Non-convulsive seizures and non-convulsive status epilepticus monitoring in the intensive care unit

A real need for the Gulf Cooperation Council countries

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ABSTRACT

مراقبة تخطيط الدماغ الكهربائي(cEEG) في وحدة العناية المركزة (ICU) أمر ضروري من أجل اكتشاف النوابات الصرعية غير الاختلاجية و الحالة الصرعية (NCSs/NCSE). في الوقت الحالي هنالك عدد من أنظمة مراقبة تخطيط الدماغ الكهربائي (EEG) الموجودة والتي تم تبنيها للإستعمال في وحدة العناية المركزة (ICU). ولكن تم تدريب هذه الأنظمة على استعمال بيانات تخطيط الدماغ الكهربائي EEG الحاصل من الأشخاص السليمين والمرضى السليمين من الناحية العصبية والذين يعانون من الصرع وعدد مختلف من مرضى العناية المركزة. تألفت الدراسة من جزئين، الجانب السريري والجانب التقني. في الجانب الأول، قمنا بتلخيص جوانب تخطيط الدماغ الكهربائي ل (NCSs/NCSE). والنماذج الأخرى المعتمدة في وحدة العناية المركزة ICU. بينما في الجانب الثاني قمنا بشرح كيفية تطوير نظام مراقبة تخطيط الدماغ الكهربائي EEG لكي يتم استعماله في وحدات العناية المركزة – اتحاد حمد الطبي – الدوحة – قطر، حيث سيمكننا ذلك من اكتشاف نماذج تخطيط الدماغ الكهربائية EEG المرضية التي تظهر بشكل شائع بين المرضى ذوي الحالة الحرجة. سيسمح وقت المراقبة الفعلي للافرازات الصرعية والمناذج الأخرى لتخطيط الدماغ الكهربائي EEG من تحديد التشخيص الصحيح والمعالجة الدقيقة في الوقت المحدد.

Continuous EEG (cEEG) monitoring in the intensive care unit (ICU) is essential for detecting non-convulsive seizures/status epilepticus (NCSs, NCSE). Currently there exist a number of continuous EEG monitoring systems adapted for use in the ICU. However, these systems have been trained using EEG data collected from healthy, neurologically intact patients with epileptic seizures, a very different patient population from ICU patients. The review consists of 2 parts, clinical and technological aspects. In the first one, we summarize the electroencephalographic aspects of NCSs/NCSE and other EEG patterns encountered in the ICU. In the second part, we explain how to develop a novel cEEG monitoring system to be used in Hamad Medical Corporation ICUs, Doha, Qatar, that is able to detect pathological EEG patterns commonly occurring in the critically ill patient. Real-time monitoring of seizure discharges, and other pathological EEG patterns will allow correct diagnosis and adequate treatment in a timely fashion.

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Continuous EEG (cEEG) monitoring provides continuous assessment of brain function of critically ill and comatose patients.[1,2] In the current standard of intensive care unit (ICU) care, EEG data are used for decision-making regarding the use of antiepileptic drugs (AEDs), the need for immediate neuroimaging studies, and for alterations in therapy to assure adequate cerebral perfusion.[3] In reality, however, cEEG is often not fully exploited. As cEEG can be performed over periods of days or weeks, for practical purposes it is important to develop methods that enable medical staff and nurses to identify important features of the EEG in real-time and to extract and visualize information that might be clinically important, but cannot be extracted by intermittent visual inspection. At present, software using raw EEG to detect seizures and status epilepticus, and quantitative EEG analysis to quantify interictal and ictal activity is limited by high false positive rates of seizure detection, namely, the difficulty in distinguishing various artifacts from seizures, interictal spikes, and sudden alterations in EEG background activity.[4] As will be discussed in the technological aspects of this review, there is a need to develop better cEEG software designed for the ICU setting, and to

test it against established gold standards to achieve appropriate predictive values of various interictal and ictal EEG patterns.[4] Real-time detection of health-state relevant electroencephalographic events and patterns in high-risk ICU patients will allow adequate treatment in a timely fashion. The development of refined cEEG algorithms will significantly reduce the costs associated with this kind of monitoring,[5,6] and provide clinicians and researchers with expert tools assisting diagnosis, treatment, and further research. The purpose of this review is to shed light into the preconditions (clinical aspects) and the way to develop an ICU cEEG system (technological aspects), which can detect non-convulsive seizures (NCSs) and non-convulsive status epilepticus (NCSE). It is hoped that such a project will help Qatar to establish itself as a center of this new technology. Hospitals in Qatar, the Gulf region, and in other parts of the world will be interested in successful and commercially available software products.

A) Clinical aspects. In this first part of the review, we shall concentrate on the electroencephalographic aspects of NCSs/NCSE and other pathological EEG patterns encountered in the ICU.

Why perform cEEG in the ICU? In comatose patients the EEG allows insight into brain function when this is inaccessible clinically. The cEEG recording in the ICU monitors treatable medical conditions as well as the effects of therapy, particularly AEDs therapy. Also, cEEG monitoring plays a role in establishing the prognosis in comatose patients, resuscitated after a cardiac arrest, and still retaining their brainstem reflexes; in such patients, there is no possibility to recover consciousness if, one day following the cardiac arrest, the EEG demonstrates complete generalized suppression (<10 microV).[7,8] However, other EEG abnormalities, like burst-suppression, periodic complexes, alpha-theta coma patterns, indicate usually a poor outcome (not invariably!!). The analysis of serial EEGs and continuous raw EEG in the ICU involves testing the reactivity of EEG to external stimuli. If complimented by automated "trending", these multiple EEG variables hold promise for an improved role in the prognostic determination in these patients. Yamashita et al[9] studied the prognostic applicability of EEGs of 79 patients within 24 hours after successful cardiopulmonary resuscitation. The EEG Hockaday's scale was used in this study.[10] Patients with EEGs showing grades I and II recovered, those with grade III had in general an unfavorable prognosis and those with grades IV and V EEGs had the worst outcome (vegetative state or death). The authors concluded that EEG is a good indicator of patient prognosis after cardiopulmonary resuscitation. However, the clinical significance of morphological differences of various periodic patterns that can occur during a cEEG remains to be established. Evoked potential monitoring is also useful in the ICU.[11] Using short latency somatosensory evoked potentials (SLSEP) for monitoring ICU patients after hypoxic-anoxic brain damage, Mesraoua et al[12] demonstrated the usefulness of these neurophysiologic tools in the outcome assessment. The result of that study was that most patients who retained P15 complex of the SLSEP 48-72 hours after cardiac arrest either recovered completely or with minimal brain damage. Those who lost this P15 complex had a worse prognosis (vegetative state, death).[12]

Indications for cEEG in the ICU are manyfold. Probably the most important is detection of epileptiform seizure activity. In critically ill patients the majority of seizures are subclinical or intermittent, and thus cannot be detected with clinical examination or with a brief routine EEG.[13-15] The diagnosis of NCSs and NCSE is important for therapy and prognosis. The cEEG can be used to classify and quantify seizures in terms of localization (focal/regional/generalized), frequency, and duration. The cEEG is also used to define the nature of clinically observed events that may or may not be epileptic. It can detect ischemia at a reversible stage. It can reveal a wide range of EEG patterns that have prognostic and therapeutic implications (see below). The cEEG also allows monitoring the level of anesthesia, particularly in patients requiring heavy sedation or anesthesia. In addition the effects of several therapeutic actions (AEDs, Pentothal coma, lowering intracranial pressure) can be monitored. The cEEG is essential for adjusting the depth of a therapeutic Pentothal coma (dose adjustment according to the duration of the suppression phase in the burst-suppression pattern).

Status epilepticus. A review of its classification with special emphasis on NCSE and borderline forms. Status epilepticus (SE) can occur in epileptic patients and *de novo*. Present in almost all epileptic syndromes, SE is more frequent in symptomatic and cryptogenic forms.[16] Whereas convulsive tonic-clonic SE is the best-known type and its diagnosis is simple, partial SE, complex partial SE, and non-convulsive SE (NCSE) present a diagnostic challenge. Particularly difficult is the differential diagnosis of confusional syndromes in the elderly and in critically ill patients in the ICU. There exists a large literature dealing with classification and electro-clinical accompaniments of SE and in particular NCSE, which is a heterogeneous condition. Its diagnosis is difficult on the basis of clinical semeiology alone, and requires emergency EEG and cEEG investigation. In humans, the underlying pathophysiology of the various subtypes of NCSE has not been investigated in detail. The underlying pathology, EEG patterns, type of treatment and prognosis remains to be studied.

Mechanistically, SE represents the failure of the natural seizure-suppressing mechanisms responsible for seizure termination. Proposed operational definitions of SE do not adequately reflect the underlying mechanisms involved in SE. The classification of SE has been a subject of discussion for many years. A pragmatic classification of SE is along 3 axes: (1) convulsive versus non-convulsive, (2) generalized versus focal, and (3) continuous versus intermittent. The most recent proposal of the International League Against Epilepsy (ILAE) Classification Core Group,[17] an attempt to complete the earlier work of the Task Force on Classification and Terminology, differentiates "Self-limited epileptic seizure types" from "Status epilepticus". Under "Status epilepticus" this report lists 9 headings: 1. Epilepsia partialis continua of Kojevnikov. A combination of focal seizures with continuous twitching in the same area. The clinical and EEG features permit distinction of 3 conditions that correlate with etiology. (a) As occurs with Rasmussen Syndrome. (b) As occurs with focal lesions (for example, dysplastic, vascular, tumor lesions), and non-ketotic hyperglycemia. (c) As a component of inborn errors of metabolism (for example, Alpers disease or Myoclonus epilepsy with ragged-red fibers (MERFF).[17] 2. Supplementary motor (SMA) SE. 3. Aura continua. 4. Dyscognitive focal (psychomotor, complex partial) SE, with 2 forms:[17] (a) Mesial temporal. (b) Neocortical. 5. Tonic-clonic SE. 6. Absence SE, with the following forms (a) typical absence SE, (b) atypical absence SE, and (c) myoclonic absence SE. 7. Myoclonic SE. 8. Tonic SE, and 9. Subtle SE.

The 1985 ILAE classification of epilepsies and epileptic syndromes (proposal: Commission, 1985; officially adopted 1989) included a few special additional syndromes: Electrical status epilepticus during slow-wave sleep (ESES - now called continuous spike-wave discharges during sleep – CSWS) and the Landau-Kleffner syndrome. In Shorvon's[18] "revised classification" of SE, we find the category "nonconvulsive" SE. The term "electrographic" as a characteristic "status seizure type" is found in "boundary syndromes" including "electrographic SE with subtle clinical signs", "prolonged postictal confusional status", and "epileptic behavioral disturbances and psychosis". The adjective "electrographic" as "status seizure type" furthermore appears in context with "CSWS" and the "syndrome of acquired epileptic aphasia", as well as in the rubric "SE confined to the neonatal period."[18]

Persistent non-convulsive status epilepticus after the control of convulsive status epilepticus. DeLorenzo et al[19] evaluated 164 prospective patients with convulsive SE at the Medical College of Virginia/VCU Status Epilepticus Program with cEEG monitoring and found that 48% demonstrated persistent electrographic seizures. Complex partial NCSE seizure type was the electrographic manifestation of more than 14% of these patients. Without the use of cEEG monitoring, these EEG results would not have been possible because the patients were comatose and did not show any convulsive activity. The authors concluded that EEG monitoring after treatment of convulsive SE (CSE) is essential for recognition of persistent electroencephalographic seizures and NCSE. These findings suggest that EEG monitoring immediately after control of CSE is important to guide further treatment plans and to evaluate prognosis. Young et al[20] proposed primary and secondary criteria for electrographic or non-convulsive seizures (**Table 1**).

How common are NCSs and NCSE in the ICU? Today, it is estimated that there are between 65,000 and 150,000 cases of SE in the USA each year, and that approximately 25% are nonconvulsive (NCSE).[21,22] The NCSs are more common than previously recognized, particularly in ICU patients. Jordan[1,23,24] recorded NCSs in 34% of their patients; 76% of them had NCSE. In one study, investigators found that 18% of their patients had NCSE.[23] Claassen et al[25] found 18% of NCSs in ICU patients with 10% of them presenting with NCSE.

Table 1 - Criteria for an electrographic seizure or a non-convulsive seizure as proposed by Young et al,[20] published with the permission of Lippincott Williams & Wilkins.

Primary criteria

1. Repetitive generalized or focal spikes, sharp waves, spike-wave and wave, or sharp-and-slow wave complexes at more than 3 per seconds.
2. Repetitive generalized or focal spikes, sharp waves, spike-wave and wave, or sharp-and-slow wave complexes at fewer than 3 per second and secondary criterion #4.
3. Sequential rhythmic waves and secondary criteria #1, #2, and #3 with or without #4.

Secondary criteria

1. Incrementing onset: increase in voltage and/or increase or slowing of frequency.
2. Decrementing offset: decrease in voltage or frequency.
3. Post-discharge slowing or voltage attenuation.
4. Significant improvement in clinical state or baseline EEG after intravenous antiepileptic drug.

To qualify at least one of the primary criteria 1-3 and one or more of the secondary criteria with discharges ≥ 10 seconds.

Similar studies of consecutive neurological ICU patients have found 27-34% with electrographic seizures.[23,26] Risk factors for and factors associated with NCSs include coma, age <18, prior convulsive seizures,[27,28] acute or remote epilepsy, abnormal eye movements (nystagmus, eye deviation and hippus), periodic discharges, and suppression-burst.[25,29] Unfortunately, there are no epidemiological data regarding SE, and particularly NCSs and NCSE in the Arab Gulf countries.

EEG patterns. General classification attempts emphasizing pathological patterns that are often seen in the ICU and their differentiation from patterns of doubtful clinical significance. Westmoreland and Klass[30] categorized and grouped EEG patterns. Their classification system takes into account the predominant frequencies involved and/or distinctive morphology or distribution. Alpha squeak, retained alpha,[31] alpha-delta sleep,[32] unilateral decrease in reactivity of alpha activity, extreme spindles involve predominantly the alpha frequency range. Fast alpha variant, posterior temporal fast activity in children, the fast spiky spindle variant, the central fast activity, and diffuse paroxysmal or continuous fast activity involves the beta frequency range. Slow alpha variant, frontal arousal rhythm, rhythmic temporal theta activity of drowsiness, middle theta rhythms, and focal parietal theta activity involve predominantly theta frequencies. Transient rhythmic slowing occurring after eye closure and the more continuous posterior rhythmic slowing involve the delta frequencies. Others patterns include the breach rhythm, periodic frontal sharp complexes, subclinical rhythmic electrographic discharges of adults,[33] the wicket spikes, the EEG pattern of holoprosencephaly,[34] and the zeta waves.[35] These EEG patterns have a distinct morphology or distribution. Continuous high amplitude EEG rhythmical synchronous slowing (CHERSS), triphasic waves, bilateral independent periodic lateralized epileptiform discharges (BIPLEDs), frontal intermittent delta activity (FIRDA), and low amplitude irregular generalized theta are other patterns.

Periodic short-interval diffuse discharges (PSIDD) and periodic long-interval diffuse discharges (PLIDD) are seen in severe and ongoing diseases of CNS:[36,37] PSIDD are usually seen in the setting of anoxia, metabolic (mostly hepatic) encephalopathy, Creutzfeldt Jakob disease, and toxic encephalopathy (in particular baclofen and lithium). Non-generalized status epilepticus can show a similar convulsive electroencephalographic pattern. The PLIDD were initially described in children with subacute sclerosing panencephalitis (SSPE) by Radermecker in 1949, and thus also called Radermecker complexes.[38] A similar periodic pattern can occur in patients with phencyclidine ("angel dust") or ketamine intoxication. Anoxia or barbiturate intoxication can produce PLIDD-like burst suppression; however, the periodicity of these bursts is generally not as regular as in SSPE. Periodic lateralized epileptic discharges (PLEDs) are often associated with clinical seizures and with destructive hemispherical lesions.

Hirsch et al[39] described ictal, quasi-ictal, and periodic discharges (stimuli-induced rhythmic periodic, or ictal discharges [SIRPIDs]), both focal and generalized and often seen following stimulation or arousal of a comatose or stuporous patient. The SIRPIDs are associated with a variety of acute brain (or severe metabolic) disorders. At present it is not clear whether SIRPIDs represent reflex seizures, abnormal arousal patterns, or a combination of both. Few patients have clinical correlates to their SIRPIDs or prior seizures, most of them were admitted because they had an acute brain injury.

Triphasic waves (TWs) very often also are encountered in ICU patients suffering from metabolic encephalopathy. Full screen laboratory testing (hepatic, renal, metabolic functions, glucose, electrolytes) is essential in patients with TWs. Generalized periodic triphasic waves occur only in patients with metabolic-anoxic encephalopathies. Claassen et al[25] summarized EEG patterns seen in the critically ill ICU patient (**Table 2**).

Table 2 - Definitions of EEG patterns in intensive care unit patients given by Claassen et al,[25] published with the permission of Lippincott Williams & Wilkins.

Electrographic seizures	Rhythmic discharge or spike and wave pattern with definite evolution in frequency, location, or morphology lasting at least 10 seconds; evolution in amplitude alone does not qualify.
Periodic epileptiform discharges (PED)	Repetitive sharp waves, spikes, or sharply contoured waves at regular or nearly regular intervals and without clear evolution in frequency or location (includes, PLED, GPED, BiPLED, triphasic waves).
Periodic lateralized epileptiform discharges (PLED)	Consistently lateralized PED.
Generalized PED (GPED)	Bilateral and synchronous PED with no consistent lateralization.
Bilateral PLED (BiPLED)	PLED occurring bilaterally, but independently and asynchronously.
Triphasic waves	Generalized periodic sharp waves or sharply contoured delta waves with triphasic morphology at 1-3 Hz with/without anterior-posterior or posterior-anterior lag.
Frontal intermittent rhythmic delta activity (FIRDA)	Moderate to high voltage monorhythmic and sinusoidal 1-rhythmic delta 3 Hz activity seen bilaterally maximal in anterior leads, no evolution.

Other patterns. Generalized periodic burst suppression and generalized periodic slow-wave complexes (GPSC) occur in patients under anesthesia or drug intoxication, and with anoxic/metabolic encephalopathies. When these conditions are excluded, GPSC might indicate the diagnosis of subacute sclerosing panencephalitis or other encephalitis. Burst suppression in comatose patients after cardiorespiratory arrest indicates an unfavorable outcome. Generalized repetitive sharp transients are observed in patients with anoxic encephalopathy.

The so-called "diffuse cortical ischemic syndrome with an extraterritorial (border zone) predilection," originally described by Gastaut and Naquet in 1965, and re-visited by Franck,[40] occurs in elderly patients presenting with a sudden disturbance of consciousness of various degree, neurological deficits, and epileptic seizures consisting of focal motor attacks, and epilepsia partialis continua. The PLEDs are frequently recorded. They can be bilateral or more often predominate over one hemisphere, usually in the parieto-temporo-occipital areas. Four main types of abnormalities, sometimes combined, seem to be important for the occurrence of this syndrome: generalized hypoperfusion, hypertension, embolic processes, and sometimes metabolic factors (alcohol, anoxia, electrolyte imbalance or nonketotic hyperglycemia) and, particularly, in the presence of pre-existing cerebral infarcts, either symptomatic or asymptomatic.[40] Evans[41] studied patterns of arousal in comatose patients. Spontaneous periodic discharges simultaneously involving EEG, cardio-respiratory and somatic motor phenomena were observed at 1/2-2 min intervals. These discharges were related to the changes in the level of arousal. Evans suggested that a physiological periodicity of the arousal mechanisms exists, which may be of importance in the understanding of the pathophysiology of comatose states. Early myoclonic epileptic encephalopathy was described by Dalla Bernardina.[42] The neurological status (initially normal) progressively deteriorates leading within a few months to a decerebrate posture with opisthotonus. The etiology remains unknown despite thorough neuroradiological, biochemical, cytological, metabolic, and ultrastructural investigations. However, the electroclinical and evolutive patterns are similar to those of some metabolic diseases (polydystrophy, non-ketotic hyperglycinemia, and so forth). The clinical picture in the first year of life is characterized by myoclonic jerks, partial seizures, and paroxysmal EEG abnormalities.

EEG patterns of doubtful clinical significance. A wide spectrum of EEG patterns may be seen that have doubtful clinical significance. These patterns, sometimes called "benign electroencephalographic variants" and "patterns of uncertain significance" include "rhythmic temporal theta bursts of drowsiness (formerly psychomotor variant)", "midline theta rhythms (formerly "Ciganek-rhythm"), "subclinical rhythmic electrographic discharge in adults (SREDA)", "wicket spikes", "small sharp spikes (SSS - formerly benign epileptiform transients of sleep - BETS)", "14 and 6 Hz positive bursts" and "6 Hz spike and wave (formerly phantom spike and wave)".[30,43] These are usually not seen during cEEG monitoring in critically ill ICU patients.

Shall ICU patients with NCSE and periodic EEG patterns receive aggressive AED treatment? Do NCSE and periodic EEG patterns damage the brain? Periodic epileptiform discharges (PEDs) which may be generalized (generalized periodic epileptiform discharges or GPEDs), lateralized (PLEDs) or bilateral but independent (bilateral independent periodic epileptiform discharges or BIPLEDs) may occur in patients with acute focal brain injury in the absence of seizures, but also appear frequently during prolonged seizures, and have been associated with poor outcome in SE.[44] There is controversy regarding the interpretation and therapeutic implications of these EEG findings. Investigators using serial EEG data, blood flow on single-positron-emission computed tomography (SPECT), and FDG-positron emission tomography (PET) findings argue that PEDs following SE are often ictal.[44,45] Others classify PEDs as postictal or simply as markers (an epiphenomenon) of severe injury or encephalopathy.[45] Some authors suggest that aggressive ICU management of NCSE in the elderly, critically ill, is harmful rather than beneficial.[46] Whether or not ICU patients with these EEG patterns benefit from aggressive treatment shall be investigated by conducting a trial with rapid-acting benzodiazepines (for example, lorazepam) and studying cEEG and clinical outcome.

Do NCSE and (some?) periodic EEG patterns damage the brain? Intimately linked with the question of treatment (addressed above) is the question whether or not further brain damage is occurring during NCSE or PEDs. This crucial question should be addressed by using cEEG monitoring, potential markers of neuronal injury like neuron-specific enolase (NSE),[47-50] MRI with diffusion weighted imaging (MRI-DWI),[51-54] and MR spectroscopy (N-acetylaspartate, choline-containing compounds, creatine plus phosphocreatine, and lactate).[55-57]

Research aspects. It is imperative to diagnose patients with NCSs and NCSE as early as possible because multiple seizures may further worsen at-risk brain tissue following acute brain injury and may cause further complications leading to higher morbidity and mortality. Since prognosis worsens with increasing duration of seizure activity,[20] it is crucial to treat NCSs early. From

this it follows that a cEEG monitoring system is crucial in establishing a correct diagnosis, assessing the patient's condition during drug therapy, detecting problems before they lead to serious neurological complications, and predicting the outcome.[58,59] As reported above, unfortunately, there are no epidemiological studies regarding NCSs and NCSE in Qatar. In Qatar cEEG is still not available, thus, patients are commonly presenting with late stage, difficult to treat NCSE, imposing often-dramatic consequences including severe morbidity or even death. The cEEG monitoring will improve medical treatment of these patients and help to reduce morbidity and costs in the long-term.[60-63] Education on the prevalence, causes, and treatment of subclinical seizures and NCSE in the ICUs of Hamad Medical Corporation (HMC), in comatose or stuporous patients, are other important tasks.[64] Of particular importance is knowledge of the underlying pathology of various EEG patterns encountered in the ICU.[65,66] Moreover, getting recent epidemiological data regarding NCSE and NCSs in Qatar for further studies will be a big achievement. The final goal of the intended research project will be to allow real time detection of subclinical electrographic events in high-risk ICU patients. This will require a dedicated ICU cEEG team to be trained, namely, a review of cEEG by skilled EEG technicians and EEG-experts and the development of refined computer detection algorithms in collaboration with experts of signal processing and companies. The aim of this work is to develop sophisticated and more useful detection software for electroencephalographic patterns frequently encountered in ICU patients (see technological aspects below). The monitoring of the immediate drug effects of the recommended first line AEDs (for example, lorazepam[67,68]), older AEDs (for example, valproic acid), and newer AEDs (for example, levetiracetam,[69-72] and topiramate[73,74]) by using modern EEG analysis and data compression techniques should be addressed as well. The efficacy and pharmacodynamic aspect of treatment should be correlated with the pharmacokinetic characteristic of these drugs and the EEG effects.

B) Technological aspects. Successful cEEG in the ICU needs better algorithms to detect non-convulsive epileptiform seizures and other paroxysmal events and better trend analysis software. Display of results should be more user-friendly and easy to interpret. A special problem is the wide variability of pathological EEG patterns, which might be seen in ICU-patients. In the clinical aspects of this review, we have reviewed the relevant EEG patterns that have to be considered and have summarized NCSs/NCSE occurring in ICU patients. In this technological part, we review the most important aspects of engineering by summarizing the relevant literature and some preliminary studies, as well as the Zurich experience with cEEG in the context of presurgical evaluation of candidates for epilepsy surgery. We introduce new software for the cEEG: the Wavelet transforms - Wavelet packet energy ratio (WPER) (The University of British Columbia, Vancouver [BC], Canada), which looked promising in preliminary studies. We present an outline describing the engineering aspects of the intended Doha cEEG ICU project, describing the rationale, and the research methodology. The latter includes the identification of differentiating characteristics of the ICU EEG signal in the various seizure morphologies and describes how to derive improved feature vectors. Important steps in this project are: (1) the development of an adaptive decision rule based on the identified feature vectors. (2) How to train the automatic seizure detector on a wide set of ICU EEG data. (3) To test the detector by statistically comparing its results on new data to the seizures identified visually. This step will allow analyzing the performance of the automatic ICU seizure detector and will provide an insight into the performance of the algorithm in the specific subsets of data, for example, seizure types, patient condition, and background EEG patterns. Possible problems and alternatives shall be described at the end.

Engineering: literature review and preliminary studies. Today in the ICU setting, EEG tools like Fourier analysis, amplitude-integrated EEG, computer seizure detection, allow trained, non-expert bedside personnel staff to recognize significant EEG changes instantaneously.[2] This combines the techniques from epilepsy monitoring and intraoperative monitoring. Raw EEG is used to detect seizures and status epilepticus, which are a major clinical indication of cEEG, whereas quantitative long-term EEG analysis is useful in quantifying interictal and ictal activity as well as evaluating the response to therapy.[75] Raw EEG interpretation remains necessary as the morphology and artifacts and drug therapy may modify spectral content. Seizure- and spike-detection software that detects time trends in background EEG parameters is helpful. At present, however, this software is limited by high false positive rates of seizure detection, namely, the difficulty in distinguishing various artifacts from seizures, interictal spikes, and sudden alterations in EEG background activity. Various tools have been utilized, including spectral analysis.[76,77] Time-frequency techniques (wavelets analysis),[78,79] nonlinear analysis techniques (Lyapunov exponents, Kolmogorov entropies),[79,80] synchronization likelihood,[80,81] as well as other techniques such as independent component analysis (ICA),[82,83] are being used for frequencies

changes and spike detection.[84] Algorithms based on synchronization likelihood,[85] neural networks,[86,87] epoched values of frequency, bandwidth, and power in the frequency spectrum and EEG complexity in the time domain have been applied on EEG and found to be potential tools for seizure detection, in particular also in infants and neonates.[88-91]

Despite positive results, no randomized studies have been performed to assess the value of these algorithms in detecting seizures in ICUs in adults.[92,93] In fact, most EEG monitoring systems use seizure detection techniques, developed during the last decades, in patients that do not present an alteration in the level of consciousness like ICUs patients. In neonates, 3 recent studies targeting these seizure detection algorithms concluded that their performances are not high enough to be used in ICUs (sensitivities of 43-63% and specificities of 56-90%).[84,94] Some of the newer techniques of data analysis and display offer hope to develop improved techniques that are able to predict seizures in the ICU setting. If commercially available software algorithms are set with this goal, the sensitivity for detecting seizures exceeds 90% (90% of the true seizures are detected), the specificity (ability of the system to detect a true absence of seizures) suffers, with 2+ false detections per hour.[95,96] Several techniques for displaying complex EEG data are now available: Compressed spectral array (CSA),[97,98] density spectral array,[99] power and ratios of power in certain EEG frequency bands,[100,101] subband coding,[102] EEG bispectral analysis,[103,104] lossless compression,[105,106] and clustering of adaptive segments using multiple frequency and amplitude based measures,[107-109] are amongst the techniques used for compressing EEG data in the ICU. The CSA has been used extensively in all ICU patients with an altered level of consciousness and in status epilepticus.[110-112] A recent study demonstrates the importance of cluster analysis of the EEG in the identification of seizures.[113]

In processing the raw EEG data, these techniques display a completely different result from the original EEG recording.[114] Nevertheless, there remains a strong need to develop better seizure detection algorithms especially designed for the ICU setting and tested against established gold standards (expert clinical neurophysiologist interpretation) to achieve appropriate predictive values of various seizure detection results. There is also a need to develop better technologies for displaying EEG data.

The Zurich experience with cEEG in the context of presurgical evaluation of candidates for epilepsy surgery. Wieser and his Zurich team have partly developed and used cEEG in the context of presurgical evaluation of candidates for epilepsy surgery. Numerous electroclinical studies have been performed using advanced computer-aided data reduction and analysis. For long-term video-EEG monitoring in the context of presurgical evaluation, particular emphasis has been put on recognizing subtle clinical accompaniments by correlating clinical behavior (video and audio monitoring, neuropsychological test performances) with the EEG using quantitative EEG analysis. Methods employed included compressed spectral array (CSA), with spectral edge frequencies (SEF - **Figure 1**, left). Special recording and monitoring systems,[115-119] integrated telemetry-computer systems, automatic spike and seizure detection methods (**Figure 1**, right), pharmacological tests,[120] direct brain recording and stimulation,[121] and pattern recognition has been used. The Zurich group has engaged in calculating correlation function and spectra including autoregressive filter methods, calculation of so-called correlation-dimension and EEG analyses within the framework of Lyapunov theory to predict seizures.[122,123] The Zurich group has published an EEG atlas illustrating the various EEG patterns with LORETA (Low Resolution Electromagnetic Tomography).[124] **Figure 2** illustrates the performance of 2 commercially available Spike Detection algorithms [F = Fricker, SPECTRALAB®, Kilchberg, Zurich, Switzerland, G=Gotman, STELLATE® Montreal, Quebec, Canada], and visual spike count [vis] together with power in band [pow]. A push-pull cannula has been inserted into the lumen of the hollow-core depth electrode #2 (left, in blue). The perfusates (**Figure 2**, left bottom) were analyzed for known and putative transmitters over one hour. Illustrated is aspartate (ASP), which correlated well with the amount of spikes and seizure discharges in depth EEG.

New software for the cEEG: Wavelet transforms - Wavelet packet energy ratio (WPER). Wavelet transforms (WTs) have been widely used with a lot of success in the analysis of transient and non-stationary signals. The WTs have been found to be an extremely useful tool for epileptic seizure detection, since EEG signals are non-stationary. Wavelet packet (WP) transform is a generalization of the discrete WT in which the decomposition procedure is performed in both lower and upper frequencies. A novel automatic wavelet based method to detect seizures in patients with temporal lobe epilepsy[77,78] with almost no delay in detection, has been developed. The EEG signals collected from patients were first decomposed using the WP transform. Seizures were detected by using the cross-data entropy algorithm to construct relative entropy measures derived from individual coefficients.[78] Pattern recognition techniques were efficiently employed, using computer software and adaptive controllers, for the extraction of relevant information from EEG signals in the detection of impending seizures. **Figure 3a**, adapted from, Khan and

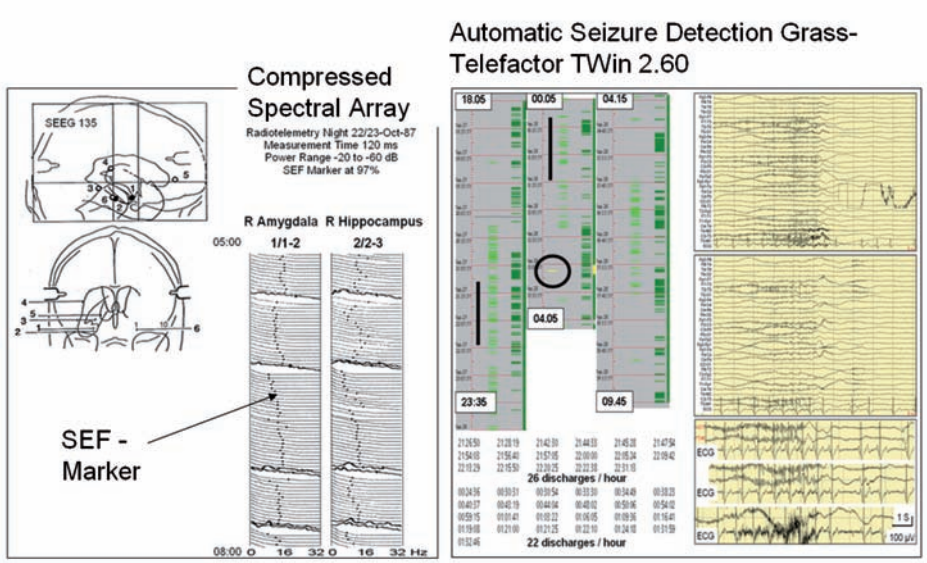

Figure 1 - Two examples of cEEG with automatic seizure detection. Left: 4 depth recorded seizures in right mesiotemporal structures (right amygdale and right hippocampus), monitored by Compressed Spectral Array (CSA with Spectral Edge Frequency, SEF). Right: Automatic seizure detection protocol (in gray) with subclinical seizure discharges (green) from scalp EEG in a patient with absence epilepsy with fast rhythmic discharges during sleep. The circle denotes an overt seizure (alarm button press). The vertical black bars have been plotted in detail exhibiting more than 20 discharges/hour. Note the electrocardiography irregularities at the end of seizure discharges (bottom right). Modified from Weiser and Fischer,[125] with permission of Demos Medical Publishing LLC.

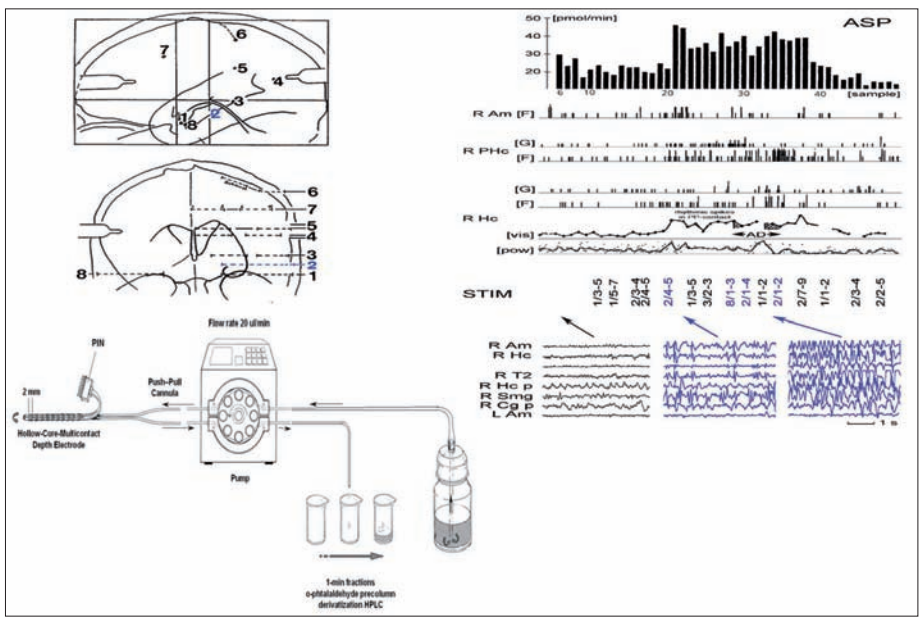

Figure 2 - Example of examination of neuromodulators and neurotransmitters (excitatory amino acids) in the primary epileptogenic zone (= hippocampus. Electrode #2, inner contacts. See top map of the inserted depth electrodes, top left). Bottom: Illustration of the experimental setting: Sterilized Gey's solution was perfused through the push-pull cannula (inserted in the lumen of Electrode #2) at a flow rate of 20 µl/min, and one minute fractions were collected over a period of one hour. Perfusates were analyzed by o-pthalaldehyde precolumn derivatization high-pressure liquid chromatography (HPLC). Top right: Concentration of aspartate (ASP) is correlated with the spike density in the EEG. Used Spike Detection algorithms are [F = Fricker, SPECTRALAB®; G=Gotman, STELLATE®], and visual spike count [vis] together with Power in band [pow]. Abbreviations: Am, amygdala. P Hc, parahippocampal gyrus. Hc, hippocampus. T2, second temporal gyrus, lateral. Smg, supramarginal gyrus. Cg p, posterior cingulate gyrus. R, right. Stim, electrical stimulation of indicated electrode contacts. The first number indicates the electrode #, the following number the contacts, numbered from inside out with 1 to 10. Stimulations indicated in blue induced a local afterdischarge. Three representative sections of the raw EEG are illustrated showing (from left to right) (a) spike-free = normal EEG, (b) EEG with moderate spiking, (c) EEG with seizure discharge. Modified from Cuenod et al.[126] Reprinted from Zumsteg et al,[124] with copyright (2008) permission from Zumsteg et al[124] and from Editions John Libbey Eurotext, Paris.

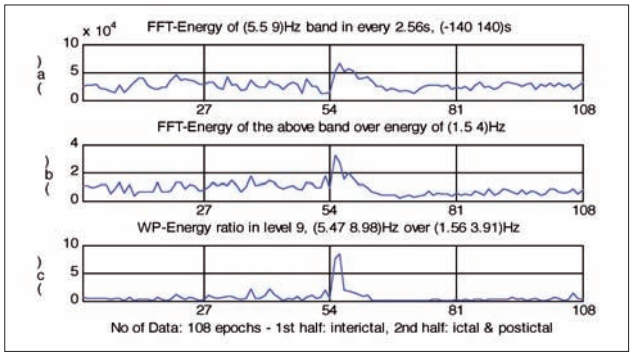

Figure 3 - Example of seizure detection in patients with epilepsy. **a**) Fourier domain energy in the 5.5-9 Hz band in every 2.56s in the 280s interval before and after seizure onset, **b**) Fourier domain energy ratio: average energy in the 5.5 to 9 Hz band over average energy in the 1.5 to 4 Hz band in the same interval, **c**) Wavelet Packet (WP-) Energy ratio: in level 9, average energies of 5.47 to 8.98 Hz band over 1.56 to 3.91 Hz. Adapted from Tafreshi et al[77] with permission of the IEEE Intellectual Property Rights Office (© 2006 IEEE).

Gotman[78] shows the energy of EEG signal in the 5.5-9 Hz band for each running window of 2.56 seconds during 140 seconds before and 140 seconds after seizure onset (a total of 108 epochs). **Figure 3b** shows Fourier domain energy ratio average energy in the 5.5-9 Hz band over average energy in the 1.5-4 Hz band in the same interval, while **Figure 3c** depicts the ratio of the same frequency bands in wavelet packet domain in level 9. Wavelet packet energy ratio (WPER) demonstrated superior performance in seizure detection. The described method was effective in detecting all 7 seizures recorded in 2 patients; there were no undetected seizures. Hence, this method could be used to improve the detection of non-convulsive seizures occurring in ICU patients.

In another related research, WPER was applied on EEG signals to detect seizures induced by electroconvulsive therapy (ECT).[127] The ECT is used to treat clinical depression that is unresponsive to drugs by inducing a generalized seizure with electrical stimulation after administering a short-term general anesthetic. The EEG is visually monitored to detect and characterize the seizure, as it is more reliable than monitoring motor activity alone. To detect seizures induced by ECT, we have developed and used an algorithm based on wavelet packet (WP) analysis of EEG signals. We also used the energy ratio of the dominant frequency bands in the ictal period during ECT. We used different approaches in detecting ECT seizures using the corresponding WP coefficients. Nine patients were studied with a total of 41 EEG recordings. Sensitivity in ECT seizure detection ranged from 76-95%.[127] Wavelet theory, neural networks, and other signal processing techniques have also been developed to other signals such as vibration signals in machines and control systems. Utilizing wavelets to extract features in the transient vibration signals present for a novel fault detection algorithm[128] have been successful. A local discriminant base algorithm has been used to choose a set of orthogonal bases from a wavelet packet dictionary, which best discriminates different states of the system. Wavelet coefficients constructed by projecting data onto the selected bases were employed as feature variables and inputs to a neural network classifier. Techniques such as the expectation-maximization algorithm have been applied to estimate parameters used in fuzzy logic networks for implementation in pattern recognition and control systems.[129,130] Fuzzy logic has been also integrated into a multi-objective optimization process in fault analysis and energy management.[131-133]

Engineering aspects of the Doha cEEG ICU project.

1. Rationale. In the last few decades, techniques for seizure detection in the ICU have made considerable progress. They are now used in the available EEG monitoring systems and some of them (adaptive time-frequency of wavelets and chaos theory and synchronization likelihood) have had considerable success and are increasingly being explored in the detection of epileptic seizures. Currently, however, in the ICU setting, a double reading by a qualified clinical neurophysiologist is needed to validate the results of the software program and to make a clinical decision. Considerable progress has been made regarding the time required to review the EEG data.[84] There is a dire need for algorithms, which are targeted specifically at detecting NCS and NCSE occurring in the ICU. The central focus of this part of the study is to develop a more accurate and robust detection technique, which can be used to identify the silent seizures that occur in ICU patients with no or only subtle clinical evidence. Time-frequency analysis to detect epileptic seizures (wavelet analysis) is an efficient analytical tool for use in the pattern recognition and classification of non-stationary signals such as the EEG. Wavelet transforms, and wavelet packet analysis should be applied on the continuous EEG to derive improved feature vectors and classification rules for automatic seizure detection in the ICU. The EEG characteristics of NCS/NCSE are heterogeneous, with a highly variable morphology. The criteria proposed by Young et al[20] for NCS detection have been listed in **Table 1**. In NCSE, changes from baseline occur, which are associated with continuous epileptiform discharges in the electroencephalogram. The EEG patterns occurring during NCS/NCSE as defined by Claassen et al,[25] have been listed in **Table 2**.

2. Research methodology. To develop an automatic ICU seizure detection, the increased resolution available in the time-frequency plane after applying the wavelet transform should be utilized. The results from the work

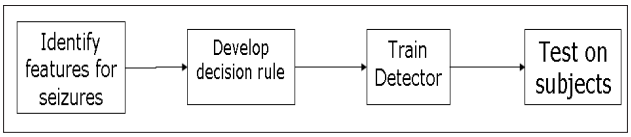

Figure 4 - Proposed methodology for developing an automatic seizure detector. Adapted from Khan and Gotman[78] with the permission of Elsevier and Copyright Clearance Center's Rightslink service.

carried out earlier[78,79] suggest that there is a potential to extract further information that can be used in detecting seizures. **Figure** 4 shows the sequence of steps involved to achieve this aim, which are detailed below.

a. Identify the differentiating characteristics of the ICU EEG signal in the various seizure morphologies and derive improved feature vectors. Digital EEG signals, in which NCS/NCSE have already been identified visually by a neurophysiologist using the criteria specified in **Tables 1 & 2**, should be collected from approximately 10 patients referred to the ICUs at HMC. The data will be collected from as wide a representation of the differing types of patients admitted to the ICUs as possible. Furthermore, the data will be verified to ensure correct seizure marking has been performed. To preprocess the signal, different techniques will be utilized to determine which is the most effective in the removal of artifacts (ECG, EMG, and so forth) present in the EEG signal. Then an appropriate analyzing wavelet will be selected to apply on the filtered EEG signal. Then the wavelet used in seizure detection should be analyzed[78] using a Daubechies-10 filter; later, and then a wavelet filter should be used that better explains the characteristics of EEG signal. The EEG signals may be also de-noised by wavelets to eliminate noise and artifacts, as they are suitable signal processing tools for the analysis of transient data and noise reduction. The signal will be segmented into windows of duration.[78] The windows, of length between 2-4 seconds, will be decomposed into a wavelet packet tree. The signal decomposition obtained from a patient to identify a seizure is shown in **Figure** 5.[79] Next, the sum energies of the chosen bands in the wavelet packet domain should be calculated to obtain the ratio of these energies in each epoch to determine characteristics of the seizures. The characteristics of the signal in the differentiated stages will then be analyzed to identify those characteristics, which vary the most amongst the seizures. An analysis of variance will be performed on the identified characteristics to determine those that are statistically most correlated with the seizures. Particular attention will be given to those characteristics, which correspond to the identified seizure criteria given in **Tables 1 & 2**. Experimentation with different windowing techniques and wavelet families to see which one offers the best differentiability should be performed.

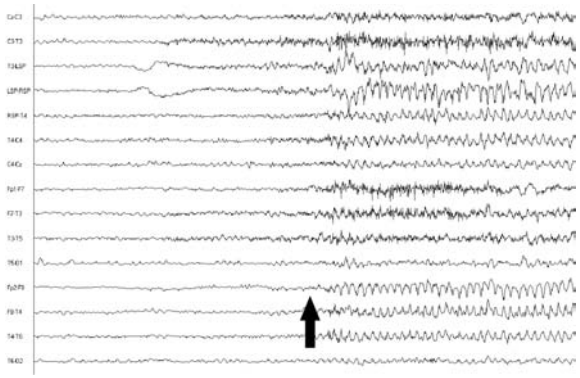

Figure 5 - A 10-second sample of a patient's EEG in bipolar montage with 28 channels, in which the arrow shows the seizure onset. Adapted from Tafreshi et al[77] with permission of the IEEE Intellectual Property Rights Office (© 2006 IEEE).

b. Develop an adaptive decision rule based on the identified feature vectors. Once feature vectors, which can be used to detect NCS/NCSE, are identified, an automatic decision rule will be developed. Existing seizure detection algorithms have used simple techniques, such as statistical thresholding,[76,134] and more complex ones such as Bayesian classification,[135] artificial neural networks (ANN),[86,87] clustering and multivariate linear discrimination. The wavelet packet energy ratio (the ratio of energies in 2 identified frequency bands) should be chosen as a discriminating feature.[77,78] The AANs have also been used to classify machine faults.[128] Several different options to determine which gives the most accurate results using the identified feature vectors will be investigated. Additional decision rules that could be explored include energy thresholds, statistical hypothesis testing, Bayesian classifiers, and Hidden Markov models (HMM). Because of the variability in the EEG of different individuals, it will be important to have an adaptive decision rule.

c. Train the automatic seizure detector on a wide set of ICU EEG data. There exist variations in the EEG signal across individuals. These variations are further pronounced, as patients will be admitted to the ICU due to varying acute illnesses. To achieve robustness against these variations, it is important to use a large amount of training data under as many input conditions as possible. Once the seizure detector is developed, it will be essential that it is trained on a wide data set from ICU patients with altered mental status admitted for different conditions. This will include data from approximately 30 patients. The EEG data, which have seizures visually identified, will be obtained from the ICUs at HMC and used for training. Different training approaches will be used to ensure that the final detector performs optimally.

d. Test the detector by statistically comparing its results on new data from the seizures identified visually. The trained automatic seizure detector should be used to analyze a new set of EEG data obtained from the ICUs at HMC. This data will have seizures visually marked by a Neurophysician. Care will be taken to use data from both patients unaffected by seizures and those suffering from varying seizure sub-types. A statistical analysis will be performed between the 2 sets of results to determine the correlation between them. The statistics obtained will allow quantifying the accuracy and robustness of the developed detector. Statistical analysis should be performed not only over the entire data set, but also on subsets of the data dividing according to the subjects' conditions. If possible, other proposed automatic detector should be tested to provide a comparison.

Interpretation of results. The statistical results from part d. will allow analyzing the performance of the automatic ICU seizure detector. It is desirable that a high overall correlation is achieved between the seizures identified by the automatic detector and visual identification. The statistics will also provide an insight into the performance of the detector in the specific subsets of data, for example, seizure types, and patient condition. In case of the scenario that the test results are extremely poor, it will prove that the implementation used is not feasible and alternative approaches need to be considered.

In summary the research project should include the following objectives and aspects: 1. To address the aims of this research project, collect continuous EEG data of critically ill or comatose patients admitted to the ICU of HMC. The data will be used to develop an automatic seizure detection system for ICU patients. 2. The cEEG recordings should be processed on-line with analysis algorithms, starting with CSA and SEF, and stored for further off-line studies with the goal of analyzing various subtypes of NCSE and several EEG patterns. The EEG data should be correlated with clinical, pathophysiological, and outcome parameters. A full screen laboratory testing (liver, kidney, and metabolic functions, glucose, electrolytes) and markers of neuronal damage, such as neuron-specific enolase (NSE), MRI-DWI, functional MRI, and MR spectroscopy (n-acetylaspartate, choline-containing compounds, creatine plus phosphocreatine, and lactate) should be considered. 3. The EEG analysis by visual inspection should be compared with computer-aided pattern classification, and the rate of correct versus false detections will be calculated in terms of specificity and sensitivity. The following EEG patterns should be analyzed in detail and modeled by algorithms: (a) Patterns of doubtful clinical significance and (b) Periodic EEG patterns, such as PSIDD, PLIDD, and SIRPIDs, PEDs (GPEDs, PLEDs, or BIPLEDs). Concerning PLEDs, it should be studied whether they are an ictal phenomenon or simply an epiphenomenon of localized brain pathology, and whether or not ICU patients with these EEG patterns benefit from aggressive treatment. Patients with PLEDs will be randomized to a trial of rapid-acting benzodiazepines and receive perictal imaging.[136] 4. Study the question of whether or not further brain injury is occurring during NCSE or PEDs. This can be achieved by using cEEG monitoring, potential markers of neuronal injury, such as neuron-specific enolase (NSE, often elevated after SE), and the noninvasive modern MRI and MR spectroscopy. These data have to be correlated with clinical outcome. 5. Study the immediate drug effects of the recommended first line AEDs (lorazepam), older AEDs (valproate) and newer AEDs (topiramate, levetiracetam) by using the to-be-developed modern EEG analysis and data compression techniques. This also should shed a light on the supposed neuroprotective effects of the new AEDs, particularly topiramate and levetiracetam. The efficacy and pharmacodynamic aspect of treatment could then be correlated with the pharmacokinetic characteristic of these drugs.

In conclusion, this project should be a collaborative effort between researchers in the field of neurology and signal processing. The outcome of this work will be an algorithm that can accurately identify NCSs and NCSE occurring in ICU patients with minimum visual validation requirements. An accurate seizure detection algorithm that can be used on cEEG signals obtained from critically ill ICU patients will provide intensive care medical practitioners with an effective tool to monitor brain function, diagnose occurring seizures, and guide treatment. It hopefully will considerably reduce the high manpower cost, and time associated with cEEG monitoring. The expected results obtained by correlation of clinical and cEEG data and measurement of signs of possible brain damage associated with certain EEG patterns will help to improve treatment protocols, and this way prevent morbidity. The outcomes of this work will also help Qatar and the Gulf Countries to establish them as a center of this new technology. Hospitals in Qatar, the Gulf region, and other parts of the world will be interested in successful commercial products of this project.

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