A Scoping Review of Protocol and Yield of Hyperventilation During Electroencephalography

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Objective: Hyperventilation (HV) is an effective activation procedure to provoke epileptic and interictal discharges in patients with epilepsy and to classify seizure types such as generalized and focal epilepsy. The objectives of this study were to establish the HV yield in clinical electroencephalography (EEG), evaluate the effect of voluntary HV on EEG, determine HV indications and contraindications, and identify the optimal HV protocol and HV mechanism during EEG.

Design: This was a scoping review study that involved identifying the initial research questions, identifying relevant studies, selecting the studies, charting the data, and summarizing and reporting results.

Setting: Literature review.

Method: We searched PubMed and Scopus databases for English articles published between 2000 and 2020 using search terms 'Hyperventilation' and 'EEG' in the title. Based on the abstract, we determined whether the article contained information about the effect of HV on EEG, the indications, and contraindications of HV, and/or the mechanism of HV. Based on the selected articles, we identified the protocol used in each study to distinguish the best protocol for HV.

Result: Among 1111 articles, 7 met our inclusion criteria, comprising 4 retrospective studies, 2 prospective studies, and 1 review. HV during clinical EEG provoked exacerbation of interictal discharge in 4.4-12.2% and induced seizure in 0.4-24%.

Conclusion: HV aids better in the diagnosis of generalized seizures, especially childhood absence epilepsy, than in the diagnosis of focal seizures.

Keywords: Hyperventilation, Electroencephalography, Epilepsy

INTRODUCTION

Epilepsy is a neurologic disease characterized by a tendency to have epileptic seizure, and it is associated with neurobiological, cognitive, psychological, and social consequences[1]. The prevalence rate of active epilepsy is 6.54 per 1000 individuals (95% confidence interval [5.48–7.60])[2]. The International League Against Epilepsy (ILAE) defined epilepsy using the following criteria: (1) having at least two unprovoked (or reflex) seizures occurring at more than 24-h intervals; (2) having one unprovoked (or reflex) seizure with a probability of further seizures similar to the general recurrence risk (≥60%) after two unprovoked seizures over 10 years; and (3) having a diagnosis of an epilepsy syndrome. This definition by ILAE indicates that electroencephalography (EEG) plays a significant role; however, only approximately 20–50% of patients with epilepsy are found to have interictal epileptiform discharges on the first routine EEG[3]. This not only creates uncertainty and stress for the patient but also increases the expense and time that will be necessary to repeat the study in order to increase the yield. There are several activation procedures for increasing the EEG yield; these include hyperventilation (HV), intermittent photic stimulation, and sleep deprivation. HV is known to provoke absence seizures and rarely evokes other epilepsy types[4]. The HV duration varies across neurophysiology laboratories, with some performing it for 3 min and others for 5 min. The American Clinical Neurophysiology Society guideline for the minimum technical requirements for performing clinical EEG recommends a minimum of 3 min of HV and to continue the recording for at least 1 min after HV. Sometimes, HV must be continued for a longer period to provoke good brain wave activation, but there is no guideline as to how long it should be continued[5].

No randomised controlled trial has evaluated the differences in the efficacy and safety between performing HV for 3 and 5 min. Thus, we conducted this scoping review to identify the gaps in the available literature. The study objectives were as follows:

1. To assess the HV yield in routine clinical EEG.
2. To evaluate the effect of voluntary HV on EEG recording during routine EEG study.
3. To determine HV indications and contraindications.
4. To determine the optimal HV protocol.
5. To determine the HV mechanism during EEG.

METHOD

We performed a scoping review to map the concepts and evidence types regarding the utility of HV in routine clinical EEG. Our approach followed the Arksey and O'Malley (2005) framework, which involves the following five steps: identifying the initial research questions,

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identifying relevant studies, selecting the studies, charting the data, and summarizing and reporting results[6].

Identifying the Initial Research Questions: The focus of our review was to explore the key aspects of HV. To ensure that a substantial range of literature was captured relating to the topic of interest, we posed the following initial research questions to guide the search:

- What is the HV protocol in clinical EEG?
- What are the indications and contraindications of HV?
- What is the mechanism of HV?
- What is the effect of HV?

Identifying Relevant Studies: We selected articles on PubMed and Scopus that have 'hyperventilation' and 'EEG' in their title, that were written in English, and that were published between 2000 and 2020. After reading the abstract of each one, we determined if the article contained information about the effect of HV on EEG, the indications and contraindications of HV, and/or the mechanism of HV. Based on the selected articles, we identified the protocol that was used in each study to distinguish the best protocol of HV. Information on the utility of HV, routine clinical EEG and its activation procedures, EEG yield, efficacy of routine HV for seizure activation, and the effect of HV on seizure activation was obtained.

We included articles on HV in patients with epilepsy representing both sexes and all ages undergoing EEG. We excluded non-English articles, unrelated articles, articles that did not answer our question and articles that assessed normal patients or performed other seizure activation procedures. We also excluded irrelevant articles regarding techniques implemented on healthy individuals or employing other activation procedures.

Study Selection: After an initial screening based on the titles and abstracts of articles, we obtained 1111 relevant articles. Out of these, 147 and 316 articles were published between 2000 and 2020 in Scopus and PubMed, respectively. We further excluded 114 duplicate articles that appeared in both Scopus and PubMed. We did not find that any relevant articles or systematic reviews that appeared in the Cochrane library databases. After the inclusion/exclusion criteria were applied, 14 articles were considered relevant for our review. The inclusion criterion was studies that reported about HV in both adult and paediatric patients with epilepsy on EEG. The process yielded only 7 English articles published between 2000 and 2020. Figure 1 illustrates the article selection process.

Summarizing and Reporting the Results: The selected articles were charted according to the framework of Arkesy and O'Malley (2005)[6]. The articles were summarized with respect to their title, author(s), year, study location, study design, sample size, and outcome. Table 1 presents the details of the included articles.

RESULT

In total we included 7 articles met all inclusion and exclusion criteria from six countries (3 from United States of America (USA), 1 from United Kingdom (UK), 1 from India, 1 from Brazil, and 1 from Turkey and Israel). There was a notable absence of studies from East Asian countries. Based on the study designs, there were 4 retrospective studies, 2 prospective studies, and 1 review found. Based on the age

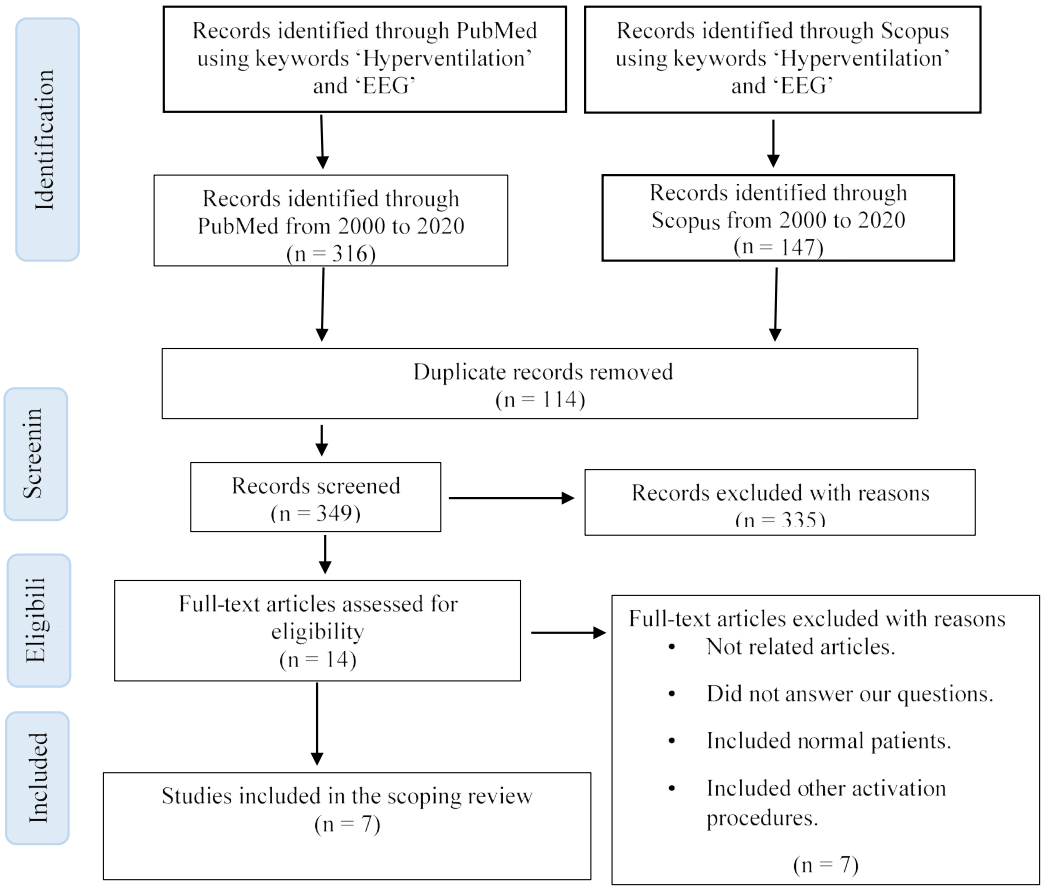

Figure 1: Process flowchart of screening the articles in our study

Subsequently, each member of our 5-member group reviewed an article in collaboration with a peer author.

Table 1: Summary of findings included in our study

	Title	Authors	Year	Location	Study design and sample	Outcome
1	Utility of Daily Supervised Hyperventilation During Long-Term Video-EEG Monitoring	Amir Arain, Patrick Arbogast and Bassel Abou-Khalil	2009	USA	N = 79 adults and paediatric. (54 with epilepsy, 24 with psychogenic nonepileptic seizures, and 1 unknown) A prospective study in the EMU HV duration was 3 min daily. Seizure was considered if it occurred during or 3 min after HV	Among 54 patients, 6 (11 %) had HV-induced seizure activation. No comment on IED activation
2	Hyperventilation during EEG: safety and efficacy	Nick Kane, Lesley Grocott, Ros Kandler, Sarah Lawrence and Catherine Pang	2014	UK	N = 3475 adults and paediatric, aged 3 months to 97 years A prospective, multi-center study on outpatients HV duration was 1–7 min (median: 3)	2.2%, seizure activation 12.2%, activated IED
3	Hyperventilation Revisited: Physiological Effects and Efficacy on Focal Seizure Activation in the Era of Video-EEG Monitoring)	Mirian Guaranha, Eliana Garzon, Carlos Buchpiguel, Sergio Tazima Elza Yacubiana and Americo Sakamoto	2005	Brazil	N = 97 adults and paediatric patients aged >10 years A retrospective study in the EMU HV duration was 5 min.	24%, seizure activation
4	Hyperventilation During Routine Electroencephalography: Are Three Minutes Really Necessary?	Nathan Watemberg, Michael Farkash, Miki Har-Gil, Taner Sezer, Hadassah Goldberg-stern and Fusun Alehan	2015	Turkey and Israel	N = 62 paediatric patients, aged 4–15 years HV duration was 3 min. A retrospective study on patients with seizure during HV EEG	The study was conducted to assess the minimum duration needed for HV in patients who had a seizure
5	Is Hyperventilation an Effective ‘‘Activating’’ Procedure in Routine Clinical EEG Studies in Children?	Chandan Raybarman	2009	India	N = 275 paediatric patients, aged 3–18 years HV duration was 5 min. A retrospective study on genetic generalized epilepsy	0.7%, seizure activation 11.6%, activated IED
6	Does Hyperventilation Elicit Epileptic Seizures?	Mark Holmes, Asanka Dwearaja and Sampsa Vanhatalo	2004	USA	N = 433, aged 10–64 years HV duration was 5 min. A retrospective study in the EMU	0.4% had seizures 4.4% presented with IED
7	Increasing the Yield of EEG	Oscar Mendez and Richard Brenner	2006	USA	A review article. HV duration was 3–5 min	After 5-minute HV, 4.4% of 433 patients showed IED

N = sample size, HV = hyperventilation, PNE = psychogenic nonepileptic event, EEG = electroencephalography, EMU = epilepsy monitoring unit, IED = interictal epileptiform discharges

groups, 4 included both adults and paediatrics patients, 1 study assessed adults only, and 2 assessed paediatrics only.

In 2004, in USA a study had 433 unselected patients with epilepsy, an age range 10 to 64 years, both females and males, and HV duration were 5 min. Of these, 384 with localization related epilepsy syndromes and 49 generalized epilepsy syndromes. There were increased in interictal epileptiform discharges (IEDs). for both groups' patients, 12.2% in generalized epilepsy syndromes and 3.4% in localization related epilepsy syndromes[7,8].

Guaranha et al. in 2005, reported in the study which had 97 patients with intractable focal epilepsies, both females and males subdivided to, positive seizure activation (PSA) (HV induced seizures), included 24 patients, age range 16 to 50 years, and negative seizure activation (NSA) (HV not induced seizures) included 73 patients age range 11 to 68 years. In total, 32 events were activated by HV. The duration of HV were 5 min, and no correlation were observed between activation of seizure and etiology, gender, age, duration of epilepsy, and ictal localization[10].

In 2009, Arain et al. recorded 79 patients in Epilepsy Monitoring Unit (EMU), an age range 12 to 85 years, both females and males, and HV duration was 3 mins. There were 54 patients with epilepsy, 24 patients with psychogenic nonepileptic seizures, and 1 patient's unknown event. Study shows seizures occur during HV in 6 (11%) of patients with partial epilepsies[9].

In 2009, in India, another study of paediatrics patient only conducted for 275 children with generalized epilepsy, an age range 3 to 18 years, both females and males, and HV duration was 5 min. The effect of HV on EEG was increased 0.7% in ictal epileptiform discharges, 11.6% in interictal epileptiform discharges, and non-clinical epileptic seizures found[12].

In 2014, kane et al. Reported in the study of Hyperventilation during EEG: safety and efficacy which had an age range of 3 months to 97 years both females and males, and HV duration were 1–7 minutes with median of 3 minutes. There were 3475 patients able to HV and 3170 were suspected to had epilepsy or possible epilepsy. Of total 3170 patients 69 had seizures provoked by HV, only one had generalized

tonic-clonic seizure, and 387 had an increase of IEDs. Furthermore, patients over 60 years comparable to 21- 60 years were reported to had increase IEDs and new IEDs[11].

Watemberg et al. in 2015, conducted a study to know the minimum time of HV to provoke seizures. There were paediatrics patients only an age range 4-15 years, both females and males. Duration of HV to provoke seizures for patients younger than 10 was 47 seconds, and older than 10 was 55 seconds. 85% of seizures occurred in less than 90 seconds of HV, 8 of patients during post HV had absences seizures, and all patients had one events at least during HV[7].

For future clinical use, the HV protocol for routine clinical EEG is not identified but according to the studies we collected is performed using the standard 10-20 International System, with 21 Grass gold-coated disk electrodes applied on the scalp and 32-channel EEG and will be best if used with video monitoring. Using sphenoidal electrodes if patient a suspect to have temporal lobe epilepsy.

Moreover, perform HV at the beginning of recording to relax the patient or at the end to compare HV changes with baseline. It is best to stop all antiepileptic medications before admission. Regarding the HV duration, it is suggested to be 3-5 minutes as minimum time, it is most effective time to increase the yield of EEG, seizure activation and interictal discharges.

HV is the oldest activation procedure for provoking seizures in children with epilepsy when it is performed correctly. It is known to precipitate absence seizures, which is a common childhood seizure type, and may trigger psychogenic nonepileptic spells. Two adverse events have been reported, which were associated with broncho-spasm and tachycardia and were relatively minor without additional complications. Furthermore, during pre-surgical evaluation of a patient with temporal lobe epilepsy, the use of HV can reduce the time and cost of multiple EEGs. Absolute contraindications to HV include cardiac conditions such as recent myocardial infarction and pulmonary disease, stroke (ischemic, subarachnoid, and intracranial haemorrhage), hypercoagulability state, sickle-cell diseases, uncontrolled hypertension, severe carotid stenosis, and Moyamoya disease[4,11]. EEG showing frequent generalized spike and wave discharges could be a relative contraindication. Moreover, some patients cannot perform HV or are uncooperative[4].

The hypoxia theory, which suggests that slowing in EEG results due to vasoconstriction and reduction in the oxygen and dextrose delivery to the cortex, has some limitations such as the observed differences in quantitative EEG due to HV and hypoxia. Moreover, EEG changes are independent of the inspired oxygen concentration and reduced cerebral blood flow. Several studies have indicated that the HV mechanism involves hypocapnia induction, which is invariably epileptogenic[8]. However, the hypocapnia theory suggests that low carbon dioxide levels cause predominance of nonspecific activation of the thalamic projection system over reticular ascending system activation. This theory has also been questioned by the observation of slow waves on the EEG of patients and normal individuals with wide-ranging arterial and expired air Carbon dioxide (CO_2) tension. There may be two mechanisms, one for slowing and another for activation)[10]. HV could decrease arterial CO_2 partial pressure, which results in reduced cerebral blood flow by at least 30%. The exact mechanism of the EEG changes associated with HV are unclear[4]. Watemberg et al. suggested that alkalosis resulting from decreased blood CO_2 levels could underlie HV-induced absence seizures[7].

DISCUSSION

Here, we summarize and convey each finding to provide an overview regarding the rules and protocol for HV in routine clinical EEG as a means for increasing EEG productivity.

In the study by Watemberg et al.[7], the HV protocol in routine clinical EEG was performed using the 10-20 International System for electrode placement on the scalp. Moreover, they used two activation procedures consisting of 3-minute HV, followed by a minimum of 10-minute post-HV recording and photic stimulation. Contrastingly, Holmes et al. reported that patients underwent 5-minute voluntary HV during standard EEG recordings with 21 scalp electrodes using a 32-channel EEG with video monitoring[8].

The HV protocol remains unclear, with some studies recommending ≥3 min and others recommending that 5 min as the minimum time to activate focal epileptiform discharges. Further, some EEG labs perform HV before the end of the study so that they can compare the baseline with the HV-induced changes, whereas others perform it early in the study as it could relax the patient[4]. Further, 2 studies employed long-term video-EEG monitoring using the same protocol; however, there were differences in the electrode type used. One study obtained recordings through electrodes applied to the scalp using the standard 10-20 International System without a specific electrode[9]. Contrastingly, Guaranha et al. used specific electrode types, which included Grass gold-coated disk electrodes and closed-spaced electrodes on the scalp[10]. An additional sphenoidal electrode was used for patients with suspected temporal lobe epilepsy. All antiepileptic medications were stopped on admission, except carbamazepine, which was tapered over 2–3 days then stopped. Under supervision, all patients performed HV with the mouth open for 3 min once daily. Patients were asked to hyperventilate as it may precipitate a seizure. Subsequently, patients were observed for 5 min after HV completion. The activation procedure was considered positive if the seizures occurred during the HV or within 3 min after the HV[10].

The included articles, which encompassed a wide range of HV effects, reported increased interictal epileptiform and ictal epileptiform discharges without a clinical seizure. For example, Raybarman (2009) observed EEG patterns that were typical and atypical spike-wave discharges in 40% and 56.4% paediatric cases, respectively, and periodic lateralizing epileptiform discharges in 3.6% paediatric cases[12].

Approximately 10% and 70% of adults and children, respectively, showed a productive response to HV. This HV-induced change consisted of a build-up of delta activity, in addition to reduction of background rhythms, especially in children aged 8–12 years. The degree of reduction was segregated into four levels: absent, discrete, moderate, and intense. Absent was defined as no change in the wave frequency and amplitude of the background rhythm in reference to the baseline at 5 min before the HV period. Discrete changes refer to reduction of the posterior dominant rhythm and/or 20% increase in the theta activity, with or without occasional delta waves. Moderate changes refer to an increase by up to 40% in the theta and delta wave activities. Finally, intense refers to delta activity of >40% of the recording time.

HV is more effective in provoking abnormality in generalized epilepsies than focal epilepsies. It can activate generalized interictal discharges and seizures in patients with epilepsy, including 3 Hz generalized spike and wave complexes in approximately 80% of patients with idiopathic generalized epilepsies and slow spike and wave complexes in approximately 50% of patients with symptomatic epilepsies[4].
The activation effect is observed from HV induction until 4 min, which is the most noted time for seizure activation. This suggests that HV in video-EEG clinics should last for >4 min. Although a few patients can tolerate >5 min of HV, there is no significant increase in the number of seizures after 5 min. Contrastingly, seizures can occur even within 3 min[10]. Localization-related and generalized epilepsies are relatively resistant to routine HV activation in adolescents and adults. However, this is not the case for younger children with typical absence epilepsy, as they have shown the strongest evidence of HV provocation of seizures. Recent evidence suggests that HV combined with EEG video monitoring is a powerful technique for eliciting events in patients with psychogenic nonepileptic seizures[8].

This scoping review has several limitations. First, HV can induce ictal or interictal discharge, the HV effect differs across different epilepsy types, and the yield was different in paediatric and adult patients. Regarding the HV protocol, some studies have recommended 3 min, whereas others consider 5 min as necessary for increasing the yield of EEG. Additionally, in our review, some studies were conducted on patients who had their antiepileptic medications tapered after admission to the epilepsy monitoring unit, and other studies included only patients who had EEG in the neurophysiology lab without changes to their antiepileptic medication; these procedural differences can contribute to the heterogenicity of the results. In addition, the studies were from patients with different ethnicities, or represented genetic epilepsies that are more susceptible for activation with HV than other epilepsy syndromes. Moreover, some studies have demonstrated 5-minute HV to be more effective to elicit active seizures and interictal discharge. This scoping review included generalized, absence, and focal epilepsy and did not discuss the effect of HV on other epilepsy types. We found that HV is more effective for generalized epilepsy than for focal epilepsy.

CONCLUSION

In conclusion, HV is effective activate clinical and electrographic seizures in routine clinic EEG for whom antiepileptic drugs have been reduced or omitted. The findings suggested that the HV yield was better for the diagnosis of genetic generalized seizures, especially childhood absence epilepsy. Its value for patients with other focally originating seizures remains less certain.

The protocol of HV during EEG with 10-20 International System for electrode placement on the scalp is not identified if patient should do voluntary HV for 3 minutes or 5 minutes to increase yield of EEG. So, we suggest a randomized control study to compare the effectiveness and safety of 3 min verse 5 min of the HV in paediatric and adult patients with genetic generalized epilepsy and focal epilepsy may help optimise the yield of EEG.

Authorship Contribution: All authors share equal effort contribution towards (1) substantial contributions to conception and design, acquisition, analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; and (3) final approval of the manuscript version to be published. Yes.

Potential Conflict of Interest: None.

Competing Interest: None.

Sponsorship: None.

Acceptance Date: 04 February 2021

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