Standardization and quality assurance in clinical electroencephalography

Laura Craciun

Main supervisor: **Professor Sándor Beniczky**

Co-supervisor: **Professor László Vécsei**

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Doctoral School of Clinical Medicine

List of scientific papers that cover the topic of the dissertation

I. **Craciun L, Gardella E, Alving J, Terney D, Mindruta I, Zarubova J, Beniczky S. How long shall we record electroencephalography? Acta Neurol Scand. 2014 Feb;129:e9-e11. doi: 10.1111/ane.12186.**

II. **Craciun L, Varga ET, Mindruta I, Meritam P, Horváth Z, Terney D, Gardella E, Alving J, Vécsei L, Beniczky S. Diagnostic yield of five minutes compared to three minutes hyperventilation during electroencephalography. Seizure. 2015;30:90-2. doi: 10.1016/j.seizure.2015.06.003.**

III. **Craciun L, Alving J, Gardella E, Terney D, Meritam P, Cacic Hribljan M, Beniczky S. Do patients need to stay in bed all day in the Epilepsy Monitoring Unit? Safety data from a non-restrictive setting. Seizure. 2017;49:13-16. doi: 10.1016/j.seizure.2017.05.006.**

Abstract

Objectives: Our objectives were to address some key issues- to determine the minimal efficient duration of the standard and sleep EEG recordings, to assess the diagnostic yield of hyperventilation (HV) and to assess whether injuries occur more often in an Epilepsy Monitoring Unit (EMU) where portable EEG amplifiers are used, and where patients can freely move within a large area during the monitoring.

Methods: For the first part of the study, we have reviewed 1005 EEG recordings and determined the shortest recording duration necessary to identify interictal EEG abnormalities. In order to assess the diagnostic yield of 5 min HV compared to 3 min HV, data were evaluated from 1084 consecutive patients, from three European centers, referred to EEG on suspicion of epilepsy. Seizures and interictal EEG abnormalities precipitated during the first 3 min and during the last 2 min of the HV period (totally 5 min) were determined. For the last part of our study, patients were monitored at the Danish Epilepsy Center. Adverse events (AEs) including injuries, were prospectively noted, as part of the safety policy of the hospital. Other data were retrospectively extracted from the electronic database, for a 5-year period (Jan 2012–Dec 2016).

Results: Standard, awake recordings shorter than 20 min yielded a significantly lower incidence of abnormal findings as compared to longer recordings. Although there was an increase in the diagnostic yield from 30 to 180 min recording duration, this failed to reach the level of significance. For sleep recordings, there was no significant increase in the diagnostic yield beyond 30 min.

877 (81%) completed 5 min HV. Seizures were precipitated during the first 3 min of HV in 21 patients, and during the last 2 min in four more patients. Interictal EEG abnormalities were precipitated in the first 3 min of HV in 16 patients, and during the last 2 min in 7 more patients. Psychogenic nonepileptic seizures occurred in eight patients during the first 3 min of HV and in two more patients during the last 2 min. No adverse events occurred during the last 2 min of HV.

976 patients were admitted to the EMU. Falls occurred in 19 patients (1.9%) but none of them resulted in injury. The rate of AEs were similar or lower than previously reported by other centers, where the mobility of the patients had been restricted during monitoring.

Conclusions: Our results provide evidence for recommending at least 20 min recording duration for standard awake EEGs and 30 min for sleep EEG recordings.

16% of seizures and 30% of interictal EEG abnormalities triggered by HV occurred during the last 2 min of HV, suggesting the clinical usefulness of prolonged hyperventilation for 5 min. The vast majority of patients (99%) who are able to hyperventilate for 3 min can complete 5 min HV, without additional adverse events.

In an EMU specially designed for this purpose, where patients are under continuous surveillance by personnel dedicated to the EMU, injuries can be avoided even when the mobility of the patients is not restricted.

Introduction

There is an increasing demand for standardizing the medical procedures and for documenting the effectiveness of the methods applied. Electroencephalography (EEG) is an essential diagnostic tool in the evaluation of seizure disorders, whether in the case of a first unprovoked seizure, a confirmed diagnosis of epilepsy or presurgical evaluation of patients whose disease is pharmacoresistant[1–9].

Our objectives were to address some key issues- to determine the minimal efficient duration of the standard and sleep EEG recordings, to assess the diagnostic yield of one of the most important activation methods (hyperventilation) and to evaluate if the risk of adverse events is higher in a center where the mobility of patients is not restricted than in other centers.

International standards for recording EEG in clinical practice have been summarized in the guidelines of the International Federation of Clinical Neurophysiology[10–12]. However, not all international guidelines adhere to the same standards.

When it comes to the duration of the standard EEG, American guidelines recommend at least 20 min [13], while European guidelines recommend at least 30 min of EEG recording[14]. All these recommendations are merely based on expert opinion, since there are no studies addressing these basic requirements.

In daily clinical practice, the recording duration of standard EEGs varies widely among different countries and EEG laboratories (from 10 min to 30 min), thus affecting the overall quality of the investigation and making communication between centers difficult.

The first part of our study tried to determine the minimal efficient duration of the standard and sleep EEG recordings in patients with epilepsy.

Hyperventilation is the oldest provocation methods, its efficiency in triggering absence seizures being observed even before the use of EEG, while the effect it has on cerebral electric activity has been observed by Berger in 1934 and further studied by Gibbs et al in 1935.[15–17]

It was proven to be more useful in generalized epilepsy, and especially in absence seizures [16–23], but also in Juvenile Myoclonic Epilepsy[20,24]. Nevertheless, some studies have shown that it can also trigger focal seizures, especially those with a temporal lobe onset [17,19,25,26] while others question its value for focal epilepsy [18,27,28]

Overall, the diagnostic yield of HV is still under debate, with studies reporting different results- ranging from 0.4 %-28.3% for seizures and 4.4 % - 24.7 % for epileptiform activity[17–19,23,26,29,30]. The great variation in these numbers comes both from the design of the study and the selected population (the diagnostic yield is higher in children than in adults, and in generalized epilepsies, particularly in Childhood Absence Epilepsy, than in focal ones) but also from the duration of the HV maneuver. In most of the studies the duration of HV was 3 minutes [16,18,19,24,31,32], in one it was 4 minutes [29], in others it was 5 minutes [17,28,29,33–35], or ranging from 3 to 6 minutes [25], from 3 to 5 minutes[36] and one of the biggest studies, on 3745 patients has durations of HV ranging from 1 to 7 minutes [21]

The American Clinical Neurophysiology Society, the British Society for Clinical Neurophysiology, the International Federation of Clinical Neurophysiology and the International League Against Epilepsy Sub-commission on European Guidelines recommend performing HV as a part of the standard EEG recordings [10,13,37]. However there is no consensus on the necessary duration of the HV: some guidelines recommend 3 min [37], or a minimum of 3 min [38], while others recommend that HV is performed for three to 5 min[39].

Our goal was to elucidate whether HV for 5 min increases the diagnostic yield of EEG compared to 3 min HV and to see what the overall yield of HV is, in a tertiary referral center for epilepsy.

Sometimes, a short, standard EEG recording just does not bring enough data. In these cases, long term video EEG monitoring (LTM) is recommended. LTM is the best diagnostic tool for characterizing the intricate electro-clinical phenomena that occur during epileptic seizures [24,40–43], which is particularly useful for presurgical evaluation of the patients with drug-resistant disease.

Though generally considered a safe investigation, with few possible complications, there have been a number of adverse events associated with the stay in an EMU, ranging from generalized tonic-clonic seizures and falls to status epilepticus or even death[44–51].

There are no generally accepted guidelines about the safety measures in the EMU [52,53], and this has created a great variability in the safety measures adopted by different EMUs [44,49,50,52,54–56].

In order to avoid injuries, and due to the lack of wireless amplifiers, in many centers the patients' mobility is restricted, and they need to spend the whole time or most of the time in bed [48,50,57–59].

In our EMU, specifically designed to decrease the risk of injuries in case of falls, patients are free to move around and perform their daily activities, under continuous surveillance by personnel dedicated to the EMU. This eliminates the need for deep vein thrombosis prophylaxis and increases the degree of comfort for the patients.

As stipulated in the Danish Healthcare Quality Program [60] and the safety policy of the Danish Epilepsy Centre, we have prospectively monitored all serious adverse events that occurred in the EMU, at the Danish Epilepsy Centre.

In this study, we present the adverse events that occurred over a period of five years (2012-2016). The major goal was to assess whether the rate of injuries due to falls is higher in our setting, compared to what previously has been reported by centers, where the mobility of the patients was significantly restricted.

Methods and materials

For the determination of the shortest minimal duration of the standard and sleep EEGs, we have retrospectively reviewed 1005 consecutive EEG recordings. For each abnormal recording, we determined the shortest duration necessary for demonstrating the abnormal findings.

For the interictal EEG abnormalities (epileptiform discharges, pathological slowing), this was defined as the shortest duration that comprised at least two examples of the same type of abnormality. When several types of abnormalities were present, two examples of each type had to be present within the shortest efficient recording duration.

We evaluated separately those recordings in which the abnormalities only occurred during hyperventilation or intermittent photic stimulation, as their occurrence depended on the timing of the provocation method during the test.

In addition, we also evaluated the time of occurrence of the ictal event in cases of recordings containing seizures.

For the second part of the study, assessing the diagnostic yield of HV, three European centers (Dianalund, Szeged, Bucharest), where local guidelines included 5 min of HV as part of the standard EEG, participated in the study. EEG recordings from 1084 patients referred on suspicion of epilepsy were prospectively evaluated by board-certified experts. All patients gave their informed consent prior to the recordings.

EEG was recorded with 19 electrodes (10–20 system) or with 25 electrodes in patients where a focal pathology was suspected (six electrodes in the inferior temporal chain were added to the 10–20 system electrodes). All the recordings also included at least an ECG trace.

Contraindications to performing HV included severe cardiac or pulmonary disease, recent myocardial infarction or stroke, intracerebral hemorrhage, hyperviscosity state, sickle cell anemia, uncontrolled hypertension, subarachnoid hemorrhage, severe carotid stenosis and Moya-Moya disease[61,62]. In one center (Danish Epilepsy Centre) age >65 years was also considered a contraindication, according to the national guidelines[62].

Patients were asked to perform 5 min of HV in room air, with a respiratory rate of 20–30 breaths per minute, under the supervision of a trained EEG technician. For children we used windmill toys. The procedures were recorded on the video and the performance of the HV was classified as sufficient or insufficient by the technician and then by the physician evaluating the EEG recordings[63,64]. The physicians graded the sufficiency of the HV by watching the video recordings.

Occurrence of interictal EEG abnormalities and of seizures was noted separately, for the first 3 min and for the last 2 min of hyperventilation. Abnormalities were classified according to the recently published European standard [63,64]. The interictal EEG abnormalities were classified into two categories: interictal epileptiform discharges (IEDs) and focal slowing (FS). Only unequivocal focal delta activity was considered FS, and special attention was attributed to distinguishing FS from normal hyperventilation response [63,64].

The EMU described in this paper is situated at the Danish Epilepsy Centre, Filadelfia, the only specialized hospital for comprehensive care of patients with epilepsy, in Denmark. Patients were monitored here, in an unit specifically designed for this purpose, and they were under continuous surveillance by personnel dedicated to the EMU. Adverse events (AEs) - including injuries, were prospectively noted, as part of the safety policy of the hospital. Other data were retrospectively extracted from the electronic database, for a 5-year period (January 2012–December 2016).

Results

We reviewed a total of 1005 EEG recordings for the first part of the study. Abnormal interictal findings were observed in 264 standard recordings (42%), 58 short-term video-EEG monitoring sessions (43%) and in 124 sleep recordings (51%).

Decreasing the recording time of the standard recordings from 30 min to 15 min caused a significant drop in the incidence of abnormal recordings ($P < 0.002$). There was no significant difference between 20 min and 30 min duration.

Increasing further the recording duration from 30 to 180 min in the batch of short-term video- EEG monitoring caused an increase in the incidence of abnormal findings. However, this remained below the level of significance.

For the sleep EEG recordings, there was no significant difference in the incidence of abnormal recordings between 30 and 60 min but decreasing the recording duration to 20 min caused a significant drop in the incidence of abnormal recordings ($P < 0.02$).

In the batch of short-term video-EEG monitoring, the incidence of ictal events dropped significantly when the recording duration was decreased to 30 min ($P < 0.03$). All other comparisons remained below the level of significance.

For the second part of the study, we enrolled 1084 patients. 595 of them were female and 489 were male. Their ages ranged from 1 to 91 years, with a mean of 33.8 years. Out of the 1084 patients, 877 (81%) successfully completed 5 min of HV.

HV precipitated seizures in 25 patients (2.9%). In 21 of them (2.4%) the seizures occurred during the first 3 min (Figure 5). Seizures were precipitated in the last 2 min in four additional patients. Thus, seizures occurred during the last 2 min of HV in 16% of the patients who had seizures triggered by HV. The main seizure-types precipitated by HV were absences (19 patients), followed by myoclonic seizures (3 patients) and complex partial seizures (3 patients).

During the last 2 min of HV two absence seizures, one myoclonic seizure and one complex partial seizure were precipitated. Patients in whom HV precipitated seizures were younger (range: 6–46, mean: 16.2 years) than the patients with unprovoked seizures ($p = 0.01$), and younger than the patients without seizures during the recording ($p < 0.001$).

Interictal EEG abnormalities were precipitated during HV in 23 patients (2.6%). However, only in 16 patients they occurred during the first 3 min (1.8%). Thus, interictal abnormalities occurred during the last 2 min of HV in 30% of the patients who had EEG abnormalities triggered by HV. The increase comprised both IEDs (during the first 3 min in seven patients, and additional three patients during the last 2 min of HV) and FS (during the first 3 min in nine patients, and additional four patients during the last 2 min of HV).

Accentuation of the EEG abnormalities pre-existing in the baseline (unprovoked) period was observed in 81 patients (9.3%). In 71 patients this occurred during the first 3 min (8.1%).

Psychogenic non-epileptic seizures (PNES) occurred during HV in 10 patients (1.1%). PNES occurred in the first 3 min of HV in eight patients and in two additional patients during the last 2 min of HV. Totally 22 PNES were recorded in our population, thus almost half of them during HV.

In total 976 patients (528 were female, 428 male) were monitored in the EMU in the 5-year period. Their mean age was 24.57 (SD = 17.9, range 1-80 years), 384 patients under 16 years of age and 592 above 16 years. The mean duration of the stay was 3.2 days (range 1–5 days). Eighty of the patients (8.1%) had severe mental or physical disability. Their mobility was restricted to their patient-room.

The AEs we observed during our study are summarized in Table 1.

Serious AE was recorded only once: a patient developed convulsive SE and did not respond to the first-line AEDs in the EMU, being then transferred to an Intensive Care Unit, where he later made a complete recovery.

None of the adverse events resulted in injury to the patients, their caregivers or the personnel. Other AEs occurred in 77 (7.9%) patients, most of them in relation to epileptic seizures, but we also recorded two non-epileptic falls.

Table 1. Summary of AEs observed in our study

	Total	AEs (total)	Seizure cluster	Falls	SE	Cardiac abnormalities	Respiratory complications	Postictal psychosis
No of patients	976	78 (7.9 %)	36 (3.6 %)	19 (1.3%)	10 (1.02%)	4 (0.4%)	2 (0.2%)	1 (0.1%)

Totally we recorded 4888 seizures, of which 177 (3.6%) GTC seizures, 729 (14.9%) tonic and atonic seizures, 674 (13.7%) myoclonic seizures, 484 (9.9%) spasms, 250 (5.1%) absence seizures, 2347 (48.01%) focal seizures and 227 (4.6%) PNES.

Duration of monitoring until the first seizure occurred was 0.4 days (range 0-5 days). 373 patients (38.2% of the whole cohort) did not have any seizures in the EMU.

The most frequent AE was seizure-cluster (3.6% of the patients). Only two of these were GTC, the rest being clusters of focal seizures. All patients responded to the oral or intravenous administration of midazolam and did not need any further intervention or transfer to another unit.

There were 10 (1.02%) episodes of SE, nine non-convulsive (NC) and one convulsive SE. All the patients with NCSE responded well to first line AEDs administered in the EMU, but the CSE patient had to be transferred to an ICU.

There was no correlation between the AED tapering and the occurrence of seizure-cluster or SE (p = 0.8). Twenty-two (2.2%) of the patients had a previous history of SE. Among them, only one had an episode of NCSE in the EMU.

We recorded 19 falls in 19 (1.9%) patients, of which 14 were in patients where the referral was for diagnostic clarification of astatic seizures and recording the episodes with falls was needed for documenting and analyzing the habitual seizure type of those patients. In all of these cases extra precautions were taken, to avoid injuries when falls occurred.

Of the 19 falls, one (5.2%) was during a GTC, four (21.5%) during tonic or atonic seizures, two (10.5%) during myoclonic seizures, two (10.5%) during spasms, four (21.5%) due to focal seizures, two (10.5%) of the falls happened during PNES and two (10.5%) were during other non-epileptic events. The falls observed in the patients with PNES were slower than those observed during seizures, practically consisting of episodes where the patients slid off a chair. None of the patients suffered any type of injury.

In order to obtain more seizures, AED tapering was done in 284 (29%) patients. The decision was made on a case by case basis, based on the usual seizure frequency and the reason for referral.

There was no significant age difference between the patients who suffered AEs (21.2 years) and those who did not (p = 0.07). The occurrence of AEs was not influenced by gender (p = 0.9), drug tapering (p = 0.8), or age younger than 16 years (p = 0.1).

Discussion

We have investigated the shortest efficient duration of EEG recordings in a tertiary referral center for patients with epilepsy. For the awake, standard recordings, we found a significant drop in the incidence of abnormal interictal findings with recording durations shorter than 20 min. For the sleep recordings, the incidence of abnormal interictal findings significantly dropped for recordings shorter than 30 min.

The incidence of ictal events in the short-term video-EEG recordings significantly dropped for recordings shorter than 60 min.

The diagnostic yield and the shortest efficient recording duration vary much with the patient population. Thus, our results reflect the referral pattern of our epilepsy center, and one should be cautious with extrapolating these results for other referral patterns. Also, the setting of the sleep EEG can influence how early during the sleep recording the abnormal findings show up. In our center, we use partial sleep deprivation and/or administration of melatonin.

Our results suggest that in epilepsy-related indications, the shortest duration of a standard recording should be 20 min and the shortest duration of sleep EEG should be 30 min.

We found precipitation or accentuation of the EEG abnormalities during HV in 104 patients (11.9%) and precipitation of epileptic seizures in 25 patients (2.9%). This is in accordance with previous studies on the diagnostic yield of HV during EEG[16,21,29,32,35,65]

Extending 3 min HV with additional 2 min proved to be feasible: 99% of patients who completed 3 min HV were able to continue it for two more minutes, and no adverse events occurred during the last 2 min of HV. When expressed as percentage of the total patient population, the increase in diagnostic yield seems to be rather modest: from 2.4% to 2.9% for seizure-precipitation, and from 1.8% to 2.6% for eliciting interictal abnormalities that were not seen in the unprovoked, baseline period. However, this is influenced by the low percentage of patients who had seizure or IEDs only during HV [21]. If we express the difference as percentage of the total number of patients who had seizures or IEDs only during HV, the difference between 3 and 5 min HV is 16% and 30%, respectively. In other words, if the patients had hyperventilated for 3 instead of 5 min, we would have missed 16% of the seizures and 30% of the interictal abnormalities triggered by HV. From a clinical point of view this is an important increase in the diagnostic yield, taking also into account that no adverse events occurred during the last 2 min of HV.

The age of the patients who had seizures precipitated by HV was younger than the rest of the studied population. This is in accordance with previous studies and it is explained by the high incidence of absence seizures in this group (19 out of 25 seizures precipitated by HV).

Another clinically relevant finding in our study was the high incidence of PNESs during hyperventilation: almost half of the PNESs in our study occurred during HV. All patients received written information about HV, and seizure-precipitation was mentioned as a possible effect. The high susceptibility of the patients with PNES could explain why HV elicited these events, based on the information provided to the patients prior to the recording.

In order to avoid injuries due to seizures and falls, and due to the lack of wireless amplifiers, many centers apply restrictive measures to limit their patients' mobility. This can be quite uncomfortable to the patients and can potentially lead to other complications, such as deep vein thrombosis.

In our center, we tried a different approach, providing an environment designed to prevent injuries, in which patients can move freely during the monitoring, ensuring the safety through continuous surveillance by specially trained and personnel, dedicated to the EMU.

We have prospectively monitored AEs including injuries for 5 years. Our sample size is higher than in the previously published studies on patient safety in the EMU [3,66–72]

Although 19 episodes with falls occurred, none of them lead to injury. In centers with restrictive measures, the proportion of injuries was up to 3.7% of the patients. This suggests that the specially designed environment in the EMU and the tight surveillance might be more important for avoiding injuries, than restricting the mobility of the patients.

Thirteen falls were recorded in patients who had astatic seizures and were referred to the EMU for further diagnostic clarification. In these cases the falls were anticipated and extra precautions were taken to prevent injuries when they occurred. This meant the use of helmets and around the clock supervision (by the medical staff or a family member). We also recorded two falls during non-epileptic events.

Overall, none of the falls resulted in injury, prolonged hospitalization or any sort of complication to the patients. The rate of AEs in our facility was 7.9% of all admissions, that is lower than in most of the previously reported studies[59,67–72]. The most common were SC and SE, that affected 4% of our monitored patients. In only one of these cases (a convulsive SE) the patient had to be transferred to an ICU.

We did not find any correlation between the reduction of AEDs and the occurrence of SC and SE. This is probably because drug tapering was avoided in the patients with a history of SE (2.2%) and in those with a high seizure frequency.

Patients who experienced AEs had a slightly shorter duration of stay (2.9 days compared to 3.2 for the whole group). This is probably because in the cases where recording astatic seizures was the main goal of the monitoring, the patients were discharged quickly after the AEs happened.

Due to the fact that our patients did not have any restrictions of mobility during their admission in the EMU and physical activity was actually encouraged in most of the cases, we did not use any methods of prophylaxis for deep venous thrombosis, nor did we record any embolic events.

A prospective multicenter national service evaluation of the occurrence of AEs occurring in EMUs in the UK concluded that the most important factor was the presence of a nurse dedicated to the telemetry beds[73]. This is consistent with our findings. A higher nurse/patient ratio has also been identified as a factor in improving safety in the EMU[52,55,74,75]. In our unit, the personnel/patient ratio is of 1/2, which is higher than what was reported from other studies[73,74,76]

Conclusions

The importance of Video EEG, be it of short or long duration, is undeniable for the diagnosis and management of patients with epilepsy. While it is a highly effective investigation, it is labor-intensive and sometimes a limited resource, so any means to increase its diagnostic yield are welcome.

Through our study, we concluded that the minimal efficient duration for a standard EEG should be 20 minutes, while for the sleep EEG it should be 60 minutes. This is important especially in places where the patient load is an issue.

Furthermore, having the patients hyperventilate for 5 minutes instead of 3 during the EEG recording is safe, posing little inconvenience for the patient and it can increase the diagnostic yield of the investigation.

And finally, our results suggest that 24 hour surveillance by a well trained staff, a safe environment and taking special precaution measures when necessary (for example the use of helmets, placing the patients on soft surfaces, not tapering down medication in patients at risk of

SE, SC, psychiatric conditions) can be just as efficient for the patient's safety as limiting their mobility, without causing any discomfort. This can, of course, be applied only in places where the human resource is not a problem.

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