

Hyperventilation and Seizures: Not a New Sense: A Literature Review

Mandeep Rana¹ Maija Steenari² Daniel Shrey² 

¹Department of Pediatrics, Section of Pediatric Neurology, Carilion Clinic, Virginia Tech Carilion School of Medicine Roanoke, Virginia, United States

²Department of Pediatrics, University of California, Irvine Division of Neurology, CHOC, 1201 W La Veta Avenue, Orange, California, United States

Address for correspondence Mandeep Rana, MD, Department of Clinical Neurophysiology, University of California Irvine, Children's Hospital of Orange County, CHOC Children's Comprehensive Epilepsy Center, 1201 W La Veta Avenue, Orange, CA 92868, United States (e-mail: docmrana@gmail.com).

Neuropediatrics 2023;54:359–364.

Abstract

Hyperventilation and seizures have a long association in the clinical literature and were known to have a relationship long before the electroencephalogram (EEG) was used to record changes in brain activity. As the use of EEG recording progressed, hyperventilation was the first activation method used to assist with diagnosis of epilepsy. Along with slowing of brain activity, hyperventilation can activate epileptiform spiking activity in patients with epilepsy. Currently, hyperventilation is used in standard practice to assist with the diagnosis of epilepsy during EEG recording. Hyperventilation activates epileptiform spiking activity more often than seizures but can trigger clinical seizures in up to 50% of patients with generalized epilepsy. It is more likely to trigger events in children with absence seizures than adults, and it acts as a trigger in patients with focal epilepsy far less often. However, while some clinicians suggest that its diagnostic value is limited, especially in adults with focal epilepsies, others suggest that it is simple, safe, and an important diagnostic tool, even in these patients. This review presents the history of hyperventilation and seizures, its use in the clinical practice, and possible mechanisms involved.

Keywords

- ▶ epilepsy
- ▶ absence
- ▶ generalized
- ▶ focal
- ▶ hyperventilation
- ▶ hypocalcemia

Introduction

Hyperventilation (HV) has been known to trigger seizures for over 90 years and was first reported by Otfried Foerster.¹ Later, when the electroencephalogram (EEG) was developed as a tool for recording electrical activity of the brain, HV was used as the first activation procedure during EEG.² EEG recording shows that in normal subjects HV provokes a physiological slowing of brain rhythms; however, in many cases of epilepsy, HV-activated epileptiform spiking activity also occurs.³ For example, spike wave discharges are triggered by voluntary HV in over 90% of patients with absence epilepsy. It was later established that HV may elicit clinical seizures in up to 50% of patients with generalized epilepsy, with it being most likely to trigger seizures in children with absence epilepsy^{4–6} (see ▶ **Fig. 1**).

At the present time, HV is routinely used as an activation technique during EEG recording.⁷ Epileptiform discharges and seizures are frequently triggered by HV in genetic generalized epilepsies.⁸ Further, similar activation has been reported, less frequently, in focal epilepsy, with temporal lobe epilepsy patients being more susceptible than others.⁹ In patients with genetic generalized epilepsies, the epileptiform discharges are 3-Hz spike-and-wave complexes, whereas slow spike and wave complexes are more commonly seen in patients with symptomatic generalized epilepsies.⁹ Despite the apparent clinical utility derived from the above, some studies question the role of HV in epilepsy diagnosis, notably in adult populations where the number of patients demonstrating altered EEG recordings due to HV can be quite low.^{10,11} The aim of this review is to present a

received
June 30, 2022
accepted after revision
August 19, 2023
article published online
October 9, 2023

© 2023, Thieme. All rights reserved.
Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI <https://doi.org/10.1055/s-0043-1774808>.
ISSN 0174-304X.

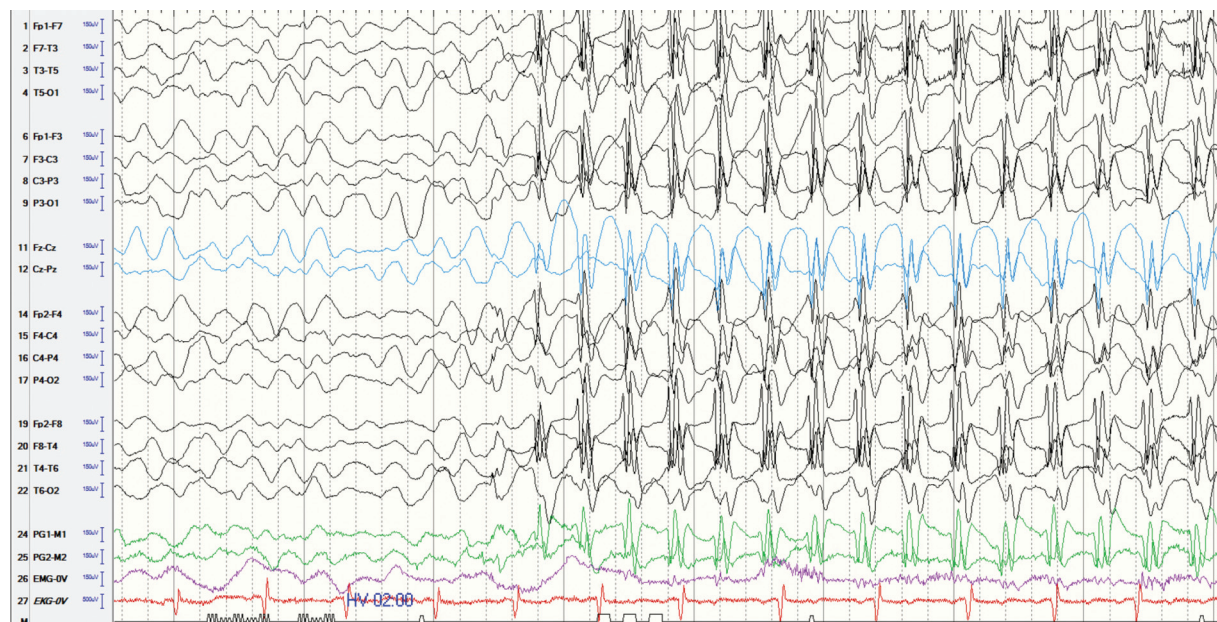


Fig. 1 A 5-year-old with childhood absence epilepsy. Absence seizure triggered by hyperventilation. Sensitivity: 10 microvolts/mm, Display: 10 seconds/page.

literature review of the relationship between HV and seizures and to discuss its mechanism and use in the clinic.

Mechanisms Involved in HV Activation of Seizures

Hypocapnia and Hypoxia

Several hypotheses have been proposed to explain why HV can trigger seizures in patients with epilepsy. These are most commonly based on two physiological mechanisms inherent to HV: (1) hypoxia due to vasoconstriction and reduced oxygen delivery to the cerebral cortex and (2) reduced carbon dioxide (CO_2) levels in the blood, known as hypocapnia.⁹ Resolution of the mechanism has been complicated by the occurrence of two distinct electrographic responses to HV: slowing of brain rhythms and spiking activity. Recent literature suggests that, of these two phenomena, spiking activity is more closely related to seizure activation.¹²

Current evidence regarding the link between HV and neuronal hypersynchronous spiking activity favors a mechanism that involves changes in arterial partial pressure of CO_2 (pCO_2), decreased cerebral blood flow velocity, and respiratory alkalosis. As a result, it is thought membrane stability is decreased in neuronal tissue, so that neurons are more easily excited with a tendency to spontaneous discharges.¹³ Both animal models and clinical studies show that a rise in pH leads to an increase in neuronal excitability and thus may produce epileptiform activity.^{6,14}

In normal subjects, HV decreases arterial pCO_2 and the resulting elevated pH causes vasoconstriction reducing cerebral blood flow.¹⁵ After 2 minutes of HV the cerebral blood flow was 50 mL/(100 g min) considered to be a critically low level for brain function.¹⁵ This physiological process likely plays an important role in HV-triggered seizures in susceptible patients. It is likely that the epileptic temporal lobe may

be particularly prone to ischemia during HV as seen by monitoring of cortical blood flow in the epileptic temporal lobe.¹⁵

There is no pCO_2 threshold that has been shown to universally cause seizures, as this threshold varies from one patient to the next, but in a particular patient the level of CO_2 that triggers seizures remains consistent over time, suggesting patient-specific sensitivities to hypocapnia.⁶ Further, it seems that the [acute?] change in pCO_2 level, not the absolute pCO_2 level, is more critical for triggering seizures.¹⁶

The reason behind why some people with epilepsy are insensitive to HV is not clear. A study into the added value of HV and intermittent photic stimulation found that because HV is easy to perform it is an important part of routine EEG, but its clinical diagnostic value was mostly realized in younger patients.¹⁷ The differences in HV response seen between the young and old may be due to the differences in decreased cerebral blood flow and the sensitivity of the central nervous system to the change in flow that have been shown to alter with age.¹⁸

Dysfunction of the Autonomic Nervous System

The autonomic nervous system that acts as an unconscious control of respiration, cardiac regulation, vasomotor activity, and some reflexive actions has been shown to be dysfunctional in a subset of patients with epilepsy.¹⁹ The sympathetic division of the autonomic nervous system is involved in the well-known fight or flight response. A study that investigated the sympathetic response to HV by looking at heart rate responses found that patients with mesial temporal lobe epilepsy showed increased sympathetic responses to HV compared to healthy subjects.²⁰ This suggests that sympathetic overactivation during HV may be an important process for triggering seizure activity in a subset of cases of focal epilepsy. Patients with epilepsy have an associated

risk of sudden unexpected death which is partly related to cardiac events.²¹ Meta-analysis shows that there appears to be a sympathovagal imbalance in epilepsy; patients with epilepsy have a low baseline vagal tone and those receiving antiepileptic drugs have a higher sympathetic tone.²² In addition, patients with refractory epilepsy that demonstrate a dysfunctional autonomic nervous system are sometimes successfully treated with vagus nerve stimulation.²³

Brain Diffusion

Quantitative diffusion magnetic resonance imaging has shown that brain diffusion is increased in the hippocampus of patients with temporal lobe epilepsy, but not in healthy control subjects. During HV, patients with temporal lobe epilepsy and hippocampal sclerosis exhibited decreased focal brain diffusion in the ictogenic hippocampus. A similar HV-related change in brain diffusion was not seen in patients with epilepsy without hippocampal sclerosis nor in controls.²⁴

Exercise

Cases of exercise-induced seizures have been reported in the literature, though these phenomena occur much less frequently than HV-induced seizures.²⁵ In contrast to HV, exercise has been reported to trigger seizures more often in patients with focal epilepsy than in those with generalized epilepsy. Although HV also occurs during exercise, this is a physiological compensatory response to expel CO₂ and raise blood pH and therefore it does not cause the same physiological changes seen when HV is performed in isolation. Further, patients who experience exercise-triggered seizures are not necessarily sensitive to HV triggers, thus the two mechanisms appear to be different.^{26,27}

Timing of HV during EEG Recording

Standard Guidelines

HV is a standard procedure during EEG recordings, as recommended by guidelines from the American Clinical Neurophysiology Society,⁷ the British Society for Clinical Neurophysiology,²⁸ the International Federation of Clinical Neurophysiology,²⁹ the International League Against Epilepsy,³⁰ and the National Institute for Health and Excellence.³¹ Therefore, HV is used routinely unless there are medical reasons that contraindicate its use, such as a recent intracranial hemorrhage, significant cardiopulmonary disease, and sickle cell disease.⁷ As HV may trigger seizures, some patients may be unwilling to cooperate due to fear of experiencing a seizure.³¹

The guidelines generally suggest HV for 3 minutes. For example, the American Clinical Neurophysiology Society guidelines suggest the following: at least 1 minute of recording with the same montage should be obtained before overbreathing begins. Then, HV should be performed for a minimum of 3 minutes, with continued recording for at least 1 minute after cessation of overbreathing. If necessary, HV can be performed for a longer period to obtain adequate activation of the EEG. The record should contain an assessment of the quality of patient effort during HV.⁷

Alternative Timings

Some clinics suggest that a longer period of HV is needed. An extended 5-minute HV has been suggested to more readily stimulate epileptiform discharges³² and has shown an increased diagnostic yield compared to 3 minutes.³³ But some clinicians suggest that prolonging the EEG recording time may be the reason for detecting the spikes rather than HV stimulation.¹¹ On the other hand, long periods of HV may be unnecessary, a study in children with suspected absence seizures found that 85.5% had an absence seizure within 90 seconds of HV onset and 68% of the children sustained a single event. The authors also suggested that once an absence seizure has been recorded HV could be stopped, reducing the amount of discomfort for the child.³⁴

HV Activation during EEG in Generalized Epilepsies and Focal Epilepsies

In contrast to standard recommendations, some studies suggest that HV is not of diagnostic value during EEG.^{10,35} While HV is certainly much more effective as an EEG activating procedure in generalized epilepsies rather than focal epilepsies,³⁶ some studies suggest that in adults, even those with generalized epilepsy, HV activation is rare. HV-induced generalized spike-wave paroxysms were found in only 12.3% of adult patients with genetic generalized epilepsy on treatment.³⁵ However, HV triggered absence seizures were seen in 67% of patients in a pediatric cohort (mean age 9.3 years) diagnosed with juvenile absence epilepsy (JAE) and childhood absence epilepsy (CAE). In untreated children, HV induces absence seizures more often in CAE and JAE (87% each) in comparison to juvenile myoclonic epilepsy (33%).³⁷ Focal interictal epileptiform discharges have also been shown to be activated by HV in some cases³⁸ (►Fig. 2). Evaluation of 433 patients with epilepsy (88.7% with focal and 11.3% with generalized epilepsy) with 5-minute HV showed that seizure occurred in 2 patients (focal seizure; ►Fig. 3) and interictal epileptiform discharges in 19 patients, so the authors concluded that HV was rarely associated with seizures or increase in frequency of epileptiform discharges.¹⁰ One study demonstrated that video EEG monitoring was assisted by HV triggering seizures in 23% of patients with medically intractable focal epilepsies. The HV-activated seizures were similar to spontaneous ones, helping to shorten the time for presurgical evaluation.⁹ It is clear that HV-induced absence seizures are more likely to occur in younger age groups, especially those with untreated CAE and JAE.³⁷ On the other hand, even though the events are not common in some patients, some clinicians find HV to be a useful method for provoking 3-Hz spike and wave discharges in a small percentage of patients who only demonstrate epileptiform activity with HV.³⁹

There is even a report of the use of HV intraoperatively to precipitate seizure in a patient with temporal lobe epilepsy.⁴⁰ While a small study, in 12 patients, using single photon emission computed tomography to show regional cerebral brain perfusion found that interictal epileptiform lateralized discharges in patients with focal epilepsy correlated with

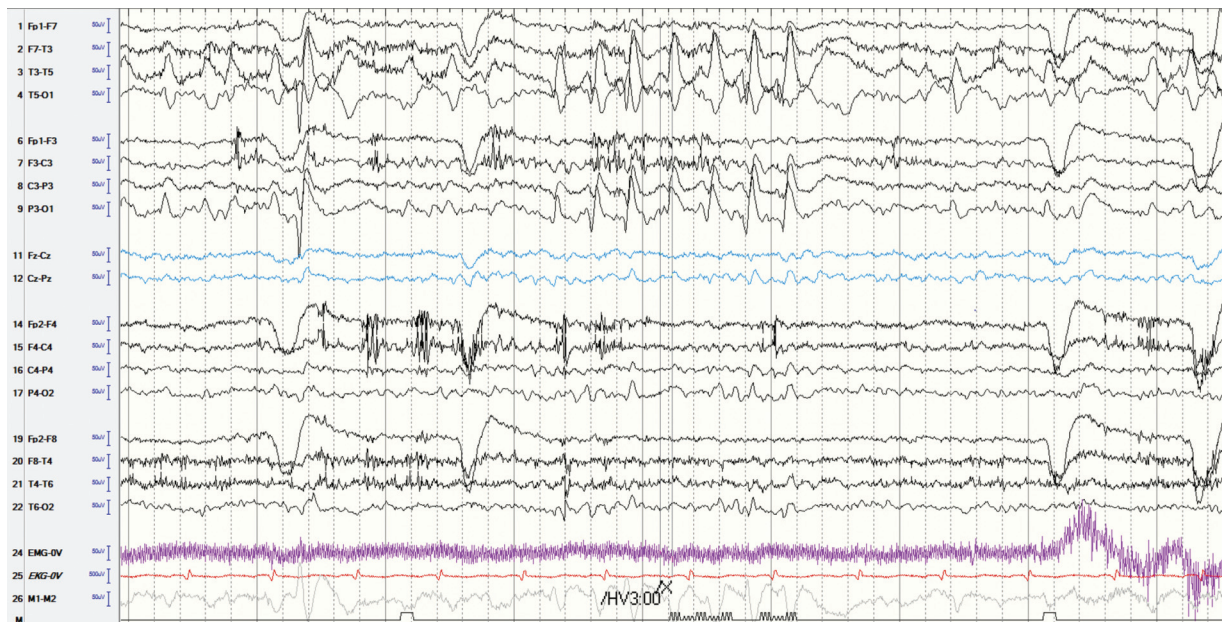


Fig. 2 An 11-year-old with history of concussion and left temporal epileptiform activity activated by hyperventilation. Sensitivity: 10 microvolts/mm, Display: 10 seconds/page.

increased cerebral brain perfusion in seven of the eight patients who experienced activation. This suggests that the spiking activities may reflect the pathophysiology of the epileptogenic area.⁴¹ Additionally, HV during routine EEG is commonly performed in supine position, while office HV is done in sitting position. Rozenblat et al showed that occurrence of absence seizures in children in sitting position is significantly higher than that seen in supine position, although the study is limited by small size of the cohort.⁴² The hypothesis behind this is decreased tidal volume of HV in the supine position due to reduced chest wall compliance.⁴²

Despite low rates of HV-triggered seizures, overall HV is an important tool for epilepsy monitoring and diagnosis even in patients with focal epilepsy.

Safety of HV during EEG

A prospective multicenter National Service Evaluation found that HV in selected patients is a valid activation technique during EEG, and the benefits outweighed the risks.⁴³

However, it is important to emphasize that there are clinical situations in which it is inadvisable to perform HV. As described above, HV may trigger the sympathetic nervous system, which

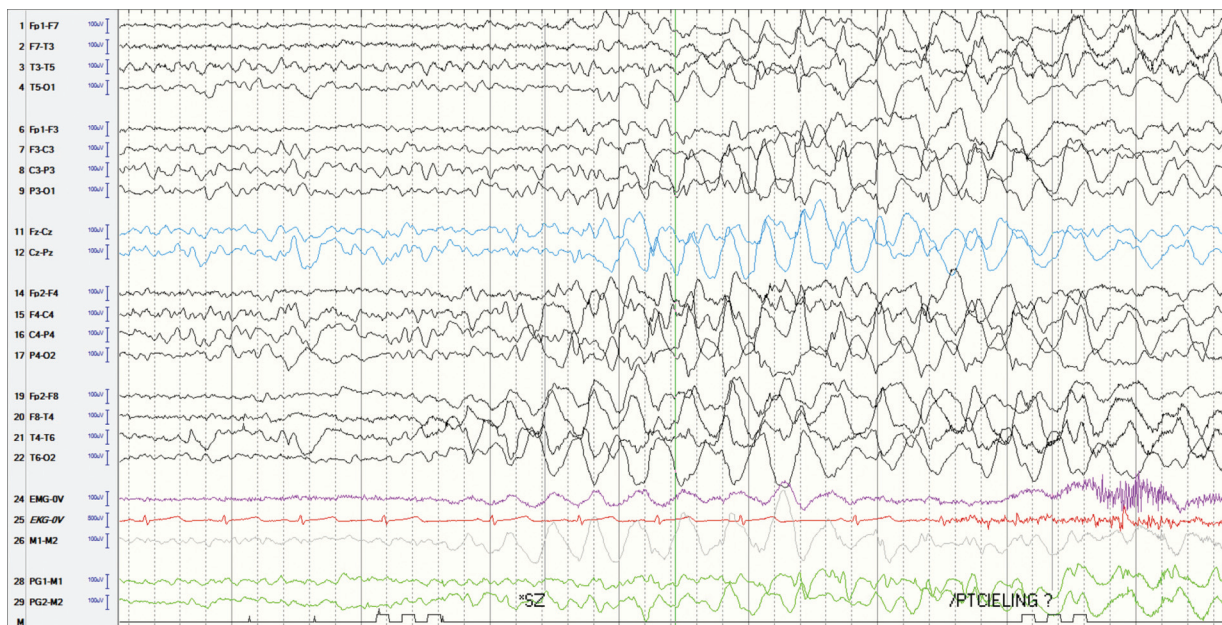


Fig. 3 An 8-year-old with history of single episode of convulsive seizure. On electroencephalogram (EEG) had focal seizure clinically characterized by behavioral arrest and right temporal onset triggered by hyperventilation. Sensitivity: 10 microvolts/mm, Display: 10 seconds/page.

may lead to unwanted sequelae in certain patients. These include patients at risk of cerebral vasospasm such as those with sickle cell and moyamoya diseases, and patients who have recently experienced cerebrovascular events, including cerebral infarction, subarachnoid and intracerebral hemorrhage, as well as those with significant coronary artery disease.^{7,43} As a part of the consent process, the patient, as well as any family and caregivers present, should be made aware that activation procedures such as HV may induce a seizure, however this risk should be stated within the context of the potential diagnostic benefits of this occurring.^{43,44}

Conclusion

HV triggers clinical seizures and epileptiform activity in a large proportion of children with generalized epilepsies and so is an obvious activation method to assist with diagnosis in children with suspected epilepsies. Epileptiform discharges, when they occur during EEG recordings, can assist in the classification of epilepsies. In patients with focal epilepsy, the location of epileptiform discharges is a good indicator of the area of the cortex from which the seizures originate or first propagate. In adults with focal epilepsies, HV remains an important part of standard EEG recording, though the likelihood of triggering focal epileptiform activity or seizures is low. HV is a simple procedure that can be easily tolerated, but careful selection of patients before HV activation is important to prevent adverse events.

Conflict of Interest

None declared.

References

- 1 Foerster O. Hyperventilationsepilepsie. *Duetsch Z.* 1924; 83:347–356
- 2 Gibbs FA, Davis H, Lennox WG. The electro-encephalogram in epilepsy and in conditions of impaired consciousness. *Arch Neurol Psychiatry* 1935;34:1133–1148
- 3 Lennox W, Gibbs F, Gibbs E. Effect on the electroencephalogram of drugs and conditions which influence seizures. *Arch Neurol Psychiatry* 1936;36:1236–1245
- 4 Dalby M. Epilepsy and 3 per second spike and wave spike and wave rhythms. *Arch Neurol Scand* 1969;40:1–183
- 5 Nims L, Gibbs E, Lennox W, Gibbs FA, Williams D. Adjustment of acid-base balance of patients with petit mal epilepsy to over-ventilation. *Arch Neurol Psychiatry* 1940;43:262–269
- 6 Wirrell EC, Camfield PR, Gordon KE, Camfield CS, Dooley JM, Hanna BD. Will a critical level of hyperventilation-induced hypocapnia always induce an absence seizure? *Epilepsia* 1996;37(05):459–462
- 7 Sinha SR, Sullivan L, Sabau D, et al. American Clinical Neurophysiology Society Guideline 1: minimum technical requirements for performing clinical electroencephalography. *J Clin Neurophysiol* 2016;33(04):303–307
- 8 Seneviratne U, Cook M, D'Souza W. The electroencephalogram of idiopathic generalized epilepsy. *Epilepsia* 2012;53(02):234–248
- 9 Guaranha MS, Garzon E, Buchpiguel CA, Tazima S, Yacubian EM, Sakamoto AC. Hyperventilation revisited: physiological effects and efficacy on focal seizure activation in the era of video-EEG monitoring. *Epilepsia* 2005;46(01):69–75
- 10 Holmes MD, Dewaraja AS, Vanhatalo S. Does hyperventilation elicit epileptic seizures? *Epilepsia* 2004;45(06):618–620
- 11 Klein KM, Knake S, Hamer HM, Ziegler A, Oertel WH, Rosenow F. Sleep but not hyperventilation increases the sensitivity of the EEG in patients with temporal lobe epilepsy. *Epilepsy Res* 2003;56(01):43–49
- 12 Engel J Jr, Lubens P, Kuhl DE, Phelps ME. Local cerebral metabolic rate for glucose during petit mal absences. *Ann Neurol* 1985;17(02):121–128
- 13 Rockstroh B. Hyperventilation-induced EEG changes in humans and their modulation by an anticonvulsant drug. *Epilepsy Res* 1990;7(02):146–154
- 14 Lee J, Taira T, Pihlaja P, Ransom BR, Kaila K. Effects of CO₂ on excitatory transmission apparently caused by changes in intracellular pH in the rat hippocampal slice. *Brain Res* 1996; 706(02):210–216
- 15 Weinand ME, Carter LP, Oommen KJ, et al. Response of human epileptic temporal lobe cortical blood flow to hyperventilation. *Epilepsy Res* 1995;21(03):221–226
- 16 Son S, Kwon OY, Jung S, et al. Relationship between hyperventilation-induced electroencephalographic changes and PCO₂ level. *J Epilepsy Res* 2012;2(01):5–9
- 17 Ahdab R, Riachi N. Reexamining the added value of intermittent photic stimulation and hyperventilation in routine EEG practice. *Eur Neurol* 2014;71(1-2):93–98
- 18 Yamatani M, Konishi T, Murakami M, Okuda T. Hyperventilation activation on EEG recording in childhood. *Epilepsia* 1994;35(06): 1199–1203
- 19 Labuz-Rozzak B, Pierzchała K. Assessment of autonomic nervous system in patients with epilepsy in the interictal state. A pilot study. *Neurol Neurochir Pol* 2009;43(04):330–336
- 20 Assenza G, Mecarelli O, Tombini M, et al. Hyperventilation induces sympathetic overactivation in mesial temporal epilepsy. *Epilepsy Res* 2015;110:221–227
- 21 Bermeo-Ovalle AC, Kennedy JD, Schuele SU. Cardiac and autonomic mechanisms contributing to SUDEP. *J Clin Neurophysiol* 2015;32(01):21–29
- 22 Lotufo PA, Valiengo L, Benseñor IM, Brunoni AR. A systematic review and meta-analysis of heart rate variability in epilepsy and antiepileptic drugs. *Epilepsia* 2012;53(02):272–282
- 23 Jansen K, Vandeput S, Milosevic M, et al. Autonomic effects of refractory epilepsy on heart rate variability in children: influence of intermittent vagus nerve stimulation. *Dev Med Child Neurol* 2011;53(12):1143–1149
- 24 Leonhardt G, de Greiff A, Marks S, et al. Brain diffusion during hyperventilation: diffusion-weighted MR-monitoring in patients with temporal lobe epilepsy and in healthy volunteers. *Epilepsy Res* 2002;51(03):269–278
- 25 Pimentel J, Tojal R, Morgado J. Epilepsy and physical exercise. *Seizure* 2015;25:87–94
- 26 Ogunyemi AO, Gomez MR, Klass DW. Seizures induced by exercise. *Neurology* 1988;38(04):633–634
- 27 Kamel JT, Badawy RA, Cook MJ. Exercise-induced seizures and lateral asymmetry in patients with temporal lobe epilepsy. *Epilepsy Behav Case Rep* 2014;2:26–30
- 28 Kane N, Grocott L, Kandler R, Lawrence S, Pang C. Hyperventilation during electroencephalography: Safety and efficacy. *Seizure* 2014;23:129–134
- 29 Recommendations for the practice of clinical neurophysiology: guidelines of the International Federation of Clinical Neurophysiology. *Electroencephalogr Clin Neurophysiol Suppl* 1999;52:1–304
- 30 Flink R, Pedersen B, Guekht AB, et al; Commission of European Affairs of the International League Against Epilepsy: Subcommission on European Guidelines. Guidelines for the use of EEG methodology in the diagnosis of epilepsy. International League Against Epilepsy: commission report. Commission on European Affairs: Subcommission on European Guidelines. *Acta Neurol Scand* 2002;106(01):1–7

- 31 Epilepsies: diagnosis and management: NICE Clinical Guidelines, No. 137 London: National Institute for Health and Care Excellence (NICE); 2021, May, 12
- 32 Miley CE, Forster FM. Activation of partial complex seizures by hyperventilation. *Arch Neurol* 1977;34(06):371–373
- 33 Craciun L, Varga ET, Mindruta I, et al. Diagnostic yield of five minutes compared to three minutes hyperventilation during electroencephalography. *Seizure* 2015;30:90–92
- 34 Watemberg N, Farkash M, Har-Gil M, Sezer T, Goldberg-Stern H, Alehan F. Hyperventilation during routine electroencephalography: are three minutes really necessary? *Pediatr Neurol* 2015;52(04):410–413
- 35 Seneviratne U, Cook M, D'Souza W. Consistent topography and amplitude symmetry are more typical than morphology of epileptiform discharges in genetic generalized epilepsy. *Clin Neurophysiol* 2016;127(02):1138–1146
- 36 Mendez OE, Brenner RP. Increasing the yield of EEG. *J Clin Neurophysiol* 2006;23(04):282–293
- 37 Seneviratne U, Cook MJ, D'Souza WJ. Electroencephalography in the diagnosis of genetic generalized epilepsy syndromes. *Front Neurol* 2017;8:499
- 38 Tsiptsios DI, Howard RS, Koutroumanidis MA. Electroencephalographic assessment of patients with epileptic seizures. *Expert Rev Neurother* 2010;10(12):1869–1886
- 39 Siddiqui SR, Zafar A, Khan FS, Shaheen M. Effect of hyperventilation on electroencephalographic activity. *J Pak Med Assoc* 2011;61(09):850–852
- 40 Kjaer TW, Madsen FF, Moltke FB, Uldall P, Hogenhaven H. Intraoperative hyperventilation vs remifentanyl during electrocorticography for epilepsy surgery - a case report. *Acta Neurol Scand* 2010;121(06):413–417
- 41 Marrosu F, Puligheddu M, Giagheddu M, Cossu G, Piga M. Correlation between cerebral perfusion and hyperventilation enhanced focal spiking activity. *Epilepsy Res* 2000;40(01):79–86
- 42 Rozenblat T, Kraus D, Mahajnah M, Goldberg-Stern H, Watemberg N. Absence seizure provocation during routine EEG: Does position of the child during hyperventilation affect the diagnostic yield? *Seizure* 2020;79:86–89
- 43 Kane N, Grocott L, Kandler R, Lawrence S, Pang C. Hyperventilation during electroencephalography: safety and efficacy. *Seizure* 2014;23(02):129–134
- 44 Salvati KA, Beenhakker MP. Out of thin air: hyperventilation-triggered seizures. *Brain Res* 2019;1703:41–52