. showed that EEG changes of hyperventilation in healthy, nonepileptic subjects were independent of the concentration of inspired oxygen (3). Van der Worp et al. (2) recorded EEGs under two sets of experimental conditions: (a) hyperventilation to obtain a $PaCO_2$ of 2.0 kPa under conditions of normal oxygenation, and (b) decreased hemoglobin oxygen saturation to 60% while the $PaCO_2$ was maintained within the normal range. They concluded that EEG changes during hyperventilation could not be explained by cerebral hypoxia (2). Yamatani et al. (4), measuring cerebral blood flow in the right carotid artery during hyperventilation, reported that decreases in pCO_2 and cerebral blood flow were the fundamental factors causing EEG slowing. Decreased cerebral blood flow paralleled the degree of hypocapnia and was not observed when hyperventilation was performed with 5% CO_2, because the pCO_2 did not decrease (4).

Hyperexcitability of neurons may be induced by respiratory alkalosis (5). Esquivel et al. (5) compared the effects or overbreathing induced by physical exercise with that of voluntary hyperventilation in induction of absence seizures in children. Seizure frequency decreased with physical exercise but significantly increased with voluntary hyperventilation. A significant, linear, positive correlation was noted between the mean change in plasma pH and the frequency of absences. With physical exercise, overbreathing is adaptive to the body's energy needs; there is no change in plasma pH or $PaCO_2$. With voluntary hyperventilation, a respiratory alkalosis is induced.

The mechanism of thalamocortical circuitry with generation of abnormal oscillatory rhythms in generalized absence seizures has been reviewed (6). Thalomocortical rhythmicity is driven by the nucleus reticularis thalami through γ-aminobutyric acid (GABA) and glutamate-mediated mechanisms. An *N*-methyl-D-aspartate (NMDA)-mediated excitatory postsynaptic potential followed by a $GABA_A$/$GABA_B$-mediated inhibition triggers a low-threshold calcium current in neurons of the nucleus reticularis thalami. This low-threshold calcium current leads to another depolarization and the cycle is repeated. Ascending cholinergic pathways projecting to the thalamus and noradrenergic and dopaminergic pathways projecting to the cortex modulate the setpoint of thalamic and cortical excitability.

Sherwin (7–9) studied the effect of hyperventilation on the excitability of neuronally isolated cortex in cats and suggested that hypocapnia primarily affects subcortical structures, which in turn modify excitability of the cortex through the nonspecific thalamic projecting system. He postulated that hyperventilation induces a shift in the primary locus of diffuse cortical afference so that activity in the nonspecific thalamic projection system predominates over the ascending reticular activating system. Bilateral interruption of the nonspecific thalamic projecting system in cats abolishes the major effects of

hyperventilation on the electrocorticogram, adding support to this theory.

Critical pCO_2 varied among our subjects with consistent activation of spike and wave discharge with hyperventilation. This variation suggests that all subjects do not have the same predisposition to seizure induction which may be related to genetic factors (10) or age. Absence seizures occur more commonly in younger patients, presumably because of a subtle developmental shift in the balance of NMDA-mediated excitation and $GABA_B$-mediated inhibition that enhances abnormal thalamocortical oscillatory rhythms. With maturation, there is an increase in both NMDA and $GABA_B$ receptors in the brain (11,12), with frequent remission of seizures.

We did not find a relation between seizure frequency at rest and higher critical PCO_2. Because there is an age-related predisposition to absence seizures, we expected younger children to have higher critical pCO_2. Our data show only a trend in this direction. Why some children did not activate with hyperventilation is not clear. Waltz (13) analyzed EEG findings from children with pyknoleptic and nonpyknoleptic absences and noted no significant difference in provocation of discharge with hyperventilation.

For each individual subject, pCO_2 at seizure induction was consistent, suggesting a unique sensitivity to a given level of hypocapnia. The value of this finding for monitoring treatment or predicting remission requires further study.

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