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Review article

Clinical neurophysiology for neurological prognostication of comatose patients after cardiac arrest

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ABSTRACT

Early prognostication of outcome in comatose patients after cardiac arrest represents a daunting task for clinicians, also considering the nowadays commonly used targeted temperature management with sedation in the first 24–48 h. A multimodal approach is currently recommended, in order to minimize the risks of false-positive prediction of poor outcome, including clinical examination off sedation, EEG (background characterization and reactivity, occurrence of repetitive epileptiform features), and early-latency SSEP responses represent the core assessments in this setting; they may be complemented by biochemical markers and neuroimaging.

This paper, which relies on a recent comprehensive review, focuses on an updated review of EEG and SSEP, and also offers some outlook into long-latency evoked potentials, which seem promising in clinical use.

Contents

1. Introduction

The present paper draws consistently on, and represents an updated version of a recent review (Rossetti et al., 2016). Adult cardiac arrest (CA) has an annual incidence of 50 to 110 per 100,000 (Berdowski et al., 2010), representing one of the more frequent reasons to be admitted to the intensive care unit. Refinement in prehospital care, access to coronary angiography, and the increasing and widening use of targeted temperature management (TTM, with targets to 33 °C or 36 °C for 24 h (Nielsen et al., 2013)), resulted over the last few years in an increase of the proportion of patients that survive (McNally et al., 2011; Fugate et al., 2012), and improvement of functional outcome (Nielsen et al., 2013; Kim et al., 2014). Beyond ischemic-hypoxic injury, iatrogenic elements, such as sedative drugs, can additionally impair brain function; this will delay recovery of cerebral function for up to 5–6 days (Samaniego et al., 2011a), leaving families and caregivers with a relatively long delay of uncertainty. In this setting, despite neurological examination being the paramount element for the patient's evaluation (Sharshar et al., 2014), increasing evidence from the literature suggests that integration of additional modalities, including electro-physiological investigations, blood biomarkers, and brain imaging, will improve accuracy of early (24–72 h) prognostication.

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For the purpose of this review, which focuses on clinical neurophysiology, outcome is defined by cerebral performance categories (CPC, categorized as good: CPC 1 [back to baseline], or 2 [moderate impairment]; versus poor: CPC 3 [severe impairment], 4 [vegetative or comatose], 5 [dead]) (Booth et al., 2004). The false positive rate (FPR) refers to prognostication of poor outcome. The reader is referred to recent review papers regarding the refined discussion of multimodal prognostication in this setting (Oddo and Rossetti, 2011; Samaniego et al., 2011b; Sandroni et al., 2014; Ben-Hamouda et al., 2014; Horn et al., 2014).

2. Electroencephalography (EEG)

It was recently shown that EEG, which is non-invasive, cheap and broadly available, allows a relatively robust correlation with the degree of neuronal injury estimated through blood biomarkers (Rossetti et al., 2012). Of, course, some degree of technical expertise is needed for its correct recording and interpretation, as illustrated in previous papers on this topic (Alvarez and Rossetti, 2015; Hirsch et al., 2013; Westhall et al., 2015).

Mild hypothermia has no major effects on EEG (Stecker et al., 2001), as opposed to sedative medications administered for TTM. Recent studies suggest, nevertheless, that drips in the range of 0.1–0.2 mg/kg/hr (midazolam) or 2–3 mg/kg/hr (propofol) do not significantly alter the EEG prognostic accuracy even during the first 24 h and under TTM (Hofmeijer et al., 2015; Oddo and Rossetti, 2014; Sivaraju et al., 2015).

EEG findings can be categorized into three main domains, as outlined in the aforementioned review (Rossetti et al., 2016):

Background activity, which appears informative of global cerebral functioning. As a general rule, brain function decline is paralleled by increasing background slowing and decreasing amplitude. Several studies focused on low voltage (<20 μV) or isoelectric (suppressed) background (FPR 0%, 95%CI: 0–17% (Sivaraju et al., 2015; Cloostermans et al., 2012)), burst-suppression (FPR 0%, 95%CI: 0–11% (Sivaraju et al., 2015)), burst-suppression with identical bursts (FPR 0%, 95%CI: 0–17% (Hofmeijer et al., 2014)), and a spontaneously discontinuous background (FPR 7%, 95%CI: 0–24% (Rossetti et al., 2012)), all these features appear consistently and strongly related to unfavourable outcome. Conversely, a continuous background observable even only 12 h after CA forecasts awakening with a relatively high positive predictive value (92%, 95%CI: 80–98% (Hofmeijer et al., 2015), 72%, 95%CI: 55–88% (Sivaraju et al., 2015)). An important exception to be mentioned is "alpha-coma", a pattern that is characterized by an anterior prominent, not reactive rhythm associated with poor prognosis (Berkhoff et al., 2000).

Background reactivity may be elicited by auditory, visual, or noxious stimulations, and appears either with transitory attenuation or increase of electrical activity, in most instances this is visible on all leads. It is the experience of the author that in case of prominent muscular artefacts and the impossibility to administer muscular relaxing agents, the electrodes recording from the midline (such as Fz, Cz, Pz) should be looked at, since they are usually devoid of muscular activity. Lack of reactivity correlates with poor outcome if assessed after (FPR 7%, 95%CI: 1–15% (Rossetti et al., 2010; Thenayan et al., 2010)), and even more strongly during TTM (FPR 2%, 95%CI: 0–9% (Oddo and Rossetti, 2014; Juan et al., 2015)). Conversely, present reactivity may forego awakening, both during TTM (positive predictive value 86%, 95%CI: 77–92% (Tsetsou et al., 2013)), and thereafter (78%, 95%CI: 64–88% (Rossetti et al., 2010)). Finally, so-called "stimulus-induced rhythmic, periodic or ictal discharges" (SIRPIDs), which do not represent physiological reactivity (Braksick et al., 2016), occur in about 15% of patients and seem to herald poor prognosis (FPR 2%, 95%CI: 0–11%), especially if they appear during TTM and pharmacological sedation (Alvarez et al., 2013a). A practical limitation of the reactivity features is the lack of generalization (Noirhomme et al., 2014; Westhall et al., 2015), to this extent, a standardized stimulation protocol may improve its reliability (Tsetsou et al., 2015; Fantaneanu et al., 2016).

Epileptiform features, such as repetitive (periodic or rhythmic) sharp waves, (poly-) spikes, spike and waves. These features after TTM are related to poor outcome (FPR 9%, 95%CI: 2–21% (Rossetti et al., 2010)), and even more so during TTM, under pharmacological sedation with GABA-ergic agents (FPR 0%, 95%CI: 0–30% (Rossetti et al., 2012; Sadaka et al., 2015)). However, it must be underscored in this context that a subset of patients with electrographic status epilepticus appearing only after TTM and sedation weaning, especially those who have preserved brainstem reflexes and somatosensory evoked potentials, as well as background EEG reactivity, may reach relatively favourable outcomes if treated (Rossetti et al., 2009; Westhall et al., 2013). A recent elegant study illustrates that patients with early Lance-Adams syndrome, a stimulus-sensitive myoclonus with epileptiform EEG, who may reach a relatively good prognosis, display relatively tiny spike over the midline region superimposed on a continuous EEG background, as opposed to subjects with massive status myoclonus and dismal outcome that show burst-suppression backgrounds with polyphasic, high voltage and diffuse epileptiform features (Elmer et al., 2016). Quantitative analysis suggests that higher background continuity, higher discharge frequency, but lower discharge periodicity is also related to better outcome (Ruijter et al., 2015). It seems that these patients should be treated aggressively with large-spectrum anticonvulsants under EEG control and, if needed, pharmacological coma. Treatment duration in this context is not known, but the author does not consider reasonable to extend therapy beyond two to three weeks after CA, if the patient does not awaken.

Standard versus continuous EEG. Several authors propose continuous EEG for up to 48 h in this clinical setting (Hofmeijer et al., 2015; Sivaraju et al., 2015). It has been shown, however, that two standard EEGs (<30 min) including reactivity stimulations, recorded within 48 h of CA, may offer comparable prognostic information (Alvarez et al., 2013b), and at lower costs (Crepeau et al., 2014). Thus, in the opinion of this author, intermittent EEG represents a valid alternative for centres with limited EEG resources. Since electrical activity has been described to evolve over the first 24–72 h after cardiac arrest (Cloostermans et al., 2012; Oh et al., 2013, 2015; Rundgren et al., 2010), and in view of the variation in terms of sedation during and after TTM, repeated assessments should be performed within this time frame. Strongly reduced montages with two channels, including amplitude-integrated analysis and bispectral index, have been reported in this clinical context (Riker et al., 2013; Rundgren et al., 2010; Oh et al., 2013, 2015): while they represent an interesting alternative for background and reactivity assessments, they seem less sensitive for epileptiform transients and epileptic seizures. Of note, EEGs recorded too early may tend to overestimate brain injury, and, on the other side, epileptiform features most commonly appear after 12–24 h following the initial event (Legriel et al., 2013): for these reasons, EEG assessments can be started at 12 h after CA (Alvarez et al., 2013b).

3. Somatosensory evoked potentials

Early latency evoked potentials are generated from the average of cortical electrographic responses to repetitive electrical stimulations delivered by an electrode placed over the median nerve at the wrist, which result at different recording sites (ipsilateral