



Review article

Clinical neurophysiology for neurological prognostication of comatose patients after cardiac arrest



Andrea O. Rossetti*

Department of Clinical Neurosciences, Centre Hospitalier Universitaire Vaudois (CHUV), Université de Lausanne (UNIL), Lausanne, Switzerland

ARTICLE INFO

Article history:

Received 19 January 2017
 Received in revised form 13 March 2017
 Accepted 13 March 2017
 Available online 20 March 2017

Keywords:

Hypoxic-anoxic encephalopathy
 Outcome
 EEG
 SSEP
 N20

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.

© 2017 International Federation of Clinical Neurophysiology. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Contents

1. Introduction	76
2. Electroencephalography (EEG)	77
3. Somatosensory evoked potentials	77
4. Other promising prognostic tools	78
5. Conclusion	78
Conflict of interest statement	79
Acknowledgments	79
References	79

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.

* Address: Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne, Service de Neurologie, BH 07, Rue du Bugnon, 46, CH – 1011 Lausanne, Switzerland.

E-mail address: andrea.rossetti@chuv.ch

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 μ V) 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%), espe-

cially 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 (Legriell 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

Table 1
Overview of prognosticators including their estimated false positive rates (1-specificity) in adult patients treated with targeted temperature (modified after (Rossetti et al., 2016)).

	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%)
	SIRPIDs	NA	Present at any time	2% (0–11%)
	Repetitive epileptiform transients	NA	Present during hypothermia	0% (0–30%)
			Present after return of normothermia	9% (2–21%)
SSEP	Bilaterally present	58% (49–68%)	Bilaterally absent after return of normothermia	0.5% (0–2%)

CI = confidence intervals, EEG = electroencephalography, NA = not assessed, SIRPIDs = stimulus induced rhythmic, periodic, or ictal discharges, SSEP = somatosensory evoked potentials.

brachial plexus at Erb's point, posterior fascicles at cervical cord over the C5 vertebra, 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 available, and 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% (Madi 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.

4. Other promising prognostic tools

Long-latency evoked potentials represent higher-order cortical reactions occurring more than 100 ms after stimulation of the pri-

mary sensory areas. It is common practice, especially in comatose patients, to record these with auditory stimulations; response to deviant stimuli in a sequence of standard stimuli, also called "mismatch negativity", has been described several years ago, in the pre-TTM era, to be strongly associated with awakening after a latency of several days to weeks following CA (Fischer et al., 2006). More recently, this approach has been developed and refined though an automated voltage topography analysis of recordings performed during acute post-CA coma, on a case by case basis: progression of auditory discriminations between the first and the second assessments (both recorded within the first 48 h after the arrival of the patient to the hospital) heralded good recovery for the vast majority of patients (Tzovara et al., 2013, 2016). This novel paradigm may identify very early patients with favourable prognosis, but needs to be replicated in different settings (Rossetti et al., 2014), moreover, it requires dedicated and skilled engineering personnel for its algorithms of decoding.

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

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.

Acknowledgments

The Swiss National Science Foundation provided financial support to AOR (CR3213_143780) for research in coma prognosis.

References

- Alvarez, V., Oddo, M., Rossetti, A.O., 2013a. Stimulus-induced rhythmic, periodic or ictal discharges (SIRPIDs) in comatose survivors of cardiac arrest: characteristics and prognostic value. *Clin. Neurophysiol.* 124, 204–208.
- Alvarez, V., Rossetti, A.O., 2015. Clinical use of EEG in the ICU: technical Setting. *J. Clin. Neurophysiol.* 32, 481–485.
- Alvarez, V., Sierra-Marcos, A., Oddo, M., Rossetti, A.O., 2013b. Yield of intermittent versus continuous EEG in comatose survivors of cardiac arrest treated with hypothermia. *Crit. Care* 17, R190.
- Ben-Hamouda, N., Taccone, F.S., Rossetti, A.O., Oddo, M., 2014. Contemporary approach to neurologic prognostication of coma after cardiac arrest. *Chest* 146, 1375–1386.
- Berdowski, J., Berg, R.A., Tijssen, J.G., Koster, R.W., 2010. Global incidences of out-of-hospital cardiac arrest and survival rates: systematic review of 67 prospective studies. *Resuscitation* 81, 1479–1487.
- Berkhoff, M., Donati, F., Bassetti, C., 2000. Postanoxic alpha (theta) coma: a reappraisal of its prognostic significance. *Clin. Neurophysiol.* 111, 297–304.
- Booth, C.M., Boone, R.H., Tomlinson, G., Detsky, A.S., 2004. Is this patient dead, vegetative, or severely neurologically impaired? Assessing outcome for comatose survivors of cardiac arrest. *JAMA* 291, 870–879.
- Bouwes, A., Binnekade, J.M., Kuiper, M.A., Bosch, F.H., Zandstra, D.F., Toornvliet, A.C., Biemond, H.S., Kors, B.M., Koelman, J.H., Verbeek, M.M., Weinstein, H.C., Hijdra, A., Horn, J., 2012. Prognosis of coma after therapeutic hypothermia: a prospective cohort study. *Ann. Neurol.* 71, 206–212.
- Braksick, S.A., Burkholder, D.B., Tsetsou, S., Martineau, L., Mandrekar, J., Rossetti, A.O., Savard, M., Britton, J.W., Rabinstein, A.A., 2016. Associated factors and prognostic implications of stimulus-induced rhythmic, periodic, or ictal discharges. *JAMA Neurol.* 73, 585–590.
- Cloostermans, M.C., van Meulen, F.B., Eertman, C.J., Hom, H.W., van Putten, M.J., 2012. Continuous electroencephalography monitoring for early prediction of neurological outcome in postanoxic patients after cardiac arrest: a prospective cohort study. *Crit. Care Med.* 40, 2867–2875.
- Crepeau, A.Z., Fugate, J.E., Mandrekar, J., White, R.D., Wijndicks, E.F., Rabinstein, A.A., Britton, J.W., 2014. Value analysis of continuous EEG in patients during therapeutic hypothermia after cardiac arrest. *Resuscitation* 85, 785–789.
- Elmer, J., Rittenberger, J.C., Faro, J., Molyneaux, B.J., Popescu, A., Callaway, C.W., Baldwin, M., Service Pittsburgh Post-Cardiac Arrest, 2016. Clinically distinct electroencephalographic phenotypes of early myoclonus after cardiac arrest. *Ann. Neurol.* 80, 175–184.
- Endisch, C., Storm, C., Ploner, C.J., Leithner, C., 2015. Amplitudes of SSEP and outcome in cardiac arrest survivors: a prospective cohort study. *Neurology* 85, 1752–1760.
- Fantaneanu, T.A., Tolchin, B., Alvarez, V., Friolet, R., Avery, K., Scirica, B.M., O'Brien, M., Henderson, G.V., Lee, J.W., 2016. Effect of stimulus type and temperature on EEG reactivity in cardiac arrest. *Clin. Neurophysiol.* 127, 3412–3417.
- Fischer, C., Luate, J., Nemoz, C., Morlet, D., Kirkorian, G., Mauguire, F., 2006. Improved prediction of awakening or nonawakening from severe anoxic coma using tree-based classification analysis. *Crit. Care Med.* 34, 1520–1524.
- Fugate, J.E., Brinjikji, W., Mandrekar, J.N., Cloft, H.J., White, R.D., Wijndicks, E.F., Rabinstein, A.A., 2012. Post-cardiac arrest mortality is declining: a study of the US National Inpatient Sample 2001 to 2009. *Circulation* 126, 546–550.
- Hirsch, L.J., LaRoche, S.M., Gaspard, N., Gerard, E., Svoronos, A., Herman, S.T., Mani, R., Arif, H., Jette, N., Minazad, Y., Kerrigan, J.F., Vespa, P., Hantus, S., Claassen, J., Young, G.B., So, E., Kaplan, P.W., Nuwer, M.R., Fountain, N.B., Drislane, F.W., 2013. American clinical neurophysiology society's standardized critical care EEG terminology: 2012 version. *J. Clin. Neurophysiol.* 30, 1–27.
- Hofmeijer, J., Beernink, T.M., Bosch, F.H., Beishuizen, A., Tjepkema-Cloostermans, M.C., van Putten, M.J., 2015. Early EEG contributes to multimodal outcome prediction of postanoxic coma. *Neurology* 85, 137–143.
- Hofmeijer, J., Tjepkema-Cloostermans, M.C., van Putten, M.J., 2014. Burst-suppression with identical bursts: a distinct EEG pattern with poor outcome in postanoxic coma. *Clin. Neurophysiol.* 125, 947–954.
- Horn, J., Cronberg, T., Taccone, F.S., 2014. Prognostication after cardiac arrest. *Curr. Opin. Crit. Care* 20, 280–286.
- Juan, E., Novy, J., Suys, T., Oddo, M., Rossetti, A.O., 2015. Clinical evolution after a non-reactive hypothermic eeg following cardiac arrest. *Neurocrit. Care* 22, 403–408.
- Kim, F., Nichol, G., Maynard, C., Hallstrom, A., Kudenchuk, P.J., Rea, T., Copass, M.K., Carlbom, D., Deem, S., Longstreth Jr., W.T., Olsufka, M., Cobb, L.A., 2014. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: a randomized clinical trial. *JAMA* 311, 45–52.
- Koenig, M.A., Kaplan, P.W., 2015. Clinical applications for EPs in the ICU. *J. Clin. Neurophysiol.* 32, 472–480.
- Legriel, S., Hilly-Ginoux, J., Resche-Rigon, M., Merceron, S., Pinoteau, J., Henry-Lagarigue, M., Bruneel, F., Nguyen, A., Guezennec, P., Troche, G., Richard, O., Pico, F., Bedos, J.P., 2013. Prognostic value of electrographic postanoxic status epilepticus in comatose cardiac-arrest survivors in the therapeutic hypothermia era. *Resuscitation* 84, 343–350.
- Leithner, C., Ploner, C.J., Hasper, D., Storm, C., 2010. Does hypothermia influence the predictive value of bilateral absent N20 after cardiac arrest? *Neurology* 74, 965–969.
- Madl, C., Kramer, L., Domanovits, H., Woolard, R.H., Gervais, H., Gendo, A., Eisenhuber, E., Grimm, G., Sterz, F., 2000. Improved outcome prediction in unconscious cardiac arrest survivors with sensory evoked potentials compared with clinical assessment. *Crit. Care Med.* 28, 721–726.
- McNally, B., Robb, R., Mehta, M., Vellano, K., Valderrama, A.L., Yoon, P.W., Sasson, C., Crouch, A., Perez, A.B., Merritt, R., Kellermann, A., Control Centers for Disease, and Prevention, 2011. Out-of-hospital cardiac arrest surveillance – Cardiac Arrest Registry to Enhance Survival (CARES), United States, October 1, 2005–December 31, 2010. *MMWR Surveill. Summ.* 60, 1–19.
- Nielsen, N., Wetterslev, J., Cronberg, T., Erlinge, D., Gasche, Y., Hassager, C., Horn, J., Hovdenes, J., Kjaergaard, J., Kuiper, M., Pellis, T., Stammet, P., Wanscher, M., Wise, M.P., Aneman, A., Al-Subaie, N., Boesgaard, S., Bro-Jeppesen, J., Brunetti, I., Bugge, J.F., Hingston, C.D., Juffermans, N.P., Koopmans, M., Kober, L., Langorgren, J., Lilja, G., Moller, J.E., Rundgren, M., Rylander, C., Smid, O., Werer, C., Winkel, P., Friberg, H., Trial Investigators, T.T.M., 2013. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. *N. Engl. J. Med.* 369, 2197–2206.
- Noirhomme, Q., Lehembre, R., Lugo Zdel, R., Lesenfants, D., Luxen, A., Laureys, S., Oddo, M., Rossetti, A.O., 2014. Automated analysis of background EEG and reactivity during therapeutic hypothermia in comatose patients after cardiac arrest. *Clin. EEG Neurosci.* 45, 6–13.
- Oddo, M., Rossetti, A.O., 2011. Predicting neurological outcome after cardiac arrest. *Curr. Opin. Crit. Care* 17, 254–259.
- Oddo, M., Rossetti, A.O., 2014. Early multimodal outcome prediction after cardiac arrest in patients treated with hypothermia. *Crit. Care Med.* 42, 1340–1347.
- Oh, S.H., Park, K.N., Kim, Y.M., Kim, H.J., Youn, C.S., Kim, S.H., Choi, S.P., Kim, S.C., Shon, Y.M., 2013. The prognostic value of continuous amplitude-integrated electroencephalogram applied immediately after return of spontaneous circulation in therapeutic hypothermia-treated cardiac arrest patients. *Resuscitation* 84, 200–205.
- Oh, S.H., Park, K.N., Shon, Y.M., Kim, H.J., Youn, C.S., Kim, S.H., Choi, S.P., Kim, S.C., 2015. Continuous amplitude-integrated electroencephalographic monitoring is a useful prognostic tool for hypothermia-treated cardiac arrest patients. *Circulation* 132, 1094–1103.
- Riker, R.R., Stone Jr., P.C., May, T., McCrum, B., Fraser, G.L., Seder, D., 2013. Initial bispectral index may identify patients who will awaken during therapeutic hypothermia after cardiac arrest: a retrospective pilot study. *Resuscitation* 84, 794–797.
- Rossetti, A.O., Carrera, E., Oddo, M., 2012. Early EEG correlates of neuronal injury after brain anoxia. *Neurology* 78, 796–802.
- Rossetti, A.O., Oddo, M., Liaudet, L., Kaplan, P.W., 2009. Predictors of awakening from postanoxic status epilepticus after therapeutic hypothermia. *Neurology* 72, 744–749.
- Rossetti, A.O., Oddo, M., Logroscino, G., Kaplan, P.W., 2010. Prognostication after cardiac arrest and hypothermia: a prospective study. *Ann. Neurol.* 67, 301–307.
- Rossetti, A.O., Rabinstein, A.A., Oddo, M., 2016. Neurological prognostication of outcome in patients in coma after cardiac arrest. *Lancet Neurol.* 15, 597–609.
- Rossetti, A.O., Tzovara, A., Murray, M.M., De Lucia, M., Oddo, M., 2014. Automated auditory mismatch negativity paradigm improves coma prognosis accuracy after cardiac arrest and therapeutic hypothermia. *J. Clin. Neurophysiol.* 31, 356–361.
- Ruijter, B.J., van Putten, M.J., Hofmeijer, J., 2015. Generalized epileptiform discharges in postanoxic encephalopathy: Quantitative characterization in relation to outcome. *Epilepsia* 56, 1845–1854.
- Rundgren, M., Westhall, E., Cronberg, T., Rosen, I., Friberg, H., 2010. Continuous amplitude-integrated electroencephalogram predicts outcome in hypothermia-treated cardiac arrest patients. *Crit. Care Med.* 38, 1838–1844.
- Sadaka, F., Doerr, D., Hindia, J., Lee, K.P., Logan, W., 2015. Continuous electroencephalogram in comatose postcardiac arrest syndrome patients treated with therapeutic hypothermia: outcome prediction study. *J. Intensive Care Med.* 30, 292–296.
- Samaniego, E.A., Mlynash, M., Caulfield, A.F., Eyngorn, I., Wijman, C.A., 2011a. Sedation confounds outcome prediction in cardiac arrest survivors treated with hypothermia. *Neurocrit. Care* 15, 113–119.
- Samaniego, E.A., Persoon, S., Wijman, C.A., 2011b. Prognosis after cardiac arrest and hypothermia: a new paradigm. *Curr. Neurol. Neurosci. Rep.* 11, 111–119.
- Sandroni, C., Cariou, A., Cavallaro, F., Cronberg, T., Friberg, H., Hoedemakers, C., Horn, J., Nolan, J.P., Rossetti, A.O., Soar, J., 2014. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European

- Resuscitation Council and the European Society of Intensive Care Medicine. *Intensive Care Med.* 40, 1816–1831.
- Sharshar, T., Citerio, G., Andrews, P.J., Chiaregato, A., Latronico, N., Menon, D.K., Puybasset, L., Sandroni, C., Stevens, R.D., 2014. Neurological examination of critically ill patients: a pragmatic approach, Report of an ESICM expert panel. *Intensive Care Med.* 40, 484–495.
- Sivaraju, A., Gilmore, E.J., Wira, C.R., Stevens, A., Rampal, N., Moeller, J.J., Greer, D.M., Hirsch, L.J., Gaspard, N., 2015. Prognostication of post-cardiac arrest coma: early clinical and electroencephalographic predictors of outcome. *Intensive Care Med.* 41, 1264–1272.
- Stecker, M.M., Cheung, A.T., Pochettino, A., Kent, G.P., Patterson, T., Weiss, S.J., Bavaria, J.E., 2001. Deep hypothermic circulatory arrest: I Effects of cooling on electroencephalogram and evoked potentials. *Ann. Thorac. Surg.* 71, 14–21.
- Thenayan, E.A., Savard, M., Sharpe, M.D., Norton, L., Young, B., 2010. Electroencephalogram for prognosis after cardiac arrest. *J. Crit. Care* 25, 300–304.
- Tsetsou, S., Novy, J., Oddo, M., Rossetti, A.O., 2015. EEG reactivity to pain in comatose patients: Importance of the stimulus type. *Resuscitation* 97, 34–37.
- Tsetsou, S., Oddo, M., Rossetti, A.O., 2013. Clinical outcome after a reactive hypothermic EEG following cardiac arrest. *Neurocrit. Care* 19, 283–286.
- Tzovara, A., Rossetti, A.O., Juan, E., Suys, T., Viceic, D., Rusca, M., Oddo, M., De Lucia, M., 2016. Prediction of awakening from hypothermic post anoxic coma based on auditory discrimination. *Ann. Neurol.* 79, 748–757.
- Tzovara, A., Rossetti, A.O., Spierer, L., Grivel, J., Murray, M.M., Oddo, M., De Lucia, M., 2013. Progression of auditory discrimination based on neural decoding predicts awakening from coma. *Brain* 136, 81–89.
- Westhall, E., Rosen, I., Rossetti, A.O., van Rootselaar, A.F., Wesenberg Kjaer, T., Friberg, H., Horn, J., Nielsen, N., Ullen, S., Cronberg, T., 2015. Interrater variability of EEG interpretation in comatose cardiac arrest patients. *Clin. Neurophysiol.* 126, 2397–2404.
- Westhall, E., Rundgren, M., Lilja, G., Friberg, H., Cronberg, T., 2013. Postanoxic status epilepticus can be identified and treatment guided successfully by continuous electroencephalography. *Ther. Hypothermia Temp. Manage.* 3, 84–87.
- Zanatta, P., Linassi, F., Mazzarolo, A.P., Arico, M., Bosco, E., Bendini, M., Sorbara, C., Ori, C., Carron, M., Scarpa, B., 2015. Pain-related Somato Sensory Evoked Potentials: a potential new tool to improve the prognostic prediction of coma after cardiac arrest. *Crit. Care* 19, 403.
- Zandbergen, E.G., Koelman, J.H., de Haan, R.J., Hijdra, A.P. ROPAC-Study Group, 2006. SSEPs and prognosis in postanoxic coma: only short or also long latency responses? *Neurology* 67, 583–586.