Summary

Anoxic/hypoxic encephalopathy is a severe neurological condition associated with a poor outcome. Neurologists, and particularly electroencephalographers, are often implicated in the assessment of comatose survivors of cardiac arrest. Therapeutic hypothermia has been increasingly implemented in the intensive care units starting less than a decade ago; in this new context, some outcome predictors previously known as reliable, such as the clinical examination, seem no more robust to decide on life support discontinuation. Conversely, the role of electroencephalography has gained in consideration, with converging new data pointing to its reliability in both hypothermic and normothermic conditions.

This article will review the EEG role in the evaluation of comatose survivor of cardiac arrest, important technical parameters and also the essential EEG patterns of this setting.

Key words: Neurocritical care, hypoxic brain injury, prognosis, cardiac arrest, hypothermia, outcome

Prognose nach einer zerebralen Anoxie bei Erwachsenen: Welche Rolle spielt der EEG-Spezialist?


Dieser Artikel gibt einen Überblick über die Rolle des EEG bei der Beurteilung von komatösen Überlebenden eines Herzstillstands, über wichtige technische Parameter und auch über die wesentlichsten EEG-Muster in dieser Situation.

Schlüsselwörter: Neuro-Intensivpflege, anoxisch-hypoxische Enzephalopathie, Prognose, Herzstillstand, Hypothermie

Pronostique après une anoxie cérébrale chez l’adulte : quel est le rôle du spécialiste en EEG ?

L’encéphalopathie anoxique / hypoxique est une condition neurologique grave associée à un mauvais pronostic. Les neurologues, et en particulier les spécialistes en électroencéphalographie sont souvent impliqués dans l’évaluation de ces patients. Cela fait environ dix ans que l’hypothermie thérapeutique est de plus en plus pratiquée dans les unités des soins intensifs. Depuis lors, certains éléments pronostiques tels que l’examen clinique, précédemment reconnus comme robustes, semblent beaucoup moins fiables quant la décision de l’arrêt de la réanimation. A l’inverse, le rôle de l’électroencéphalographie a gagné en importance, avec de nouvelles données montrant sa fiabilité tant durant l’hypothermie que durant la normothermie.

Cet article va examiner le rôle de l’EEG dans l’évaluation des survivants à un arrêt cardiaque restant dans le coma, les paramètres techniques importants, ainsi que les patterns EEG essentiels à connaître dans ce contexte.

Mots clés : soins intensifs neurologiques, encéphalopathie anoxique, pronostique, arrêt cardiaque, hypothermie

Introduction

Anoxic/hypoxic encephalopathy is a severe neurological condition associated with a dismal outcome. In recent years, therapeutic hypothermia (TH) has been progressively implemented [1, 2], leading to an improvement of functional outcome; its impact is illustrated by the relatively low number needed to treat
(NNT=7). Neurologists and electroencephalographers are often involved in the assessment of comatose survivors of cardiac arrest, in order to distinguish as reliably and rapidly as possible between patients who will benefit from maximal care, and those who will not recover. In this context, neurological examination, EEG and somatosensory evoked potential (SSEP) have been extensively studied and shown to be useful and reliable in outcome prediction [3]; however, those findings and related guidelines are based on data obtained essentially before the TH era. Indeed some recent data show that those recommendations have to be reconsidered in patients undergoing TH [4]; clinical examination, in particular regarding motor response to pain, seems considerably less reliable than the EEG evaluation. Of note, the EEG has also an important role in the pediatric population suffering from brain anoxia [5], but this is beyond the field of this brief review, which will focus on the prognostic role, technical parameters and important EEG patterns in adults.

**EEG in the assessment of adult survivors of cardiac arrest**

**Outcome prediction**

According to a meta-analysis performed by the American Academy of Neurology (AAN) [3], clinical examination appeared a reliable parameter in outcome prediction of comatose survivors of cardiac arrest. Indeed, absence of brainstem reflexes and of motor response to painful stimuli was considered as strong and reliable predictors of bad outcome with a false positive rate (FPR) of 0% (95% CI: 0-3%). This information was mainly based on class II studies performed before the TH implementation [6, 7]; however, recent data challenge these findings [4, 8]. Indeed a recent study of 111 survivors of cardiac arrest, performed in Lausanne [9], showed that those clinical predictors are no more precise enough after TH. For example, motor reaction to pain no better than extension assessed within the third day after cardiac arrest showed an FPR of poor outcome prediction as high as 24% (95% CI: 14-49%). This appears clearly suboptimal and dangerous when one has to decide on life support discontinuation. In the same study, absent brainstem (papillary, oculocephalic, or corneal) reflexes (FPR: 4%; 95% CI: 1-15%) and early myoclonus (FPR: 3%; 95% CI: 0-11%) resulted as better clinical predictors.

There are also some important updates regarding electroneurophysiological data since TH era. In the AAN recommendations, so-called “malignant” EEG patterns (such as generalized background suppression; burst-suppression with generalized epileptiform activity; periodic, or epileptiform complexes on a flat background) during the three first days after cardiac arrest were associated with poor outcome (death) with a FPR of 3% (95% CI: 0.9-11%). Since TH implementation, EEG background reactivity (assessed off sedation and after rewarming) has received increasing consideration [4, 9]. Reactivity has been shown to be a relatively reliable predictor of bad outcome in the cohort from Lausanne (FPR: 7%; 95% CI: 1-18%). Moreover, the same group evaluated the predictive performance of this parameter during hypothermia in 37 patients in a preliminary study [10], with very encouraging results showing a FPR of 0% (95% CI: 0-18%) for bad outcome (death) in patients without any background reactivity in the early phase of treatment. The predictive performance of hypothermic EEG resulted significantly higher than that of somatosensory evoked potentials during normothermia. Of note, “malignant” EEG patterns (see above) seem still associated with dismal outcome as it was before TH [9, 11]. These findings have been confirmed in an expanded assessment of 61 patients (FPR for lack of reactivity during TH: 0%, 95% CI: 0.15%) [12]. In the same direction, a score of prediction has been recently proposed [13]: age and the first EEG registration were the most robust variables whereas the Glasgow Coma Scale (traditional clinical examination of comatose patients) was much more unreliable.

In conclusion, the importance of EEG in the outcome prediction of survivors of cardiac arrest has received increasing attention after TH implementation, and seems to represent a robust predictor, especially as regards to the lack of reactivity during both hypo- and normothermia.

**Seizures identification**

Electrographic status epilepticus can occur in as much as 30% of patients suffering from brain hypoxia [11] and is considered as an independent factor predicting bad outcome. However a small subgroup of patients suffering from myoclonic post-anoxic status epilepticus may still experience a reasonable outcome and thus warrant an aggressive anti-epileptic treatment; in a recent study, all patients with a favorable outcome after an electrographic post-anoxic status epilepticus were associated with poor outcome (death) with a FPR of 3% (95% CI: 0.9-11%). Since TH implementation, EEG background reactivity (assessed off sedation and after rewarming) has received increasing consideration [4, 9]. Reactivity has been shown to be a relatively reliable predictor of bad outcome in the cohort from Lausanne (FPR: 7%; 95% CI: 1-18%). Moreover, the same group evaluated the predictive performance of this parameter during hypothermia in 37 patients in a preliminary study [10], with very encouraging results showing a FPR of 0% (95% CI: 0-18%) for bad outcome (death) in patients without any background reactivity in the early phase of treatment. The predictive performance of hypothermic EEG resulted significantly higher than that of somatosensory evoked potentials during normothermia. Of note, “malignant” EEG patterns (see above) seem still associated with dismal outcome as it was before TH [9, 11]. These findings have been confirmed in an expanded assessment of 61 patients (FPR for lack of reactivity during TH: 0%, 95% CI: 0.15%) [12]. In the same direction, a score of prediction has been recently proposed [13]: age and the first EEG registration were the most robust variables whereas the Glasgow Coma Scale (traditional clinical examination of comatose patients) was much more unreliable.

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Practical parameters

EEG recordings

The International Federation of Clinical Neurophysiology (IFCN) recommends that the usual technical EEG requirements should also be applied when assessing comatose patients [15]. The importance to rule out some confounding factors is emphasized. Indeed, drugs frequently used in Intensive Care Unit (ICU), body temperature and metabolic disturbances could massively influence the EEG and therefore should be carefully taken into account during interpretation. The international 10-20 system is recommended, with the use of 21 electrodes. A reduced electrode number could be applied in some particular situations; 11 electrodes are acceptable for neonates and for diagnosis of brain death if EEG is needed (of note, this particular application is not required nor recommended in Switzerland). EEG with ECG and video recordings are clearly preferred, due to the easiness of identifying potential artifacts and clinical manifestations.

It is generally recommended to assess EEG reactivity with auditory (hand clapping, taking care of avoiding air displacements near the electrodes) and noxious stimulations at bedside, under video recording. Because sternal rub often induces movement artifacts, and painful stimuli application to fingers or toes may be proven unreliable (reduced nerve conduction in cold conditions, ICU polyneuropathy) we recommended nipples quenching. Stimuli should be repeated at least twice, and be separated by at least 20 sec of recording, in order to identify reliably the baseline background.

EEG monitoring or routine EEG recordings?

This question is highly relevant, the subject of a lively debate, but still unresolved, and the IFCN recommendation does not answer it. On the one side, EEG monitoring is highly “resources-consuming”, depending on the institutional availability of recording machines. Conversely, a continuous EEG undoubtedly appears appealing in this setting and may allow the follow-up of the evolution of the patient. As stated earlier, EEG background reactivity seems one of the most important aspects of the outcome prediction: several hours of recording without stimulations probably do not increase the precision of forecast, at least in our experience. Continuous EEG could possibly identify subclinical seizures that punctual EEG evaluation might miss, but this has not been shown convincingly in this particular clinical setting. It is also not clear if treatment of those seizures would change the patient’s outcome [16]. Moreover, seizures are seldom isolated and mostly manifest as repetitive or continuous, defining status epilepticus, which should be caught with repetitive “standard” re-

Table 1: Synek Score (adapted from [17])

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Dominant reactive alpha activity with some theta activity</th>
<th>REACTIVE PATTERN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2</td>
<td>Dominant theta activity, preservation of normal sleep features, and with frontal monorhythmic delta activity</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>Small amplitude, diffuse, irregular, non reactive delta activity</td>
<td>INTERMEDIATE PATTERN</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Burst suppression, epileptiform discharges, and low-output nonreactive activity or Alpha/theta coma</td>
<td>NON-REACTIVE PATTERN</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Isoelectric</td>
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cordings. It seems reasonable to recommend that two video-EEG evaluations of at least 20-30 min (one during hypothermia and one after rewarming, off sedation), with 21 electrodes, should represent the minimum standard, with repeated background reactivity testing performed by trained personnel.

Important EEG patterns

Background activity

As already illustrated above, the background reactivity represents one of the most important EEG parameter in outcome evaluation (Figure 1). EEG reactivity is mostly defined as a clear, reproducible change in background frequency (and mostly amplitude) following auditory or noxious stimulation. EEG background reactivity has the advantage to represent a simple, reproducible and dichotomous evaluation.

The EEG background activity has also been suggested to be a marker of the future cognitive status. A small study (15 patients) showed that chronic (mean delay between the EEG evaluation and the cardiac arrest: 48 days) EEG activity graded according to the Synek score (Table 1) [17] was correlated with cognitive function at three months [18]. Of note, the Synek scale implies that discontinuous patterns are not reactive, this at times proves incorrect in our experience.

“Malignant” patterns

So called “malignant” patterns include, according to the AAN recommendations: diffuse background suppression below 20µV, burst-suppression (Figure 2), alpha and theta coma, and generalized periodic complexes on an isoelectric background [3]. We observed also a sort of “seizure-suppression pattern”, in which electrographic seizures alternate with flat background during TH [12]. These represent a grouping of EEG features, which have been showed to be clearly associated with poor outcome in patients without therapeutic hypothermia. Unfortunately, there are not enough data to assess every pattern independently, but a study [7] showed that generalized epileptiform activity or diffuse suppression lower than 20µV shows a stronger association with poor outcome than other patterns (e.g., alpha/theta-coma or burst-suppression pattern);

Figure 1: Background reactivity: clear change in background frequency (and mostly amplitude) following stimulation (red mark). Bipolar montage. Filter: highpass: 0.5 Hz / lowpass: 70 Hz / notch: 50
however, confidence intervals were too large to make these conclusions reliable. The “alpha coma pattern”, a nonreactive trace with (slow) and poorly developed alpha frequencies, appears uncertain as regards outcome prediction. Regaining consciousness or dying during hospitalization did not differ significantly among unconscious patients with or without alpha frequencies in their EEGs [19]. Another work indicated a high mortality and morbidity associated with alpha coma, but patients with some EEG reactivity (which strictu sensu excludes the classical alpha coma pattern) could regain a reasonable functional outcome [20]. Of note in these two studies, “alpha coma” was defined as a comatose patient with alpha frequencies on EEG without any further detail on its reactivity.

Another pattern called “Stimulus Induced Rhythmic, Periodic or Ictal Discharges” (SIRPIDs) (Figure 3) is also important in comatose patients, albeit only few studies have been dedicated to it, probably because it has been described only recently [21]. Periodic, rhythmic, or ictal-appearing discharges were defined as consistently induced by alerting stimuli or patient care activities. The original report included only one patient suffering from post-anoxic coma. A recent analysis by our group [22] observed this pattern in 13.3% (14/105) comatose survivors of cardiac arrest. None of the patients with SIRPIDs during TH survived, whereas three survived when SIRPIDs occurred only after rewarming (one reaching a good functional outcome). In view of the relatively low numbers, this observation needs confirmation, but SIRPIDs, particularly if appearing during TH, seem to reflect a severe neuronal damage and thus suggest a tendency towards poor outcome.

In conclusion, the principal and cardinal parameter of the EEG of comatose survivors of cardiac arrest is background reactivity evaluation.

Conclusions

Outcome prediction of comatose survivors after cardiac arrest is a major challenge for the involved clinicians, as following their evaluation, life support can be withdrawn. Several studies have been performed in this field, and multiple prognostic tools are available. We have shown in this short review that the EEG represents one of the most important assessments, especially since the implementation of therapeutic hypothermia. Obviously it has to be included in a comprehensive multimodal evaluation including somatosensory evoked potentials, clinical examination, biological parameters (neuron-specific enolase), and neuro-imaging. The absence of EEG background reactivity and the so-called “malignant EEG patterns” seems robust
indicators of bad outcome, but decisions upon interruption of supporting care should never be taken based on a single parameter [23]. EEG recordings should be obtained in the best possible conditions, with all confounding factors under control, and assessed in view of the clinical context. It is to hope that more data will add to the current understanding of prognostication after cardiac arrest, and the implementation of integrated assessments using cognitive evoked potentials [24] may improve the reliability of this prognosis.

References

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