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.

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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 pre-hospital 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.
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, non 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 transient 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” (SIRPDs), 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; Fantaneau 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 GABAergic 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 (Ruiter 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...
brachial plexus at Erb’s point, posterior fascicles at cervical cord over the C5 vertebræ, and the contralateral postcentral gyrus (Koenig and Kaplan, 2015). The negative wave appearing at about 20 ms over the scalp is called “N20”. Although evoked potentials are less broadly used than EEG, they have been extensively studied for prognostication after CA. As a matter of fact, the bilateral absence of N20 highly correlates with poor outcome, after (FPR 0.5%, 95%CI: 0–2% (Bouwes et al., 2012; Leithner et al., 2010; Oddo and Rossetti, 2014; Samaniego et al., 2011a; Hofmeijer et al., 2015), but also during TTM (FPR 0%, 95%CI: 0–2% (Sandroni et al., 2014; Leithner et al., 2010)). It has recently been suggested that quantitative assessment of the N20 amplitude may offer additional prognostic information (Endisch et al., 2015), however this study needs to be replicated before this item can be used routinely. While early-latency SSEP accuracy is extremely high for prediction of poor prognosis, they have no role to forecast favourable outcome, with positive predictive values of a present N20 ranging between 40% (29–50%) (Hofmeijer et al., 2015) to 58% (95%CI: 49–68%) (Oddo and Rossetti, 2014). These estimates seem to lie clearly lower than a continuous, reactive EEG background activity (>80%) (Tsetsou et al., 2013). Furthermore, early latency SSEP have also a lower sensitivity to detect patients who will not awaken (43%; 95%CI: 31–57%), if compared to an absent EEG background reactivity during TTM (74%; 95%CI: 62–84%) (Oddo and Rossetti, 2014). Somewhat not unexpectedly, given the aforementioned data, SSEP do not seem to offer any additional prognostic information when EEG, clinical evaluation and serum biomarkers are also considered together (Hofmeijer et al., 2015; Oddo and Rossetti, 2014).

**Middle latency evoked potentials** are elicited by cortico-cortical projections, and appear up to 100 ms following stimulation of the median nerve. They are believed to better reflect functional connectivity and thus allow prognostication of awakening, but due to challenging technical and practical issues they are used far less commonly than early-latency potentials. An Austrian study before the TTM era reported a PPV for awakening as high as 97% (Madl et al., 2000); however, this was challenged by a subsequent Dutch observation suggesting that only 28% of those showing these responses reached a good outcome (Zandbergen et al., 2006). Recently, evoked potentials with painful stimuli have been described to inform upon consciousness recovery (PPV 100%, 95% CI 87–100%) even before EEG reactivity can be assessed (Zanatta et al., 2015). Again, this promising observation needs replication before wider implementation.

### 5. Conclusion

Neurointensivists, neurologists and clinical neurophysiologists are nowadays confronted with high expectations for an accurate and timely outcome prediction after CA. Over the last decade, this prognostication evolved towards a multimodal approach, which relies on clinical examination and integration of the information by multiple tests, where EEG and SSEP represent very important tools (Table 1). In this context, it is very important to underscore that the so called “self-fulfilling prophecy” represents an important setback, common to nearly all clinical studies on prognostication after CA: if in clinical practice a specific tool is used to forecast prognosis and decide upon interruption of intensive care support, it is logical that it will appear extremely robust when assessed retrospectively (Bouwes et al., 2012; Rossetti et al., 2010). But this only represents circular thinking. The fact that the aforementioned tools have been assessed by many clinical researchers using different approaches to decide upon discontinuation of life supporting measures tempers some concerns, along with the fact that several newer variables, especially EEG background and reactivity, have been repetitively studied without openly influencing such decisions. Prognostication should in any case never be based on a single indicator: while some variables may show very low FPRs for poor outcome, in practice they virtually never occur in isolation; furthermore, multimodality provides a well needed reassurance about the reliability of prognostic estimations by offering evidence from different sources, which should in the end all make sense together (Oddo and Rossetti, 2011; Samaniego et al., 2011b; Sandroni et al., 2014; Ben-Hamouda et al., 2014; Horn et al., 2014). While in current practice the vast majority of prognosticators are highly specific for poor outcome, an important challenge

### Table 1

| Feature related to good outcome | Positive predictive value 95%CI | Feature related to poor outcome | False positive rate 95%CI |
|---------------------------------|---------------------------------|---------------------------------|--------------------------|
| EEG Background                  | Continuous at 12–24 h           | Diffuse suppression or low voltage at 24 h | 0% (0–17%)               |
| Reactivity to stimuli           | Normal voltage at 24 h          | Burst-suppression at 24 h        | 0% (0–11%)               |
|                                | Present during hypothermia      | Absent during hypothermia        | 2% (0–9%)                |
|                                | Present after return of normothermia | Absent after return of normothermia | 7% (1–15%)               |
| SIRPDs                          | NA                              | Present at any time              | 2% (0–11%)               |
| Repetitive epileptiform transients | NA                             | Present during hypothermia       | 0% (0–30%)               |
| SSEP                            | Bilaterally present             | Present after return of normothermia | 5% (2–21%)               |

CI = confidence intervals, EEG = electroencephalography, NA = not assessed, SIRPDs = stimulus induced rhythmic, periodic, or ictal discharges, SSEP = somatosensory evoked potentials.
for the near future will be to refine the current understanding of tools that may predict good functional recovery, thus offering to clinicians, caregivers and families a comprehensive and complementary approach of prognosis.

Conflict of interest statement
The author does not have anything to disclose.

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