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Feasibility of online seizure detection with continuous EEG monitoring in the intensive care unit

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ABSTRACT

Introduction: Continuous EEG (cEEG) is of great interest in view of the reported high prevalence of non-convulsive seizures on intensive care units (ICUs). Here, we describe our experiences applying a seizure warning system using cEEG monitoring.
Methods: Fifty comatose ICU patients were included prospectively and monitored. Twenty-eight patients had post-anoxic encephalopathy (PAE) and 22 had focal brain lesions. A measure of neuronal interactions, synchronization likelihood, was calculated online over 10 s EEG epochs and instances when the synchronization likelihood exceeded a threshold where marked as seizures.
Results: Five patients developed seizures. Our method detected seizures in three patients, in the other patients seizures were missed because of they were non-convulsive and had a focal character. The average false positive rate was 0.676/h.
Discussion: This is our first attempt to implement online seizure detection in the ICU. Despite problems with artifacts and that we missed focally oriented seizures, we succeeded in monitoring patients online. Given the relatively high occurrence of seizures, online seizure detection with cEEG merits further development for use in ICUs.
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1. Introduction

In modern intensive care units (ICUs) almost all of a patient's vital functions are continuously monitored. However, facilities for monitoring brain function are still missing in most ICUs, despite recommendations in the literature.[1–4] Unfortunately, neurological function of these patients, who are mostly intubated and sedated, is therefore only intermittently assessed (scoring the Glasgow Coma Scale and pupillary light reactions), often by ICU-nurses. These 'neurochecks' are discontinuous and subject to inter- and intra-observer variations, even when carried out by experts.[5]

The importance of brain function monitoring is stressed by the fact that the neurological complication rate is high in comatose patients.[6] An objective of cerebral monitoring is to recognize early changes in brain function and thus prevent secondary injury. Recognition of seizures is essential, since most seizures in the ICU occur without clear clinical manifestations, a phenomenon called non-convulsive seizures (NCS).[7] NCS can only be detected by electroencephalography (EEG). It has been proven that continuous EEG (cEEG) has a contributing impact on medical decision-making in 82% of monitored neurological patients.[5] Since the use of cEEG, NCS are being recognized more frequently and are associated with an unfavorable outcome[2,8–10] (see Table 1 for an overview). cEEG is the only method to monitor the brain's electrical activity as a surrogate for brain function, and the only way to detect NCS. Almost all studies concerning cEEG in the ICU are performed in a few centers, mostly in the USA (Table 1).

To deal with the shortcomings of EEG monitoring, several recommendations have been proposed in the literature. Firstly, it is recommended to review cEEG at least twice a day.[4] Secondly, it is suggested to train ICU-nurses in basic principles of EEG. In this way expertise is partly transported to the ICU.[5,11] Although this might be an option for specialized neurological ICUs, in general ICUs this expert training is too time-consuming in relation to the number of patients. Besides, in a study in which ICU bedside caregivers had been educated in identifying epileptiform discharges, recognition of seizure patterns still remained low.[12] Thirdly, certain basic

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Table 1
Series of continuous EEG monitored patients. Prevalence of acute seizures.

Study	Center	Design	Patients	Monitoring type	Inclusion criteria	Seizures (%)
Jordan[37]	Jordan Neuroscience Inc, San Bernardino, CA, USA	Retrospective	100	cEEG (length?)	ICU patients (no PAE)	29% (65% NCSE)
Young et al.[38]	University of Western Ontario, Canada	Retrospective	350	EEG	Comatose ICU patients	11.7% epileptiform activity
Jordan[5]	Jordan Neuroscience Inc, San Bernardino, CA, USA	Retrospective	124	cEEG (length?)	NICU patients	35% (76% NCSE)
Litt et al.[39]	Sinai Hospital Baltimore, USA	Retrospective	239	EEG	NICU patients	11% NCSE
Privitera et al.[40]	University of Cincinnati, USA	Prospective	198	EEG (emergency)	Unconscious patients	34%
Jaitly et al.[41]	Medical College of Virginia, USA	Prospective	180	cEEG	SE	–[a]
DeLorenzo et al.[42]	Medical College of Virginia, USA	Prospective	164	cEEG (min. 24 h)	After CSE	48%
Vespa et al.[10]	University of California, Los Angeles, CA, USA	Prospective	94	cEEG (3.5–11.5 days)	Adult TBI	22%, 6 pt SE (57% NC)
Towne et al.[8]	Medical College of Virginia, USA	Retrospective	236	min. 30 min EEG	ICU pts, comatose, no clinical seizure activity ook PAE pt	8% NCSE
Claassen et al.[9]	Colombia University, New York, USA	Retrospective	570	cEEG	Unconscious patients	19% (92% NC)
Pandian et al.[43]	Mayo Clinics, Rochester, USA	Retrospective	105	Video-cEEG (1–17 days)	ICU patients, also CSE	–[a]
Young and Doig[11]	University of Western Ontario, Canada	Prospective	55	cEEG	Comatose patients	20%
Ronne-Engstrom et al.[44]	University Hospital Uppsala, Sweden	Prospective	70	cEEG	TBI	33%
Ponten et al. (2010)[b]	VU University Medical Center	Prospective	50	cEEG	Comatose patients	10% (4% NC)

ASBL, acute structural brain lesion; EPC, epilepsia partialis continua; TBI, traumatic brain lesion; PAE, postanoxic encephalopathy; NCSE, nonconvulsive status epilepticus; (G)CSE, (generalized) convulsive status epilepticus.
[a] Because of inclusion criteria (status epilepticus) not possible to calculate the prevalence.
[b] Current study.

conditions are needed to make cEEG effective. The ICU is not at all like the standard EEG laboratory. There are many sources of exogenous artifacts (e.g. other electronic devices, manipulation of the patient). Finally, continuous recordings are long-term, which means that the requirements of the apparatus are different with ample opportunity for electrode dislodgment.[13]

The clinical neurophysiologist is not continuously present in the ICU. However, continuous assessment of the EEG to detect seizures is preferred so that treatment can be adjusted immediately. With the appearance of digitally recorded EEG, quantitative analysis can be used for automatic detection of seizure activity; previous studies used for example amplitude integration, compressed spectral array analysis, spike detection methods or the brain symmetry index (BSI).[14–20] Amplitude integrated EEG (aEEG) is widely used to detect neonatal seizures, despite the fact that the accuracy of seizure recognition can be moderate, especially in brief, low amplitude, focally oriented seizures.[15,21] Neonatologists analyze the aEEG signals at the patient's bedside, where in our opinion clinical neurophysiologists should at least be involved in this interpretation, as they are specially trained in EEG reviewing. In a recent study Young et al. compared a four-channel EEG monitoring device with 16 channel EEG recordings and found a sensitivity of 68% and specificity of 98% with visual interpretation of the signals.[22] In our clinic we have experience with another quantitative analysis approach for EEG, namely synchronization likelihood (SL).[23] SL is a nonlinear measure of statistical interdependencies between time series, which has shown to be a promising measure for detecting seizures in neonatal EEGs and frontal lobe epilepsy.[24–26] Furthermore, a retrospective study has shown that the mean SL can distinguish between seizure and non-seizure epochs in comatose ICU patients.[27] We do realize that the SL is most sensitive for generalized synchronization, although we do not know another method sensitive for both very focal and more generalized seizures. The goal of this study is to introduce SL as an online automatic detection method for real-life EEG monitoring, and explore the feasibility of its use, as the system automatically alarms when seizures are suspected, thus providing an opportunity to analyze the cEEG on demand, in a general tertiary university ICU. This procedure will be much more complicated than retrospectively analyzing EEG recordings detecting seizures, nonetheless it is necessary to improve the treatment of critical ill patients suffering from seizures.

2. Materials and methods

2.1. Patient selection

From October 2005 until January 2007, patients with a comatose state due (at least partly) to central neurological damage were enrolled prospectively in this non-blinded, non-randomized observational study. cEEG was performed according the protocol of daily care and treatment at the general tertiary ICU of our hospital (VU University Medical Center). The ethical committee of our hospital gave its approval for this study. Recordings started only at daily working times. Patients were eligible for this study if the following inclusion criteria were met: admission to the ICU, 18 years of age or older, any central neurological damage and coma ($GCS < 8$). Life expectancy should exceed 24 h, there should be no planned intervention (surgical or diagnostic imaging) in the first 6 h, and electrode placement should be possible. An EEG apparatus as well as an EEG technician had to be available. Patients were selected daily, based on the information on their medical charts and cEEG was started when permission was obtained from the treating intensivist. Patients using sedative drugs were included, as well as patients who underwent mild therapeutic hypothermia (approximately 32 °C) following cardiopulmonary resuscitation, or traumatic brain injury. We registered the following patient characteristics: age, gender, medical history, diagnosis at admission, clinical and neurological examination before and after registration, and (sedative) medication during cEEG (Table 2).

Table 2
Patients characteristics.

Acute seizures	All patients		PAE[b]		Other	
	Y	N	Y	N	Y	N
Number of patients	5 (10%)	45 (90%)	2 (7%)	26 (93%)	3 (14%)	19 (86%)
Age (mean ± SD)	61.1 ± 3.0	59.2 ± 19.1	59.7 ± 4.0	67.7 ± 14.9	62.0 ± 2.7	47.6 ± 18.4
Female	1 (20%)	18 (40%)	0 (0%)	10 (38%)	1 (33%)	8 (42%)
Hypothermia	2 (40%)	19 (42%)	1 (50%)	16 (62%)	1 (33%)	3 (16%)
Sedation[a]	4 (80%)	37 (82%)	2 (100%)	23 (88%)	2 (67%)	14 (74%)

[a] Fentanyl excluded.
[b] PAE, post-anoxic encephapolapthy.

2.2. Continuous EEG protocol

EEGs were recorded with an OSG digital EEG apparatus (Brainlab®) against an average reference electrode. Twenty-one surface electrodes were placed at the Fp2, Fp1, F8, F7, F4, F3, A2, A1, T4, T3, C4, C3, T6, T5, P4, P3, O2, O1, Fz, Cz and Pz loci of the 10–20 International System. We used Ag/AgCl electrodes, fixed with Ten20® paste. Electrode impedance was below 5 kΩ at the start of the recording. A low pass filter with 70 Hz cut-off and a time constant of 1 s was used, sample frequency was 500 Hz and analog-digital resolution of 16 bit. During monitoring the electrodes were inspected once a day. As a result of the maximum storage capacity of our EEG system and the high sample frequency we used, recordings were limited to 22 h. When clinically necessary, cEEG could be prolonged by starting a new recording outside this study protocol. cEEG was not paralleled with video-monitoring.

2.3. EEG analysis

In order to get an impression of the neurological status of the patient the EEG was analyzed visually at the start of the recording. As gold standard for EEG interpretation, in particular to demarcate the presence or absence of electrographic seizures, we used offline visual analysis. Two people (SP), as well as a clinical neurophysiologist (CS, HR or RS) reviewed the whole EEG dataset. Inter-observer agreement was always reached in diagnosing epileptic seizures during a meeting between the two involved observers. Seizures were scored using the only available criteria for critically ill patients on the ICU,[28] revised recently.[29] The distinction between convulsive and nonconvulsive seizures was based upon the presence of muscle artifacts in the EEG, since no simultaneous video monitoring was available. If muscle artifacts were present simultaneously with seizure discharges in the EEG we assumed the seizure was convulsive; otherwise we assumed it was nonconvulsive. We do realize though that subtle clinical signs can be missed this way. During the monitoring, we used our online seizure detection method (see below) to select suspect parts of the EEG to be reviewed by the neurophysiologist on duty.

2.4. Online seizure detection

We used synchronization likelihood (SL) as an online seizure detection method. SL has been described in detail elsewhere.[23,30] SL is a measure of statistical interdependencies between time series such as in EEG channels, both sensitive for linear and nonlinear interdependencies. The basic principle of the SL is to divide each time series into a series of 'patterns' and to search for a recurrence of these patterns. The SL is the probability that pattern recurrence in time series X coincides with pattern recurrence in time series Y. SL ranges between 1 in case of maximally synchronous signals and P_{ref} (a small number close to zero) in case of independent time series. P_{ref} is the small but non-zero likelihood of coincident pattern recurrence in case of independent time series. The end result of computing SL for all pair-wise combinations of channels is a square $N \times N$ matrix of size 21 (21 is the number of EEG channels used in this study), where each entry $N_{i,j}$ contains the value of the SL for the channels i and j. Specialized software for online computation and display of SL was developed at our department (WdR). In the automatic detection software we used the average synchronization by taking the mean of all these values. This resulted in a single overall SL value for each epoch (10 s). SL is influenced by e.g. neurological damage, medication and hypothermia and individual thresholds were therefore set by one of the authors (SP) on the basis of SL calculations for the first 10 min of EEG recording. For the remainder of the recording, when the mean SL value exceeded the threshold two times successively, after at least two epochs below the threshold, an alarm status was displayed on the computer screen. The EEG pages causing the alarm were stored on the computer and an USB-stick, with the possibility for intensivists to e-mail this selection to the neurophysiologist in charge for detailed analysis of the EEG. In this way cEEG was embedded in routine clinical care (see Fig. 1 for the clinical flow chart).

3. Results

3.1. Patients characteristics

cEEG was performed in 50 patients over a 15-month period. All patients were admitted to the Department of Intensive Care of the VU University Medical Center (Amsterdam, The Netherlands). Patient's characteristics are shown in Table 2. One patient was under the age of 18 years (15 years of age), but admitted to the adult ICU, and therefore we decided to monitor him. Twenty-eight (56%) patients suffered from post-anoxic encephalopathy (PAE), five (10%) had an intracerebral hemorrhage, five (10%) a subarachnoidal hemorrhage, eight (16%) suffered from a severe head trauma and four (8%) had another admission diagnosis (one subdural hematoma, one meningitis, one respiratory insufficiency and brain metastasis and one pneumonia causing respiratory insufficiency and cerebral ischemia).

3.2. Medication

Almost all patients received sedative drugs during cEEG. Most patients used the combinations of midazolam or propofol and fentanyl. Only two patients did not receive any of these drugs during the entire monitoring period. In 21 patients medication was reduced or even stopped (five patients) during cEEG. This change of medication level can also cause alterations in the synchronization pattern in the EEG recording, and is therefore a possible cause of false alarms in the automatic detection device. Three patients received clonazepam: two for post-anoxic myoclonus and one for the treatment of epileptic seizures.

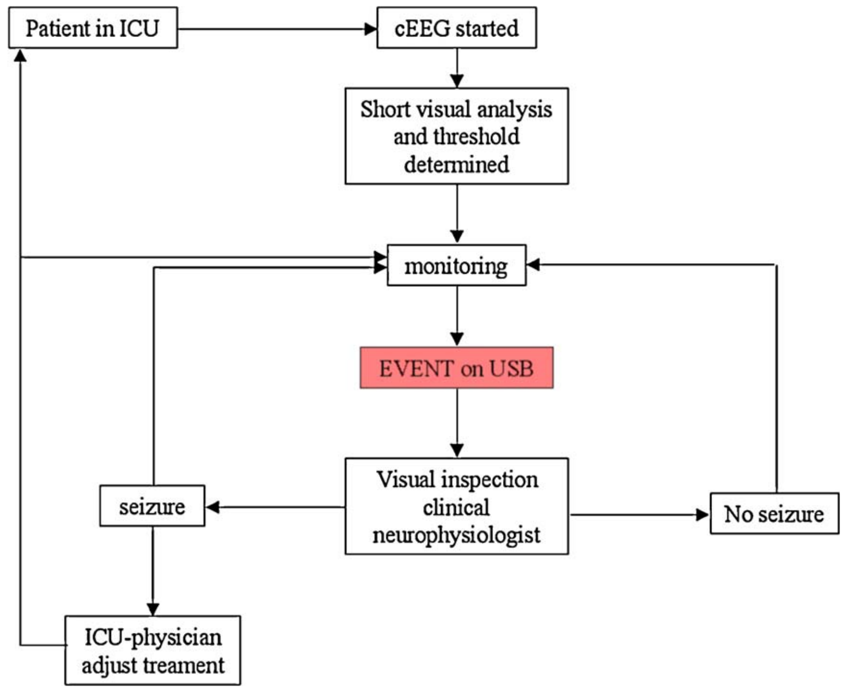

Fig. 1. Flowchart online seizure detection.

3.3. EEG recording

The mean time between admission at the ICU and start of the monitoring was 77 h. During the study period 15 patients could not be included due to either EEG apparatus unavailability (eight times), unstable clinical condition of the patient (four times), awakening of the patient before enrolment (two times), or medical intervention (one time). cEEG was limited to 22 h due to the technical limitations, in three patients we prolonged the monitoring for clinical reasons. Nineteen (38%) recordings were stopped before 20 h was reached. Various reasons can be pointed out. Ten were caused by technical problems such as electrode dislodgement, five were due to unexpected emergency situations e.g. computed tomography scan (CT-scan) or surgery. One patient died after resuscitation during monitoring. The average monitoring duration was 18:20 (±5:56) h.

3.4. Online seizure detection

The threshold was set manually during the first 10 min of the recording. This threshold varied between 0.15 and 0.23 with a mean of 0.17. Overall five patients (10%) showed epileptic seizures (Table 3 Fig. 2). The overall alarm rate was 489 in 50 recordings. Thirteen alarms were in the context of starting up or finishing the EEG recording, so 476 events took place during monitoring. Forty events were caused by epileptic seizures, 35 in patient B and five in the PAE patients (three in patient E versus two in patient D). The others were false positive alarms (436). Most false alarms were caused by artifacts such as electrode dislodgment, a medication purge or movement artifacts. In six EEGs over 30 events occurred, with a maximum of 75 events in 22:19 h. On the other hand twenty-two EEGs showed no false positive events. The median false positive rate per hour (FPR) per patient was 0.05 (0–9). The FPR per patient is given in Fig. 3. The highest FPR (9.1 events/h) occurred in a patient (suffering post-anoxic encephalopathy, seen during hypothermia) who was registered for only 33 min and showed dilated, nonreactive pupils and the EEG recording showed continuous relative suppression. Because of these findings an emergency CT-scan was performed, which showed a massive unilateral infarction.

In the recording from the patient suffering from a status epilepticus (patient B), 39 alarms occurred (35 detecting seizures),

Table 3
Patients characteristics patients suffering seizures.

Patient	Diagnosis	Previous EEG	Seizures	Detected	Duration (h)	Outcome
A	Traumatic brain injury	Convulsive seizures	4 focalized non-convulsive seizures, >30 min	No	17:28, ended because of electrode dislodgement	Died
B	Metastatic brain disease with respiratory insufficiency due to seizures	Convulsive seizures	Status epilepticus (671 seizures) with clinical features	Yes, 35 seizures were detected	22:56 next day continuation with high doses of medication	Died
C	Intra-cerebral haemorrhage	No seizures	7 focalized non-convulsive seizures, 15 min	No	18:17	Discharged to a nursing home
D	Post-anoxic encephalopathy	–	28 reflex-induced seizures in first 40 min	Yes, twice detected	8:50, ended because of electrode disturbances	Discharged to a rehabilitation clinic
E	Post-anoxic encephalopathy	–	5 seizures in first hour with clinical features	Yes, 3 seizures were detected	19:24 a nurse stopped the recording by accident	Awake transported to another hospital

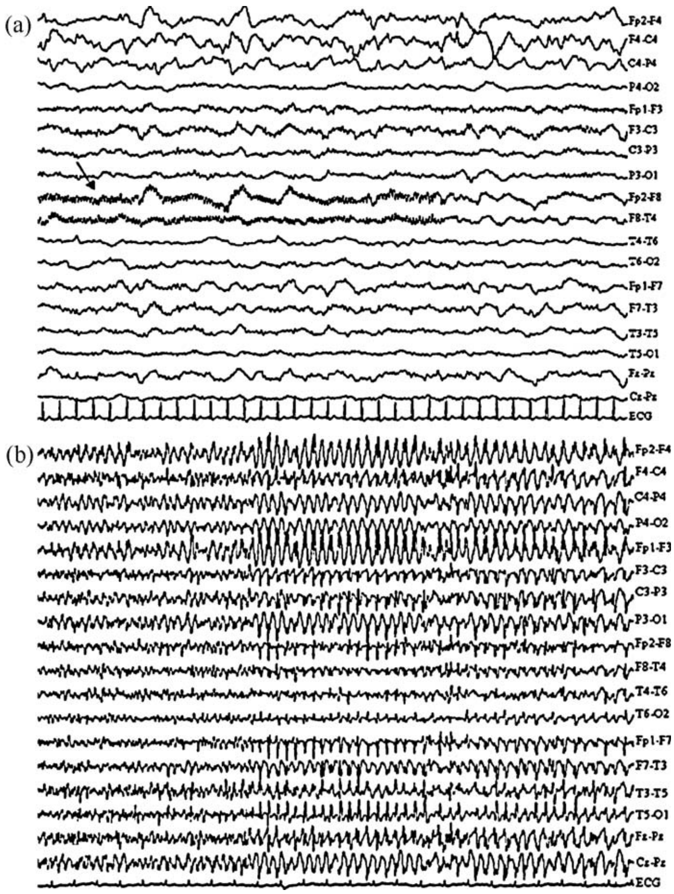

Fig. 2. (a) The end of a non detected seizure in patient A EEG: 20 s, bipolar montage, filter settings 0.30–30 Hz. Seizure is indicated by the arrow. (b) Seizure in patient E which caused an event. Bipolar montage, filter settings 0.30–30 Hz.

and approximately 636 seizures were missed. For the two patients suffering from PAE (patients D and E), reflex seizures were detected two times out of 28 (patient D), and for patient E three out of five seizures set the alarm. Focal seizures (patients A and C) (according to the artifact free EEG signals during the seizure) were not detected with this method but by visual analysis afterwards only.

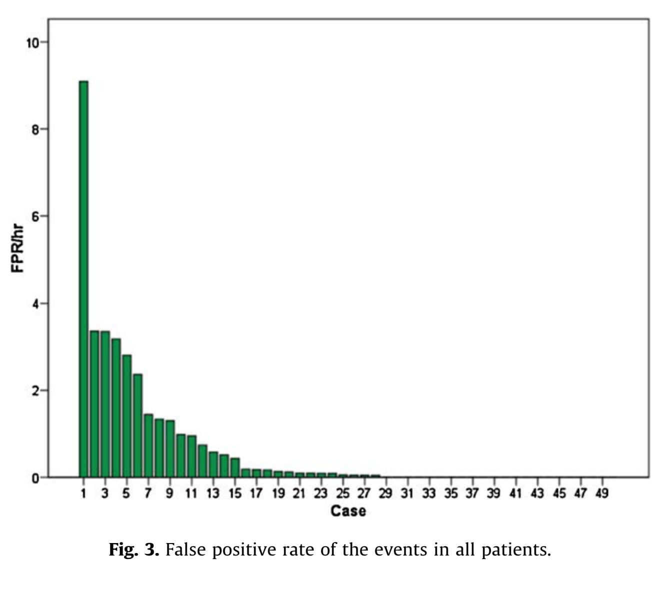

Fig. 3. False positive rate of the events in all patients.

4. Discussion

Although the routine use of cEEG in ICUs is recommended, it is still not part of standard care in many institutions. We believe that one of the important problems of using cEEG in clinical practice is the lack of a reliable method (online automatic seizure detection) to determine when immediate expert evaluation is required. This prospective, descriptive study is our first attempt to explore the feasibility of an online seizure detection method combined with cEEG monitoring. In this way the opportunity is created to analyze EEG signals 24 h a day to recognize critical ill patients suffering from seizures in an early state. Online automatic seizure detection proved to be difficult for several reasons. First, because the online calculation of the mean SL did not detect seizures in two out of five patients (both localized and non-convulsive). Although, in our opinion it is more important to recognize the patients who suffer seizures as to start treatment in time, than to detect all seizures separately. Second, because many false positive alarms occurred due to artifacts and electrode disturbances (median FPR 0.05/h/patient). Because of the relatively low frequency of seizures (10%), and even less frequent non-convulsive seizures (4%), most events generated by the online detection method were false-positives. In previous studies in neonatal ICU settings amplitude integrated EEG has been used for online seizure detection. However, this method only uses two to four EEG channels and heavily depends upon the expertise of the neonatologists on duty.[21]

We included a heterogeneous group of 50 patients to explore the feasibility of our detection method. Five patients (10%) showed seizures. Remarkably, we only found two patients with non-convulsive seizures, whereas other studies found non-convulsive seizures in 8–19% of the patients (Table 1). Although the other studies did not specify the way they classified seizures, they might have scored various types of periodic discharges as seizures as well. It should be noted that the epileptic nature of this EEG pattern is controversial.[31] We scored seizures using the revised criteria introduced by Young, where two observers reached agreement about the seizure appearance.[28,29] In a retrospective study it was found that the inter-observer reliability in classifying seizures is not very high in ICU patients.[32] Thirty seconds of EEG were used to answer the question if a seizure was present, where we used the complete recording to decide if seizures were present. The simple dichotomy of EEG patterns in ictal and nonictal activity is an oversimplification and practice shows that what is ictal to one observer is not necessarily ictal to another.[33] One should always be aware of these limitations and keep in mind that seizures cannot always be distinguished from EEG patterns in encephalopathies.[34] Another explanation for the low incidence of seizures might be the high proportion of patients who received sedative drugs during cEEG, such that seizures might have occurred after these drugs were withdrawn. Besides the seizures, seven patients with PAE had generalized periodic discharges (GPDs) during at least part of the cEEG.[35] We did not consider this phenomenon as epileptic, instead we assumed that GPDs reflect severe post-anoxic encephalopathy. We should stress that there is no consensus in the literature about these periodic phenomena. The need to treat this condition is not known, although most experts think that anti-epileptic medication will not improve clinical outcome. There is also little evidence that non-convulsive seizures in ICU patients are destructive. Deciding which EEG patterns are harmful, and how aggressively cessation of this activity should be pursued, can only be established through large multi-center clinical trials.[29,33] Other reasons for the low incidence of seizures might be the various monitoring times in the study, and the various time windows between the incident and monitoring start. We started as soon as possible during standard daily working hours, and despite the thorough selection, this caused a delay in some patients.

For the five patients with seizures, our online alarm function detected seizures in three patients. The other two patients had localized non-convulsive seizures, which were missed by our method. One of the patients (patient B) suffered from a status epilepticus. In this patient most seizures were missed, but we think that it is striking that the status epilepticus was recognized at all, as the continuously changing EEG signals were hard to interpret even by visual inspection. Because of our extensive experience with SL, and the promising results in our previous retrospective studies, we used SL as detection method. Moreover, it is sensitive for changes in synchronization over multiple time series. Beforehand we knew that focally oriented seizures might be missed, although we do not know for sure if these seizures are as harmful as generalized seizures. We suggest that a combination of methods might improve the detection rate in ICU patients, although we realize that combining parameters may result in a reduced specificity. Future studies should focus on different detecting methods, in particular taking into account the variable appearances of seizures in ICU patients. Additionally, the SL algorithm could be used differently, for example by taking the maximum SL value per epoch, instead of the mean.

We did not calculate specificity because in detection systems the false positive rate (FPR) is clinically much more relevant, and there were only five patients with seizures. The average FPR was 0.676/h. A false alarm was most often caused by electrical disturbance, electrode dislodgment or movement artifacts. Another issue which caused false alarms was a change in the administration of sedative agents. In six cEEG recordings more than 30 alarms were registered during monitoring. However, this does not imply that intensivists contacted the neurophysiologist that often, since no more alarms were reported after the cause of the alarm had been clarified, In contrast, 22 recordings did not have any false-positive events. To implement online detection in daily clinical care, the amount of disturbances causing false alarms must be reduced. In this context, improvement of the electrodes will be useful, for example electrodes that are easy to apply and with stable impedance over time.[22] May be needle electrodes can play a role in this improvement.[36]

5. Conclusion

Our first attempt to implement online seizure detection in the ICU succeeded in detecting seizures in three out of five patients with seizures. Only two patients (4%) had non-convulsive seizures. To improve the detection rate and reduce FPR, future studies could attempt various detection tools, and try to limit false-positive events by improving electrode placement. Extra training for ICU personnel, to learn how to pause the system during maneuvering of the patient, would further reduce FPR. A reliable monitoring system based on cEEG should be introduced in multiple centers in order to gain experience with its use in clinical practice. Following this, a multi-center trial could provide insight in harmful EEG patterns and their treatment.

Conflict of interest statement

The authors report no conflicts of interest.

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