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Hyperventilation during electroencephalography: Safety and efficacy

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ABSTRACT

Purpose.: To determine safety and efficacy of hyperventilation (HV) during electroencephalography (EEG).
Methods: We report the findings of a prospective multicentre National Service Evaluation of the occurrence of adverse events, seizures and interictal epileptiform discharges seen in association with HV during EEG, in a relatively unselected, largely out patient population of 3475 being investigated predominantly for possible epileptic seizures.
Results: Adverse events occurred rarely, and there were no reported significant cerebrovascular, cardiovascular or respiratory events. Of the 3170 patients suspected of 'epilepsy or possible epilepsy' 69 patients (2.2%) had seizures provoked by HV, but only one (0.03%) had a generalised tonic clonic seizure. The elicitation or increase of interictal epileptiform discharges (IEDs) was seen in 387 (12.2%) of the total 3170 patients with suspected epilepsy who hyperventilated. Furthermore 31 patients (0.9%) had psychogenic non-epileptic seizures.
Conclusion: HV is rarely associated with adverse events, but contributes to the diagnosis and classification of seizure disorders in an appreciable proportion of patients with epilepsy and non-epileptic attacks. These findings confirm that HV in selected patients is a valid activation technique in diagnostic EEG, where the potential benefits out weigh the risks, and also provide information that may assist the informed consent process.

1. Introduction

Voluntary hyperventilation (HV) was known to provoke epileptic seizures[1,2] prior to the advent of electroencephalography (EEG) as a clinical investigation. It is no surprise then that HV provided the first EEG 'activation procedure'.[3] However, in spite of its widespread use, surprisingly little is known about the risk of adverse events during voluntary HV, the incidence of epileptic seizure provocation, and its diagnostic efficacy in terms of eliciting or increasing interictal epileptiform discharges (IEDs). There is a single centre retrospective analysis reviewing 1000 EEG investigations, which gives some indication of the occurrence of both seizures and IEDs during activation procedures.[4] Twelve seizures (2.1%) were reported occurring in the 580 relatively unselected patients who were hyperventilated for 3 min, and an increase in IEDs in another 60 of their patients (10.3%).[4]

A review of the literature on HV as an activating procedure noted that it is considerably more effective in generalised epilepsies than in focal epilepsy syndromes.[5] Indeed the early exponents of HV identified that children with 'petit mal epilepsy' (Childhood Absence Epilepsy) were the most sensitive to its effects; 77% of patients with that diagnosis (from 1107 with epilepsy) had "three-per-second wave and spike pattern" in the resting record, but an additional 8% were only revealed by over-ventilation (HV).[6] The role of HV in Childhood Absence Epilepsy was secured by an extensive study which found that HV provoked 3 per second generalised spike and wave in 88% of 234 patients.[7] What is less clear is how efficacious it is in focal (or partial) epilepsies, although it has recently been pointed out that because focal IEDs, and sometimes seizures, can be activated by HV it should not be neglected in patients with focal epilepsy.[8] Early work is confounded by the exact interpretation of paroxysmal abnormalities in the EEG during HV; but in the modern era rates of IED activation have been reported between 6.6% of 255 patients and 3.4% of 383 patients, diagnosed with focal or partial epilepsy.[9,10] However, the induction of partial seizures appears to be more variable in patients diagnosed with focal epilepsies; with rates ranging from either none in 159 patients[11] or as low as 0.46%[10] up

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to 4.4% [9] in standard recordings. In medically intractable focal epilepsies 17.5% of 80 patients[12] and 24.7% of 97 patients[13] had seizures with repeated HV and anticonvulsant drug reduction in patients during prolonged video EEG monitoring.

The American EEG Society (AEEGS, 2004),[14] International League Against Epilepsy[15] and National Institute for Health and Clinical Excellence (NICE, 2012)[16] all recommend that HV is performed as part of a standard EEG. The AEEGS provides contraindications to HV including recent subarachnoid haemorrhage, intracranial haemorrhage, or significant cardio-pulmonary disease. NICE (CG 137) recommends that "the child, young person or adult and family and/or carer should be made aware that such activation procedures may induce a seizure and they have a right to refuse". In order to provide informed consent it is necessary to quantify these risks in an unselected population, reflecting actual clinical referral practice, and to place them in the context of the potential benefits of increased diagnostic sensitivity of the standard EEG. Patients should not only be advised of the risk of epileptic seizures but also potential non-epileptic events, as well as the likely positive outcomes in terms of diagnostic information. Useful diagnostic information includes eliciting generalised absence seizures, an increase in IEDs, and perhaps even psychogenic non-epileptic seizures. This prospective multicentre National Service Evaluation, organised by two professional organisations in the UK (the Association of Neurophysiological Scientists and the British Society for Clinical Neurophysiology), attempts to address this relative deficiency in the EEG literature.

2. Methods and patients

In line with the UK NHS National Research Ethics Service's guidelines Ethical approval was not deemed necessary for this service evaluation of routine clinical practice. However, all the patients in this service evaluation were given informed consent and provided with the option not to hyperventilate during their EEG recording. Data was collected prospectively by the professionally trained recording Clinical Physiologist in 56 participating UK Departments of Clinical Neurophysiology (see Acknowledgement) from 6242 consecutive patients referred for a standard EEG between beginning October and end December 2011 (see Appendix: Questionnaire). A total of 3475 (56%) patients could be hyperventilated, for periods ranging from 1 to 7 min (with a median of 3 min in 83% of patients). Some 2767 (44%) did not hyperventilate; either because it was against department protocol (46%), the patient could not co-operate (29%), was too young (19%), refused (1%), or some other reason not specifically defined (5%). There were 3129 females (50.1%) and 3113 males (49.9%) with an age range of 3 months to 97 years (mean 33.1 years). In terms of the provisional primary clinical diagnosis of those who hyperventilated 3170 patients (91%) were referred with 'epilepsy or possible epilepsy', 102 (3%) with possible psychogenic non-epileptic seizures, and 203 (6%) with some other diagnosis which was not defined.

Adverse Events are defined by the General Medical Council as "any unintended or unexpected event which could or did lead to harm of one or more patients". Such Events that were deemed to be caused by or temporally associated with HV were identified by the recording Clinical Physiologist, and classified as either a cardiovascular, respiratory or cerebrovascular event, a psychogenic non-epileptic seizure or an epileptic seizure. Predictable side effects of hyperventilation, such as dizziness, light headedness, paraesthesias and headaches, were not recorded. Any activated epileptic seizures were broadly classified by their electro-clinical characteristics as either focal or generalised, with a clinical description of seizure type where possible, along with spontaneous seizures occurring during the resting record (i.e. not activated). In order to determine efficacy the recording Physiologist identified if HV produced unequivocal epileptiform activity or IEDs (defined as 'sharp waves, spikes with or without slow waves') not seen in the resting record, or if HV exacerbated epileptiform activity seen in the resting record. All the information was submitted anonymously into a Microsoft Access database to the Organising Committee for analysis.

3. Results

Of the 3475 patients who were able and willing to HV there were only two reported symptomatic cardiovascular, respiratory or cerebrovascular adverse events. A known asthmatic complained of wheeziness and a second patient experienced symptomatic tachycardia (130 bpm from 100 bpm) during a non-epileptic seizure, both of which were self-limiting and stopped on cessation of HV. Non-epileptic attacks or psychogenic non-epileptic seizures were reported in 31 patients (including 'disorientation, jerks, twitching, eyelid flickering and other abnormal rhythmic movements involving the limbs or torso'), where there were no accompanying abnormal EEG changes.

Epileptic seizures were precipitated by HV in 69 patients (2.2%), with 59 (85%) identified as generalised, 8 (12%) as focal, and 2 (3%) as undetermined or unspecified. The 59 generalised seizures were classified as absences in 54, generalised tonic clonic seizure in 1, eyelid myoclonia in 1 and not specified in 3. The mean age of patients with generalised seizures was 10.3 years (range 3–33 years), and 29 (54%) of these patients had spontaneous seizures (all absences) during the resting record as well (i.e. not activated). This suggests that HV gives a nearly twofold increase in generalised absence seizures (although of course HV typically only accounts for around 3 min of a standard 20 min recording). The 8 focal seizures

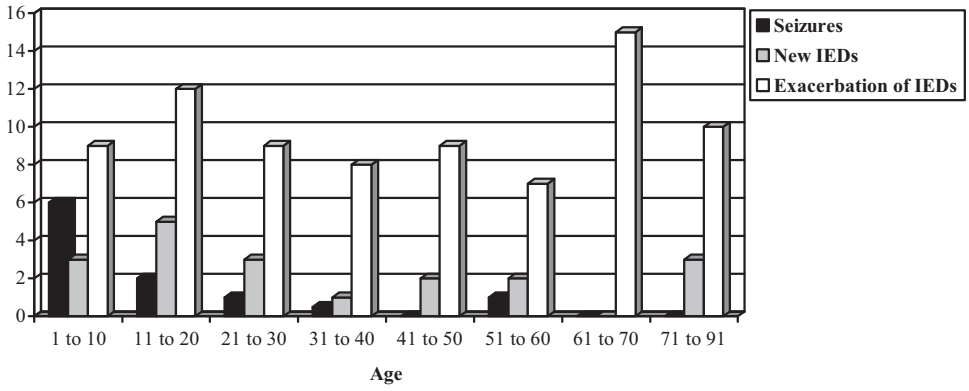

Fig. 1. Percentage hyperventilation activation of seizures and new interictal epileptiform discharges (IEDs) or their exacerbation by 10 year age groups.

were described as temporal lobe epilepsy in 6, parietal lobe (sensory) in 1 and not defined in 1. The mean age of patients with focal seizures was 36.5 years (range 10–55 years).

Of the 3170 with a pre-test clinical diagnosis of 'epilepsy or possible epilepsy' interictal epileptiform activity not seen in the resting record was reported in 95 patients (3.0%) and exacerbated in another 292 patients (9.2%). This gives a combined yield of 12.2%, where HV may have contributed directly to a diagnosis of epilepsy, lent support to it, and helped classify the seizure type. In the 135 (3.9%) patients over 60 years of age there were no recorded seizures or adverse events, but the overall yield of new IEDs and exacerbation was comparable to that for adult patients between 21 and 60 years (see Fig. 1).

4. Discussion

The findings of this multicentre service evaluation give some indication of the incidence of adverse events, non-epileptic episodes or psychogenic non-epileptic seizures, epileptic seizures and interictal diagnostic information that may be elicited by HV during a standard EEG in an unselected population of patients, predominantly suspected of having had seizures. The two adverse symptomatic events in this population were relatively minor and without sequelae; both HV-induced tachycardia and bronchospasm in asthma are known to occur.[17] Careful selection of patients, through the use of departmental protocols, may have contributed to this low complication rate. There are case reports in the literature of HV precipitating death in a patient with cardiorespiratory disease,[18] myocardial infarction both without[19] and with[20] known coronary artery disease, apnoea in a patient with hypoxaemia[21] and even asystole with syncope in healthy athletes.[22] Whilst these may be rare adverse events, for the most part in patients with pre-existing medical conditions, there is little room for complacency and a need for clear guidelines. Indeed there are clinical situations where HV is best avoided all together, particularly when there is a risk of cerebral vasospasm-induced transient ischaemic attack or stroke, a recognised complication of HV in patients with sickle cell and moyamoya disease.[23,24] Even though the EEG 'rebuild-up' (slow wave) response after cessation of HV can be diagnostic in moyamoya disease,[25] it seems prudent to omit HV in known cases. For similar reasons it is sensible to avoid HV in patients with known recent cerebrovascular events (including cerebral infarction, subarachnoid and intracerebral haemorrhage) and significant coronary artery disease, as recommended by the AEEGS (2004).[14]

This service evaluation did not intentionally set out to investigate psychogenic non-epileptic seizures (PNES), although 31 PNES were reported in association with HV (usually consisting of significant motor symptoms without concomitant epileptiform EEG changes). Some of these were described as habitual by the patients, and in the 102 patients referred with a provisional diagnosis of PNES who performed HV12 (11.8%) had such typical attacks during HV. In one study HV provoked PNES in as many as 16 of 19 (84%) patients with suspected PNES, and in another randomised controlled trial of 30 patients HV 'with suggestion' doubled the yield of PNES (as compared to 'without suggestion'), leading these authors to suggest a role for the cost effective outpatient EEG confirmation of PNES using HV.[26,27] On the other hand, NICE (CG 137, 2012) states that provocation "has a limited role and may lead to false-positive results in some people".[16] It is possible that some patients may be incorrectly diagnosed with PNES, for example several of the patients in our survey experienced 'disorientation and twitching' (that could be due to tetany), which are recognised neurological manifestations of the 'hyperventilation syndrome'.[28,29] Overall our findings do lend support to the use of hyperventilation during EEG as a cost effective and efficacious way of screening for PNES, as suggested by others, [26,27] when compared to the more costly standard prolonged ambulatory EEG recording over several days.

Of the 3170 with a pre-test clinical diagnosis of 'epilepsy or possible epilepsy' 69 patients (2.2%) had seizures evoked by HV, which is virtually identical to the 2.1% of the single centre retrospective review of 580 patients who hyperventilated.[4] This then would appear to provide a reasonable estimate of the number of seizures that can be expected in a relatively unselected out patient population, referred for a diagnostic EEG when epilepsy is suspected. This could therefore form the basis for informing patients of the seizure risk associated with HV, as part of the consent process. Whilst no seizure should be viewed as risk free, or without potential adverse consequence (e.g. loss of driving licence), it is worth bearing in mind that in our survey the vast majority were generalised absences in children without any apparent sequelae. Indeed provocation of this seizure type is the intention of HV during a diagnostic EEG, and does not pose a significant risk to the child. There was in fact only one unexpected generalised tonic clonic seizure in our survey (0.03%). The proportion of our patients having focal seizures was much less than those having generalised seizures, with only 8 (0.25%) occurring in association with HV; although we do not know the overall proportion of patients classified clinically as having either generalised or focal seizure syndromes. None the less our findings lend support to the observation that both focal IEDs and seizures can be activated by HV,[8] and can therefore be contributory in patients with focal epilepsies, backed up by a number of case reports in the literature.[1,2,30,31] The incidence of focal or partial seizures in published series ranges from none[11] up to 24.7%[13]; although this appears to be influenced by the intractability of the seizure disorder, anticonvulsant drug reduction, and duration of both the EEG recording and HV itself. One prospective study calculated that the rate of seizure induction by HV was almost six times more than without it, in 54 patients with medically intractable localisation-related epilepsy,[32] where HV may have a specific diagnostic role.

The elicitation or increase of interictal epileptiform discharges (IEDs) was seen in 387 (12.2%) of the 3170 patients with possible epilepsy who hyperventilated, which is also similar to the 10.3% reported in the single centre study.[4] Once again this would appear to give a reasonable approximation of the potential diagnostic benefit when counselling patients on the role of HV during a standard EEG, in a relatively unselected out-patient population when seizures are suspected. Most other series publish marginally higher rates of 'new IEDs' during HV than our figure of only 3.0%, where this adds unique diagnostic information not seen in the resting record. For example, one group reported localised abnormalities in 13 (8.1%) of 161 and generalised abnormalities in 15 (6.7%) of 223 patients,[33] another found spikes in 17 (6.6%) of 255 patients,[9] and a third saw IEDs in 3 (5.5%) of 55 patients.[34] However, it should be borne in mind that these activation rates are reported from patient populations who carry a clinical diagnosis of definite epilepsy, in contrast to our own who may only have been suspected of having had an epileptic seizure. It is clear that the type of epilepsy and its severity may also have a bearing on the yield from HV; for example, in small series (of $<$100 patients), 22% in juvenile myoclonic epilepsy,[35] 31% in symptomatic secondary generalised epilepsy,[36] and over 50% in the 'malignant' Lennox–Gastaut syndrome.[37] Whilst it is difficult therefore to generalise based on different patient populations it is clear that HV does indeed add valuable diagnostic information, which cannot be obtained in short standard EEG recordings alone. This information can help with the early diagnosis and appropriate treatment of the epilepsies, in the hope of reducing seizure related injuries and sudden unexplained death in epilepsy. We have not discussed the

role of other standard activation techniques, namely photic stimulation, sleep deprivation and sleep; but we are about to embark on a similar prospective multicentre study of both photic stimulation and sleep deprivation versus melatonin induced sleep to address this.

Conflict of interest

None declared.

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Appendix. Questionnaire completed for each patient

BSCN Founded as the EEG Society in 1942 — Joint National Audit Project — Association of ANS Neurophysiological Scientists

Postcode of Centre (Please complete)		**Project Code** (Do not complete. For office use only)	

1. What is the age of the patient?	
2. What is the gender of the patient?	M/F
3. What was the referral diagnosis?	Epilepsy/possible epilepsy Non epileptic attack disorder Other
4. Was hyperventilation performed? **If "Yes" go to question 6 and continue questionnaire** **If "No" answer question 5 only**	Yes/No
5. Why was hyperventilation not performed?	Against department protocol Child too young Insufficient co-operation from patient Patient refused Other
6. Was there a significant clinical change during HV? **Do not include common effects of HV e.g. dizziness/light headedness**	Yes/No
If "No" go to question 11	
7. If "Yes" was it: **If no epileptic seizure occurred go to question 11.** **If an epileptic seizure did occur please answer questions 8, 9 and 10.**	An epileptic seizure A non epileptic seizure Cardiovascular event, please describe Respiratory event, please describe Cerebrovascular event, please describe (Please use reverse of form for description)
8. If an epileptic seizure was precipitated by HV, was it:	Focal Generalised
9. Can you be precise about seizure type e.g. Absence, Myoclonic etc. Please describe.	
10. Did similar seizures occur in the resting record?	Yes/No
11. Did hyperventilation produce unequivocal epileptiform interictal EEG activity **NOT** seen in the resting record? (i.e. sharp waves /spikes with or without slow waves.)	Yes/No
12. Did hyperventilation exacerbate epileptiform activity previously seen in the resting record?	Yes/No
13. For how long was hyperventilation performed (to nearest minute)?	
14. Was HV well performed?	Yes/No

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