Standardization and quality assurance in clinical electroencephalography

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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.**

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]

Indeed, interpretation of EEG abnormalities is useful in identifying epileptogenic foci, structural abnormalities, and/or electrographic patterns associated with specific epilepsy syndromes, being helpful not only in making a correct diagnosis, but also informing on treatment options or evaluating the possible course of the disease[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. This is important not only for having a uniform, standardized practice throughout different clinical centers but also to reduce the cost of investigations. Both points are especially valuable in developing countries with limited time and financial resources.

Ever since EEG was introduced in clinical practice, several methods were used in order to increase its diagnostic yield- hyperventilation (HV), intermittent photic stimulation (IPS), sleep deprivation, sleep, antiepileptic drug tapering and more complex activation methods, like cognitive tasks.

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] Over time, its diagnostic value has been certified by several studies and it has become a part of most standard EEG recordings[16–25] and it is also of use in intracranial EEG recordings [26] .

Through mechanisms that are still to be fully understood, HV can trigger different patterns of EEG abnormalities- generalized and/or focal slowing, generalized or focal interictal epileptiform abnormalities, clinical or infra-clinical epileptic seizures and psychogenic non-epileptic seizures (PNES). As a provocation method, it has proven to be more useful in generalized epilepsy, and especially in absence seizures [16,17,19–21,27–29], but also in Juvenile Myoclonic Epilepsy[29–31]. Nevertheless, some studies have shown that it can also trigger focal seizures, especially those with a temporal lobe onset [17,22,23,26,28] while others question its value for focal epilepsy [18,24,27]

In addition to epileptiform discharges, HV can also elicit slow activity. Sometimes this is a normal phenomenon, especially in children or young adults, but it can also point to a specific cerebral disease. There are distinctive EEG findings, observed in pediatric moya-moya patients, including the high amplitude slow waves called posterior or centrotemporal slowing and the rebuild-up phenomenon, which is indicated by the reappearance of high amplitude slow waves at 20–60 s after the cessation of HV[32–34].

One also needs to be aware of the appearance of HV-induced high-amplitude rhythmic slowing with altered awareness, which mimic absence seizures but are a different and characteristic EEG finding [27,35–38]

Several studies have also shown that HV is useful in precipitating PNES[21,39,40] and thus reducing the EEG recording and the hospital stays of these patients that can be a burden on the health system before the right diagnosis is reached.

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[17,20,22,27,28,41,42]. 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 [16,23,27,28,31,43], in one it was 4 minutes [41], in others it was 5 minutes [17,24,41,44–46], or ranging from 3 to 6 minutes [26], from 3 to 5 minutes[38] and one of the biggest studies, on 3745 patients has durations of HV ranging from 1 to 7 minutes [21].

Miley and Foerster were among the first to suggest that increasing the duration of HV above the standard 3 minutes could be useful, but the impact of the duration of HV on the diagnostic yield of the EEG has not been systematically investigated yet.

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 [10,13,47]. However there is no consensus on the necessary duration of the HV: some guidelines recommend 3 min [47], or a minimum of 3 min [48], while others recommend that HV is performed for three to 5 min[49].

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 [31,50–53], which is particularly useful for presurgical evaluation of the patients with drug-resistant disease. But its indications also include making a differential diagnostic between epileptic seizures and other paroxysmal events, characterized by intermittently occurring behavioral changes including psychogenic nonepileptic events and sleep disorders, particularly those involving paroxysmal movement disorders[42,54–58] , documentation of diurnal or circadian variation in occurrence of epileptiform paroxysms, in conjunction with monitoring the effect of pharmacological interventions on the seizure frequency [54,57–60], documentation of specific patterns in the occurrence of epileptiform paroxysms during sleep and of disruption of sleep architecture (particularly in the pediatric population) [54] and monitoring in the intensive care unit

(ICU) for the effectiveness of treatment of status epilepticus and for the identification of subclinical seizures and subclinical status epilepticus, conditions that have been shown to be more frequent than usually thought in the ICU[54].

Even if recent advances in technology have led to miniaturization of equipment that have made multichannel EEG recording portable enough to allow high-quality ambulatory recording and data transmission over long distances possible, most of the times LTM requires elective admission of the patient in an Epilepsy Monitoring Unit (EMU). This poses some risks, by placing a patient that is already more prone to injuries than the general population[61–63] in an unfamiliar environment, where, in order to be able to record the patient's habitual seizures, they will be exposed to provocative measures (HV, IPS, sleep deprivation) or AED withdrawal [55,63]. 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[55,57,63–68].

There are no generally accepted guidelines about the safety measures in the EMU [69,70], and this has created a great variability in the safety measures adopted by different EMUs [55,57,63,69,71–73].

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 [59,63,67,74,75]. Other measures taken to ensure patients' safety vary widely from center to center, depending on the design of the EMU, the number and level of training of the staff, permanent access to an on-call doctor and the possibility to transfer the patient to an ICU in case of an emergency. Sometimes this can be very limiting or uncomfortable for the patients, especially if the duration of the stay is longer [63,72,76,77]. Some centers use low molecular weight heparin or compression stockings in order to reduce the risk of deep vein thrombosis associated with prolonged immobility [55,67,74] while others report using in-dwelling catheter in order to limit the trips to the toilet [59,78] or the use of a restraint vest and loose wrist restraints[59] for patients undergoing invasive EEG recordings. Other, less restrictive measures include: the use of padded side-rails [55,57,63,67,74], use of helmets when the patients are out of bed[59,74], specially designed toilets[74], anti-suffocation pillows [63,75] and physical protections in the monitoring rooms (including floormats, shielding of hard edges, removal of obstacles)[79].

However common sense some of them seem, not all of the safety measures being used at present have proven efficient in decreasing the risk of injuries [63,77,80].

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 [81] 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.

EEG recordings were retrieved from our standardized database. All recordings were evaluated by at least two of the authors. Controversial or ambiguous cases were discussed by a multidisciplinary team comprising clinical neurophysiologists and epileptologists.

Six hundred and twenty-six recordings were ‘standard EEGs’, recorded according to the European guidelines, with 30 min duration[47]. One hundred and thirty-five recordings were ‘short-term video-EEG monitoring’, with 180 min duration. Two hundred and forty-four recordings were ‘sleep EEG recordings’, with 60 min duration.

Sleep EEG recordings were carried out following partial sleep deprivation in adult patients. Children and those adults who could not fall asleep received melatonin.

The age of the patients was between 1 and 90 years (mean: 30 years, median 26 years); 489 female, 516 male.

Table 1 shows the indications for the EEG recordings, according to the categories suggested by the recently published European consensus statement, SCORE[82]. This reflects the referral pattern of our clinical neurophysiology department, at a national epilepsy centre.

For the batch of standard (30 min) recordings (n = 626), the incidence of abnormal recordings with shortest efficient recording duration within 15 min, within 20 min and within 25 min was compared with the total incidence of abnormal recordings (30 min) using chi-square test.

For the batch of sleep EEG recordings (n = 244), the following durations were compared: 10, 20, 30, 40, 50 and 60 min. For the short-term video-EEG monitoring, the following durations were compared with the total incidence (180 min) of abnormal findings: 30 min, 60 min, 90 min and 120 min.

Table 1

Indications for EEG recordings

Epilepsy-related indications	**855**
Classification of a patient diagnosed with epilepsy	580
Clinical suspicion of epilepsy or seizure	131
Reconsider the initial diagnosis of epilepsy	108
Considering stopping AED	26
Nonconvulsive status epilepticus	10
Differential diagnosis	**88**
PNES	55
Other	33
Other	**62**

For the second part of the study, assessing the diagnostic yield of HV, 3 European centres (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 of 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[83,84]. In one centre (Danish Epilepsy Centre) age >65 years was also considered a contraindication, according to the national guidelines[84].

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[82,85]. The physicians graded the sufficiency of the HV by watching the video recordings. Similar to the assessment of the sufficiency of HV, adverse effects were first noted by the technician and then by the physicians.

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 [82,85]. 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 [82,85].

Precipitation of seizures and of interictal EEG abnormalities during HV was considered when these did not occur in the baseline, unprovoked period. In addition, we noted the cases where an accentuation of the phenomena already occurring in the baseline was observed.

As the highest diagnostic added value is for the cases where HV induced precipitation of abnormalities not recorded in the baseline period, we focused our study on this. However, to compare our results with previous studies that lumped together precipitation and accentuation, we also noted the accentuation of the pre-existing abnormalities.

Age had normal distribution in our patient population. We used t-test to compare the age of the patients who had seizures or interictal EEG abnormalities only during HV with the age of the rest of the patients.

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. The hospital was founded in 1897, and it is a tertiary referral center. Together with the Copenhagen University Hospital, Rigshospitalet, it constitutes the network for the Danish epilepsy surgery program. The EMU is part of the Clinical Neurophysiology Department, and it was built in 2005, being specially designed for this purpose.

The unit comprises four single-patient bedrooms, each with own bathroom. The dining room, the living room and the terrace are shared by all patients, and there is a play room for children (Figure 2). There is a surveillance room and a technical room in the unit, which is physically connected both to the Clinical Neurophysiology and to the Neurology departments (Figure 1)

Four patients are simultaneously monitored in the EMU, usually two children and two adults. Children are admitted together with one of their parents or another caregiver.

The portable EEG amplifiers are wirelessly connected to access points located in the EMU and the patients are not restricted in their mobility within the unit. Patients can use exercise bikes, a home video game console with a handheld controller device which detects movements (Nintendo Wii) allowing the patients to play games involving physical activity, and children have access to a broad spectrum of toys, matching their age and development (Figure 2).

The rooms are specially designed for epilepsy monitoring: besides electric shielding, this includes measures to prevent injuries in case of falls: soft material of the flooring, rubber tiles on the terrace, avoiding sharp edges of the furniture, placing soft, protective materials on edges and hard surfaces. Patients with suspected hypermotor seizures, sleep on a mattress directly placed on the floor.

Only the mobility of patients with severe physical and intellectual disability is restricted to their rooms, and extra personnel is continuously present in their room.

In this setting only non-invasive monitoring is done. Patients with implanted electrodes are monitored at another EMU facility (Rigshospitalet).

The lower age-limit in the EMU is 4 months. There is continuous surveillance of the patients in the EMU.

The personnel in the EMU consists of two neurophysiology technicians and one nurse from 8 am to 4 pm, one technician and one nurse from 4 pm to 12 pm, and two nurses (one in the

EMU and the other in the video surveillance room) from 12 pm to 8 am. The personnel are specifically trained for the tasks in the monitoring unit, and the hospital has a program for continuous professional education, including aspects relevant for the EMU.

Three consultant physicians (board certified neurologists, with sub-specialty training in clinical neurophysiology) are responsible for the EMU, and they take shifts of one week each. During their shift in the EMU, these physicians do not have other duties. Each morning, a multidisciplinary team including adult and pediatric neurologists, clinical neurophysiologists and the personnel in the EMU discuss the seizures that occurred during the previous day, and they decide on continuing or stopping the monitoring, for each patient. Within two hours after the discharge of the patient from the EMU, a preliminary report is issued, while the final, detailed report is issued latest two weeks after the monitoring. EEG is recorded using electrode arrays including the inferior temporal chain.

Polygraphic channels include ECG (for all patients), surface electromyography (patients with motor seizures), respiration monitors (for PSG and in patients suspected for ictal apnea).

A standardized behavioral testing battery has been used in the EMU since 2012, and during the last two years, this was replaced by the European standardized ictal testing battery (ITB) [53]. The ITB was prospectively evaluated on 250 seizures in 10 centers to assess feasibility and was found to be feasible in 93% of the included seizures. Difficulty in implementation was related to short-lasting seizures, such as myoclonus, absence seizures and other brief seizures of focal origin. The ITB provides information on subtle feature of semiology including autonomic features; responsiveness to verbal command and/or touch; comprehension; orientation; verbal and visual memory. Clinical examination is suggested to assess for tone, Todd's paresis and Babinski reflex. The ITB is dynamic and adjusted according to the seizure and takes 2-9 minutes to complete.

Totally 31 video-cameras are located in the EMU. The staff in the surveillance room chooses the optimal camera for each patient and makes sure the patients are always in focus. The monitoring is tailored to the individual needs of each patient (Figure 3), the list of items in the electronic referral system, and the items discussed during the planning of the monitoring for each patient. This included a risk assessment, as evaluated at the pre-monitoring multidisciplinary team meeting (Figure 4).

When AED tapering is planned, this is started before the video-EEG monitoring, but in the hospital, under continuous video surveillance. Patients sign an informed consent before admission to the EMU.

At the annual patient-safety audit, adverse events and the potential adverse events are analyzed and then measures to avoid them are developed. The safety-team includes the staff in the EMU and external auditors.

Severe adverse events (AEs) were monitored prospectively. Other data were extracted retrospectively from the electronic database. We considered the following to be AEs: status epilepticus (SE), seizure cluster, falls, serious cardiac abnormalities (asystolia, severe brady- or tachycardia), psychiatric symptoms (post-ictal psychosis, panic attacks, post-ictal aggression). When we calculated the total number of generalized tonic-clonic seizures (GTCS), we included both the primarily and the secondarily generalized ones. We did not consider these as AEs, unless they were in clusters or were prolonged over 5 minutes.

The following were considered severe AEs: death (including SUDEP), injury to the patient or the personnel, status epilepticus that could not be resolved with first-line AEDs in the EMU, and any other condition that lead to the discharge of the patient from the EMU earlier than planned. Injury was considered in the case it needed any medical intervention (diagnostic or therapeutic) or any additional care.

We collected demographic data (age, gender), data regarding the clinical history (reason for referral, a history of SE, post-ictal psychosis or falls) and the stay in the EMU (length of stay, drug tapering, number, type and time of occurrence of seizures, adverse events).

All the recording and medical records were reviewed by at least two of the authors. The period of the survey was between January 2012 and December 2016.

For statistical analysis, we used Chi square or Fisher’s exact test for categorical data, and for univariate analysis we used a parametric test (t test).

Figure 1.

The plan of the EMU

The red dots indicate the placements of the cameras. Patients wear wireless amplifiers and they move freely within the EMU.

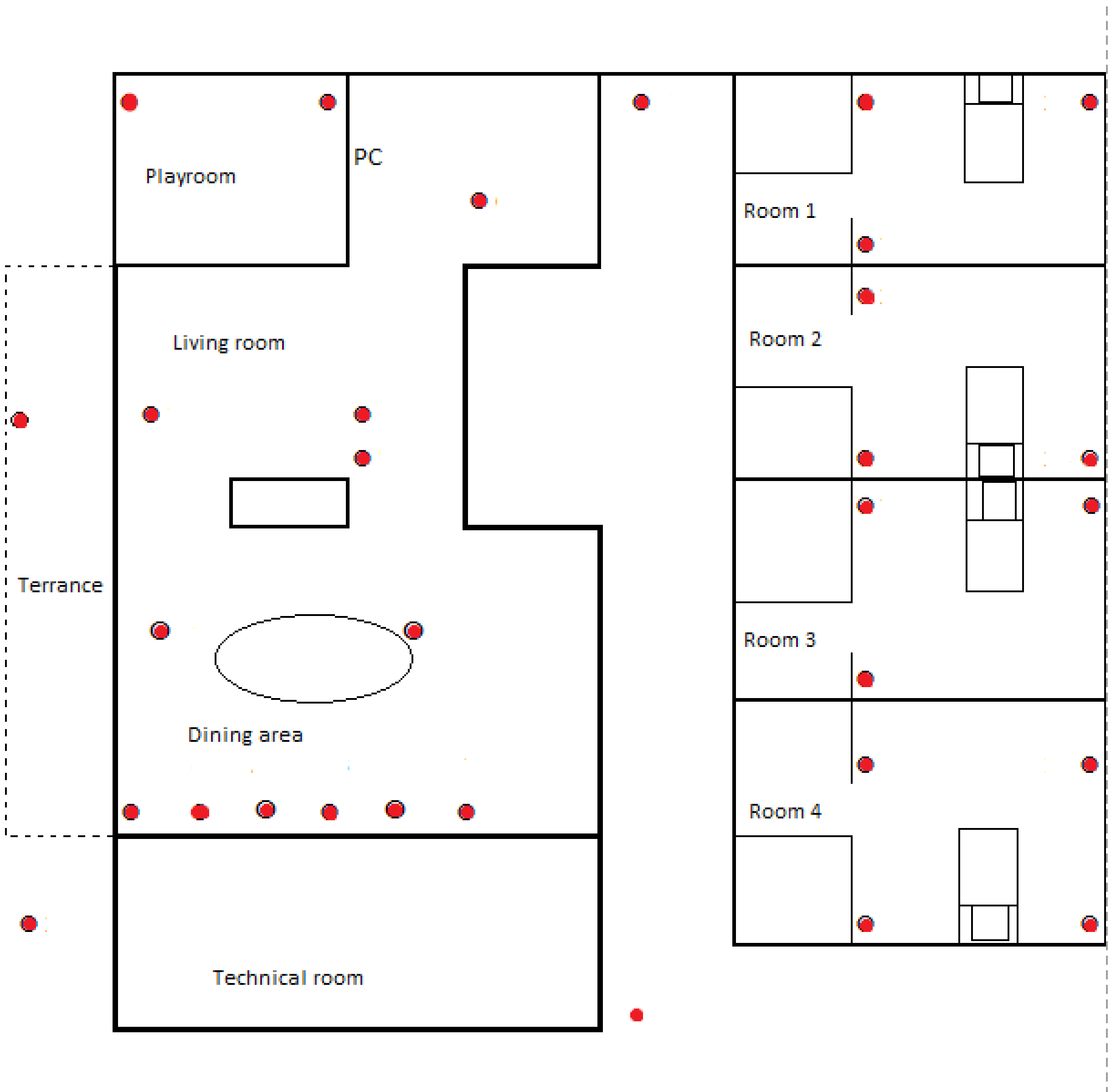
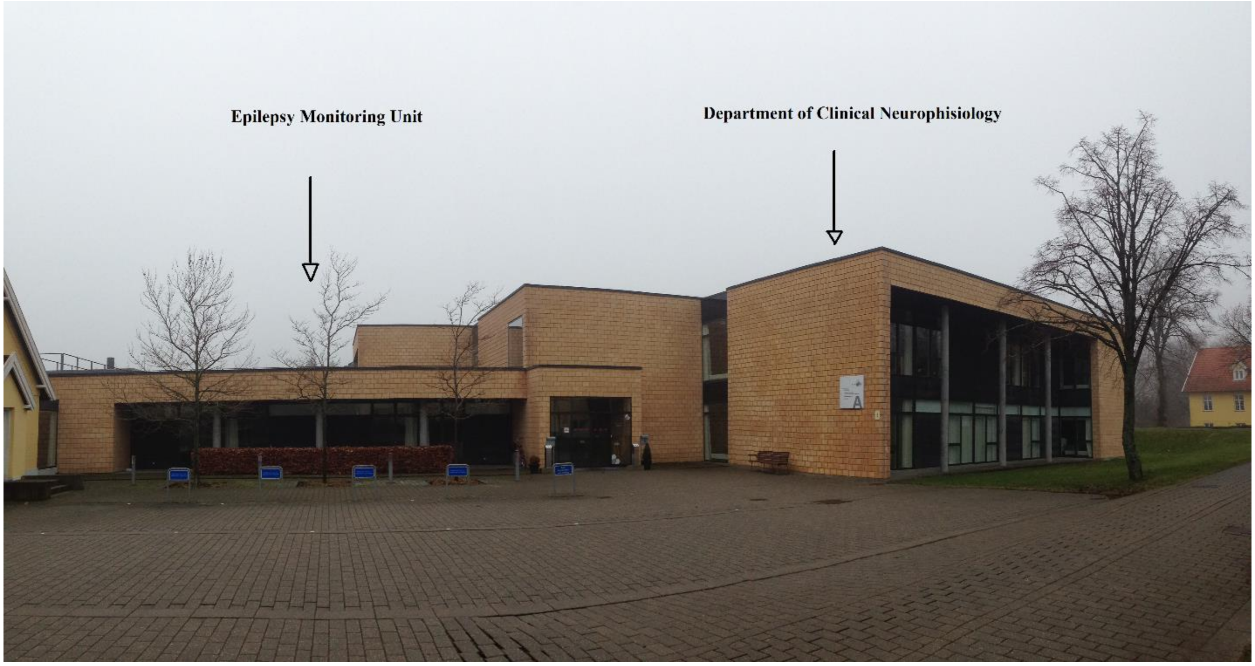


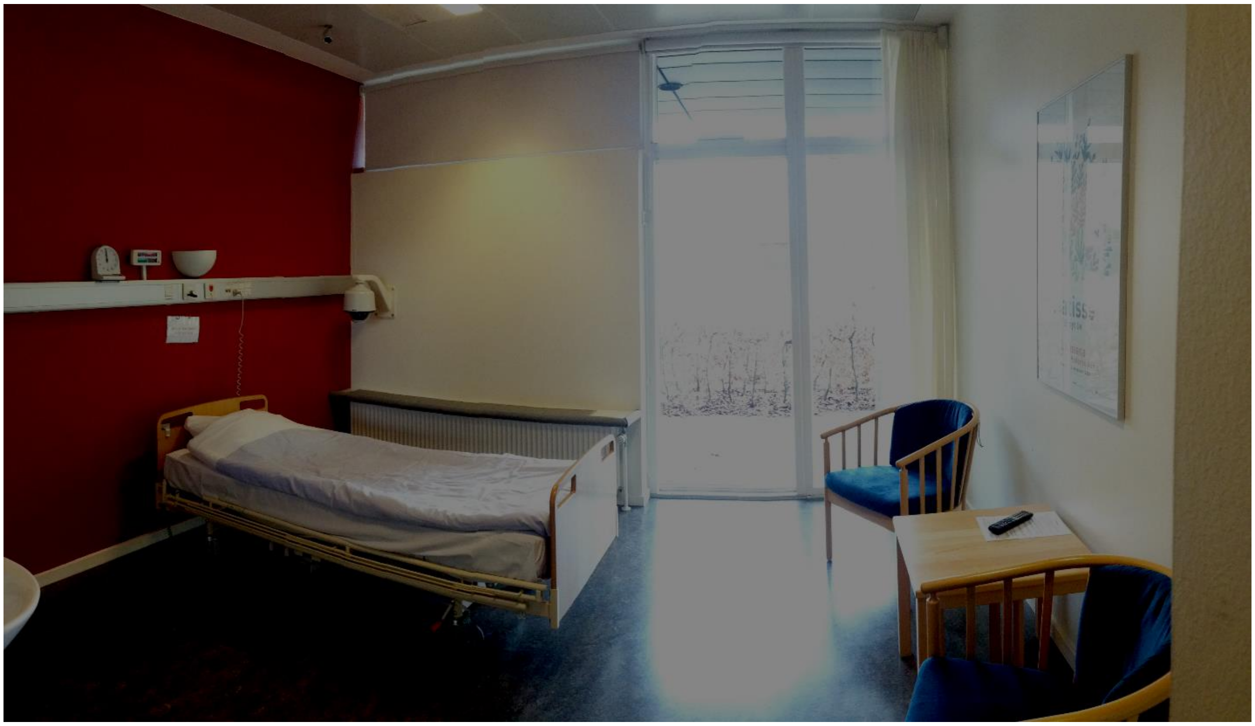
Figure 2

A. External view on the EMU. *The EMU is a self-contained building, specifically designed for this purpose.*



B. The technical room.

C. The bedroom of the patients. *There are four single-rooms in the monitoring unit. When children or disabled patients are admitted, an additional bed is added for parents / care givers.*



D. *In case hypermotor seizure is anticipated, the matrass is placed directly on the floor to avoid injuries.*

E. Dining room in the EMU

F. Living room.

G. Playroom for children

H. Patient using the kitchen facility in the EMU

I. The monitored terrace with rubber-tiles.

Figure 3.

The flowchart of the monitoring process

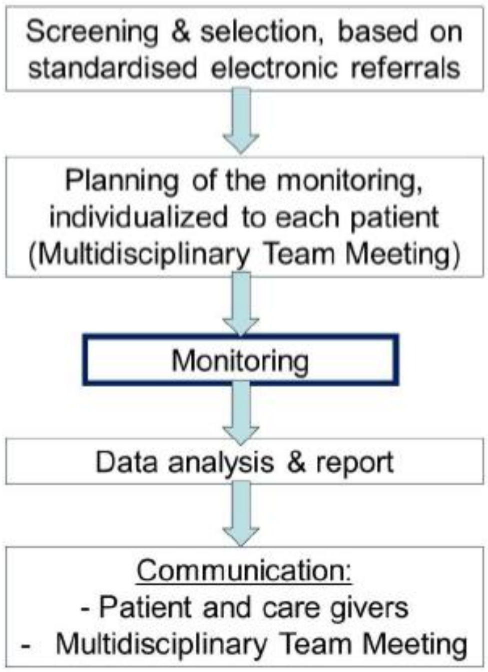


Figure 4.

List of items in the electronic referral system

I. Diagnosis at referral (ICD code)

II. Indication:

- Diagnosis
- Reconsidering the diagnosis
- Classification of seizures / epilepsy
- Epilepsy surgery
- Quantification / Monitoring the seizure frequency
- Other

III. Semiology

IV. Seizure frequency

V. AEDs

VI. Is withdrawal suggested?

VII. Factors facilitating and provoking seizures

VIII. Status epilepticus in the patient history?

IX. Postictal psychosis in the history?

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%) (Table 2).

Table 2

Incidence of abnormal recordings depending on the duration

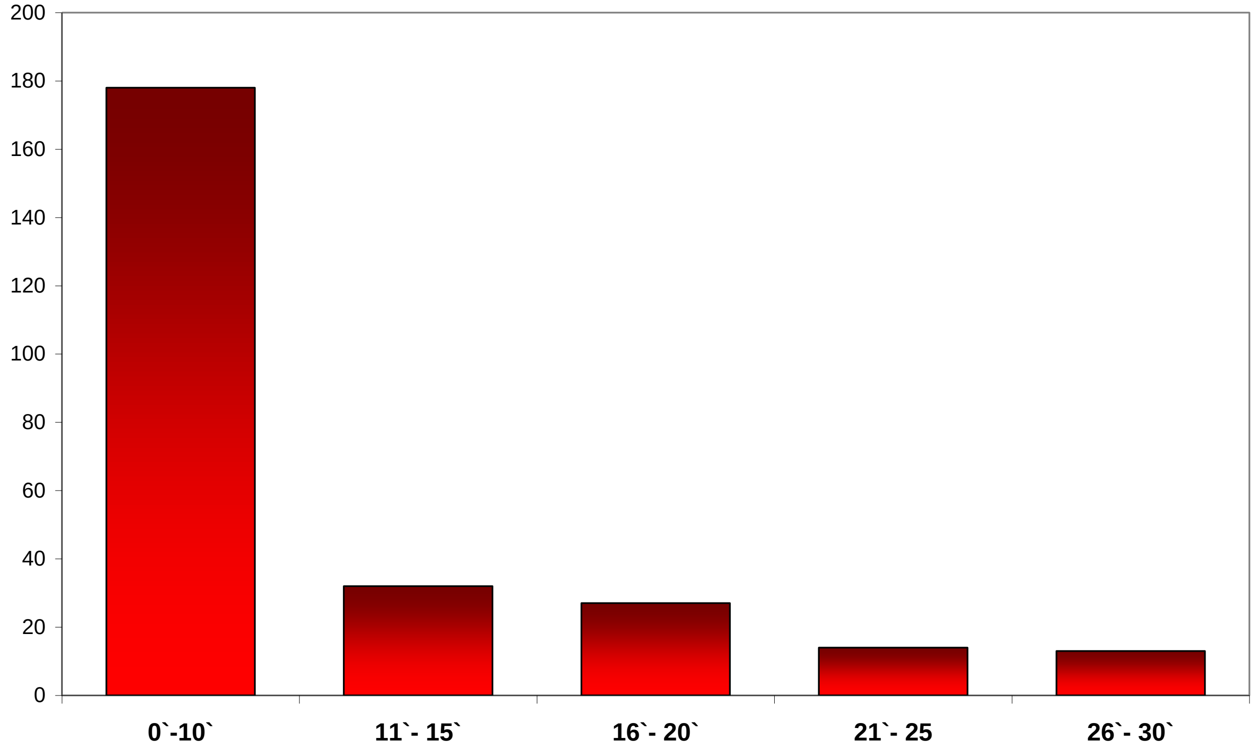
	Standard Recording (n=626)					Short-term monitoring (n=135)				
	10`	15`	20`	25`	Total abnormal	30`	60`	90`	120`	Total abnormal
Interictal	178	210	237	251	264	43	52	55	57	58
Ictal	12	14	16	18	23	12	24	29	31	35

Sleep (n=244)						
	10`	20`	30`	40`	50`	Total abnormal
Interictal	68	98	110	118	123	124
Ictal	1	3	4	7	8	10

Figure 4

Distribution of the shortest efficient durations for standard recordings

(Y-axis: number of abnormal recordings; X-axis: duration epochs in minutes)



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 ($P < 0.02$).

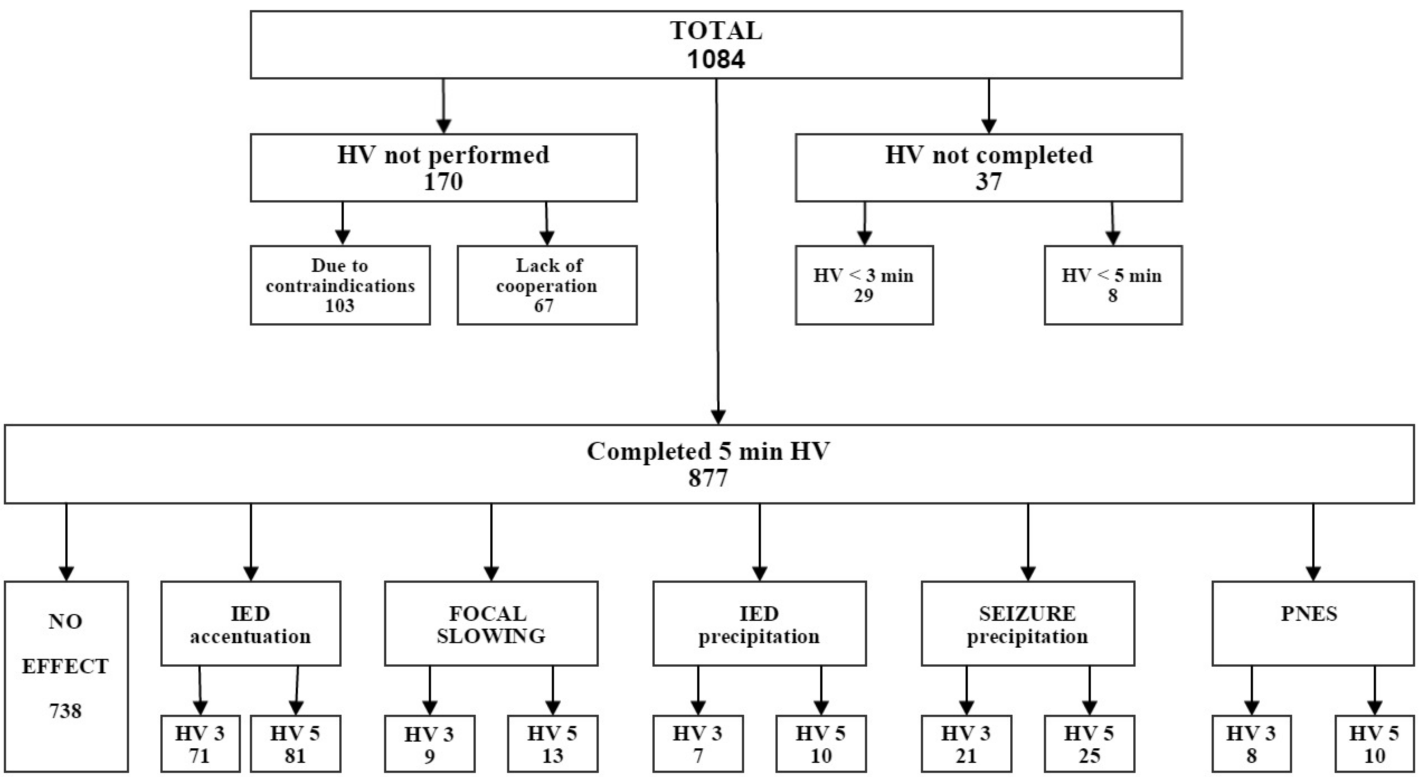
In the batch of short-term video-EEG monitoring, the incidence of ictal events dropped significantly when the recording duration was decreased to 30 min ($P < 0.03$). All other comparisons remained below the level of significance.

In 15 patients, the interictal abnormalities occurred only during provocation methods: hyperventilation (8 patients) and intermittent photic stimulation (7 patients). In additional 5 patients, the intermittent photic stimulation elicited myoclonia with EEG correlate.

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 (Figure 5).

Figure 5

Flowchart of the study indicating the number of patients in the various categories



HV 3: 3-minutes of hyperventilation; HV 5: five minutes of hyperventilation; IED: Interictal Epileptiform Discharges; PNES: Psychogenic Non-Epileptic Seizure

One hundred seventy patients did not perform HV at all due to contraindications or lack of cooperation. Five patients had cardiovascular disease and three patients had asthma. Ninety-five patients aged >65 years were excluded because that was considered contraindication in one of the participating centres. Sixty-seven patients were not able to cooperate to the HV: due to intellectual disability in 58 patients and due to young age (<1.5 year) in 9 patients.

One hundred seventy-five out of the 877 patients who completed 5 min HV were between 1 and 16 years (Table 3). Thirty-seven patients started HV but were not able to complete it, most of them because the cooperation with the technician was not optimal. Twenty-nine patients stopped before reaching 3 min of HV (2 patients were feeling uncomfortable, 1 patient had tetany, 1 patient had a movement disorder that was accentuated during the maneuver and in 25 patients the HV could not be continued because of lack of cooperation).

Eight patients stopped after 3 min of HV and before reaching the 5 min limit (Figure 2), because they were not able to hyperventilate longer, but no adverse event occurred, either during the first 3 min or during the last 2 min of HV.

Table 3

Number (and %) of patients who had seizures or interictal EEG abnormalities only during HV during the first three minutes of HV, as compared with the whole period of five minutes HV

	Seizures precipitated by HV			Interictal abnormalities only during HV		
age groups	1 - 16 years (n=175)	>16 years (n=702)	all patients (n=877)	1 - 16 years (n=175)	>16 years (n=702)	all patients (n=877)
HV 3 min	12 (6.9%)	9 (1.3%)	21 (2.4%)	1 (0.6%)	15 (2.1%)	16 (1.8%)
HV 5 min	14 (8%)	11 (1.6%)	25 (2.9%)	2 (1.2%)	21 (3%)	23 (2.6%)

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 (Table 3) 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 ($p < 0.001$).

In the same patient population, we recorded 4 absence seizures, 26 myoclonic seizures and 19 complex partial seizures during the baseline (unprovoked) period. Thus, most of the absences occurred during HV (19 out of 23).

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).

The age of the patients who had interictal epileptiform abnormalities precipitated by HV was not different from the rest of the population (range: 13–52, mean 34.1 years).

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.

We tried to assess if HV is more effective in women than it is in men. We found that the number of abnormalities, comprising both slowing and epileptiform discharges is higher in women than in men (68 vs 36) and the total number of seizures elicited by HV is also higher in female patients than in male ones (17 vs 8). But none of this reached a level of statistical significance. In the population of patients with PNES, the number of women was higher both in the group with episodes triggered by HV (9 females to 1 male) and in the group with spontaneous events (9 females vs 2 males) and this was statistically significant (p=0.02).

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 4.

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.

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.

The patients who experienced falls were overall younger than the general population- mean age 17.8 years (range: 3-63 years), but this was not statistically significant (p = 0.8).

Table 4.

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%)

Cardiac abnormalities occurred in 4 (0.4%) of the patients: three cases of ictal or post-ictal bradycardia and one case of bradycardia followed by an asystole with a duration of 5 seconds. Ictal bradycardia was recorded during focal seizures, two of them with seizure onset zone in the right temporal region and one in the left fronto-temporal region and post-ictal bradycardia was observed after a seizure with secondary generalization, whose onset was in the right temporal lobe. The mean age of the patients who had cardiac abnormalities was 32.5 years (range 5-43 years), older than the general population (24.6 years), (p = 0.3).

Two (0.2%) patients had respiratory problems: one of them had an episode of post-ictal hypopnea, during which his blood oxygen level dropped to 93% and came back to normal shortly thereafter, and one patient had central apnea, of non-epileptic origin.

Seven seizures (0.7% of patients) were missed by the personnel, one of which was a GTC. In six of the cases it was because the patients were inside the bathroom when the events happened and could not be properly observed, and in the other case, the patient had a seizure and fell after the recording was over and the electrodes were removed.

In total, there were two falls that were not caught on camera. Even though they took place in the toilet and were not witnessed by the medical staff, none of these incidents resulted in injuries.

Only one (0.1%) of our patients had post-ictal psychosis after a GTC. The patient did not have a history suggestive of post-ictal psychosis or other psychiatric illness. Three patients had a history of post-ictal psychosis, and none of them experienced a similar episode during or after the stay in our EMU.

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.

In this study, we only focused at recordings up to 180 min. As in a previous study, we have already evaluated the recording duration for long-term monitoring, and in this study, we only analyzed EEG recordings up to 180 min duration.

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.

Hyperventilation is a part of most standard EEG recordings and has been so almost from the dawn of this technology[15,21,83] Even so, the mechanisms through which HV can determine changes in the EEG activity are still not very clear. The hypoxia theory suggests that the slowing effect is due to vasoconstriction and diminution of oxygen and dextrose supply to the cerebral cortex [17,27,45,86] but this has many arguments against it. Another possible explanation comes from the hypocapnia theory, according to which low levels of CO2 lead to the predominance of nonspecific thalamo-cortical projections over the activating ascending reticular pathway system[17,83,87–89]

The different effect of HV in patients with epilepsy could be a consequence of the activation of diffuse thalamocortical projections on long-range connections, passing through the epileptic focus, that are uninhibited during HV, thus making easier the spreading of normal and, if present, abnormal electrical activity. As a consequence, these abnormal potentials can involve a bigger neuronal population and become more easily recognizable on the EEG, concerning a wider cortical area and reaching higher voltage[87] Another possible mechanism is the change in pH[22,87,90], that can affect NMDA receptors [87].

In normal subjects, HV can lead to a physiological slowing of the background rhythm, more pronounced in children and young adults[17,21,83,88], and low blood glucose level and an upright position of the patient seem to contribute.[83] HV in children can lead to HV-induced high-amplitude rhythmic slowing (HIHARS) on the EEG which is sometimes associated with altered awareness and concomitant semiological features.[17,36,38,86] This is what makes overinterpretation of EEG during HV a common problem[27,35,37].

In our study, we tried to counteract this bias by having every recording reviewed by at least two trained neurophysiologists and more complex cases were discussed in a multidisciplinary team meeting.

The diagnostic yield of HV during EEG has been the object of several studies, most of them concluding that it is a safe and useful procedure[17,21,22,28,83] while others found that it is of limited use, particularly in adults [20,23,27,41]. The differences in results could probably be explained by the differences in the population of patients studied (Arain et al[28] excluded children under 10 years, Guaranha et al[17] excluded children under 10 years and only looked at patients with drug-resistant focal epilepsy, while Raybarman et al[24] only included children with generalized epilepsy), but also in the methods applied and in the duration of HV itself.

A study that found the highest yield for seizure precipitation (28.3%) used 5 min of HV, repeated every 3 hours until seizures were successfully recorded[17] and found that the activation effect occurred in an ascendant fashion, from the beginning until min 4. In fact, there are several studies suggesting that HV should be performed longer than the usual 3 min[17,21,22].

Not all the studies looked separately at the changes in EEG that occurred only during HV and not during baseline and most of them only took in account the epileptiform discharges and seizures, or even just the seizures.

We found precipitation or accentuation of the EEG abnormalities during HV in 104 patients (11.9%) This is in accordance with previous studies on the diagnostic yield of HV during EEG[21,22,41,43,91] The diagnostic yield for interictal epileptiform discharges in the literature varies from 6,6 %[22] to 12,2 %[21], depending on whether the study included both patients with focal and generalized epilepsy, and a similar variation is also seen in the yield of seizure induction, which varies from no seizures at all [24,27] to 28.3 % yield for focal seizures, but in a study where the AEDs were tapered in all patients and HV was performed repeatedly[17].

Our study found precipitation of epileptic seizures in 25 patients (2.9%), which is also in line with most previous findings [21,22,28,41,83,91]. As was expected, the main type of seizures recorded during HV was absence seizures (19 patients). The relationship between HV and the typical 3 Hz spike-wave discharge of absence seizures has been well described ever since the first studies on EEG[23,46,92] and has been reconfirmed by multiple others[21,41].

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 and the total diagnostic yield for PNES during HV was 1.1%. This is also in accordance to previously published data, as precipitation of PNES by provocation methods is well described [21,28,39,40,45,83,93]. 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. This is a very useful finding, as the recording of such an episode as fast as possible can not only shorten the duration of the EEG recording, making other, more complex investigations unnecessary, but most of all can help doctors guide these patients towards more adequate treatment and care. For PNES, the delay in diagnosis averages 7 years and almost 80% of PNES patients receive AEDs[94], sometimes for years before the right diagnosis is made. So, any means of getting to the right diagnosis earlier is beneficial not only for the patients, but to the whole healthcare system.

Even though some studies have reported that HV can be more effective in female patients [18,28], our findings were inconclusive. The number of women with abnormalities or seizures during HV was higher than the number of men, but this was not statistically significant. We did, however, find that the number of women with PNES and the number of women with PNES during HV were significantly larger than the number of men with PNES. But this is most likely due to the fact that PNES are known to be more common in women[95–97].

Adverse events during HV have previously been described [21,31,83,98], including post-hyperventilation hyperventilation syndrome, post-hyperventilation apnea, triggering of asthma attacks, syncope or pre-syncope[99–102]. In our study we only had 5 patients stop before reaching 3 min of HV, all of them because of minor AEs (one patients had asthma, two patients felt an uncomfortable sensation in their lungs, one patient had a movement disorder that was worsened during HV and one patient fell asleep). We did not consider seizures during HV to be AEs.

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.

Improving patients' safety during their stay in an EMU is an ongoing goal and there are numerous recent studies addressing the overall safety of the patients in an EMU [63,74,103–106] and the measures that can be taken to increase it.

In order to avoid injuries due to seizures and falls, and because of 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, over the course of 5 years. Our sample size is higher than in the previously published studies on patient safety in the EMU (Table 5).

The rate of AEs reported by different studies and surveys varies to some degree, ranging from 9% of admissions [103] to 14% [107]. There are multiple possible explanations for this. One of them could be the different patient population- in centers performing both invasive and non-invasive EEG studies, the AEs are both higher and more serious, like pulling out of intracranial electrodes or subdural grids[103,104] or intracranial hematomas [103,104,107].

Another reason could be the difference in the way the centers are organized and staffed. The results suggest that having a separate unit for the EMU (and not having beds that are on a general neurology ward)[63,70,108], having in place a protocol for treating status epilepticus or seizure clusters [65,74] and having trained staff, dedicated to the epilepsy patients and their monitoring [58,74,79,108,109] could lead to a better and safer environment.

Table 5

	Our study	Doberberger et al, 2011	Fahoum et al, 2016	Kandler et al, 2013	Noe and Drazowski, 2009	Rheims and Ryvlin, 2014	Pati et al, 2013	Atkinson et al, 2012	Sauro et al, 2016	DiGennaro et al, 2012	Moien-Afshari et al, 2009
Patients (tot no)	976	507	524	272 seizures	149	-	116	20	-	54	50
Falls (%)	1.9	3.3	1.1	7	-	1-20	2.3	3.5	-	5.6	2
Injuries (%)	0	3.7	-	3	2.6	-	-	0.6	-	-	-
SE (%)	1.02	-	3.2	2	0.6	0-3.5	-	0.6	-	0	-
Seizure cluster (%)	3.6	2.5	7.6	-	2.3	-	-	-	-	11.1	-
Cardiac abn (%)	0.4	3.3	1.6	-	1.3	0.2-0.4	-	-	-	0	-
All AEs(%)	7.9	9	9	12	14	10	-	-	7	-	-
Psychiatric (%)	0.1	3.3	1.6	-	1.3	5	-	1.2	-	-	-

Surveys on the intensity of patient observation revealed the following data: in a US survey, constant observation of patients during VEEG was conducted by 68.6% of the respondents[110], in a European survey, patient observation was continuous in 80%, performed only during the daytime in 10%, and intermittent in the remaining 10% of EMUs [74], in a UK survey, 56% used continuous and 44% intermittent observation [58] and in a survey of the E-PILEPSY network, continuous observation of patients was performed in 81% of EMUs during regular working hours and in 63% of EMUs outside of regular working hours[111]. The quality guidelines of the “Austrian, German, and Swiss Working Group on Presurgical Epilepsy Diagnosis and Operative Epilepsy Treatment” require 24-h continuous supervision in patients in whom AEDs are reduced[2].

In our center, supervision is continuous and is performed by two neurophysiology technicians and one nurse from 8 am to 4 pm, one technician and one nurse from 4 pm to 12 pm, and two nurses (one in the EMU and the other in the video surveillance room) from 12 pm to 8 am..

The rate of AEs in our facility was 7.9% of all admissions, that is lower than in most of the previously reported studies (Table 5). 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, while the rest of the events could be safely handled by our personnel.

We did not find any correlation between the reduction of AEDs and the occurrence of SC and SE. There are multiple reasons why this could be. First, the drug tapering was done on an individualized basis and it was avoided in patients with a history of SE (2.2%) and in those with a high seizure frequency. When it was considered mandatory, AED withdrawal was done gradually, always one drug at a time and was only started under medical supervision. These patients and their accompanying caregivers were made aware that they could experience an increase in seizure frequency, duration or intensity. There are several other studies who reached the conclusion that AED withdrawal, while done under correct medical supervision, does not necessarily lead to an increase in AEs [57,112].

Although 19 episodes with falls occurred, none of them lead to injury for 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 PNES, that posed no risk and caused no injury to the patients. Overall, none of the falls resulted in injury, prolonged hospitalization, or any sort of complication to the patients.

In centers with restrictive measures, the proportion of injuries varied from 0.6 % [63] up to 3.7% [104] 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.

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. Even though there are studies showing a higher predisposition for thromboembolism in epilepsy patients[113,114] embolic events are rare in the reported series, either with [55,63] or without[57] deep vein thrombosis prophylaxis.

Ictal or postictal cardiac arrythmias have been well described in the literature[74,79,115,116] and can sometimes be serious AEs. Some authors suggest that these may be among the underlying causes of SUDEP[65,79]. Van der Lende et al[117] performed a systematic literature search on seizure-related cardiac arrhythmias during LTM and noticed that ictal asystole, bradycardia, and AV-conduction block were self-limiting in all but one of the cases and were seen during focal dyscognitive seizures. Seizure onset was mostly temporal (91%) without consistent lateralization. Postictal arrhythmias were mostly found following convulsive seizures and were often associated with near SUDEP or SUDEP. They concluded that the different clinical profiles of ictal and postictal arrhythmias suggest different patho-mechanisms and that postictal rather than ictal arrhythmias seem of greater importance for the pathophysiology of SUDEP. The same conclusion was reached by the MORTEMUS[65] study on SUDEP.

The rate of cardiac abnormalities in our study was low (0.4% of all patients) and lower that what was reported in other studies. We recorded 3 cases of ictal or post-ictal bradycardia and one case of bradycardia followed by an asystole with a duration of 5 seconds. Ictal bradycardia was recorded during focal seizures, two of them with seizure onset zone in the right temporal region and one in the left fronto-temporal region and post-ictal bradycardia was observed after a seizure with secondary generalization, whose onset was in the right temporal lobe.

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.

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[108]. This is consistent with our findings. A higher nurse/patient ratio has also been identified as a factor in improving safety in the EMU[58,107,108,118,119], a recent report of a national survey and workshop including EMUs in the UK[58] proposed an ideal ratio of no more than 2 patients per one qualified staff member, especially under conditions of AED reduction. In our unit, the personnel: patient ratio is of 1:2, which is higher than what was reported from other studies.

Conclusion

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 very effective investigation, it is labour-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 very 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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