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Points of View

# Neurophysiology contributes to outcome prediction after cardiac arrest

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ABSTRACT

This "Points of View" paper discusses the role of neurophysiology in predicting outcome in patients who have initially survived a cardiac arrest but remain in coma. The authors, from different clinical backgrounds, discuss their individual approaches to neuroprognostication.

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## Introduction

In 1991 Salvatore Goodwin and colleagues asked the question "Is it time to use evoked potentials to predict outcome in comatose children and adults?" After much endeavor the answer now really seems an unequivocal 'yes', but with certain caveats. Yes but probably only in adults with hypoxic-ischemic brain injury after cardiac arrest (CA), where short latency somatosensory evoked potentials (SSEPs) have been shown to reliably predict poor outcome (Zandbergen et al., 1998, 2006; Robinson et al., 2003). Indeed such was the confidence that a Quality Standards Subcommittee of the American Academy of Neurology (AAN) recommended that "the assessment of poor prognosis can be guided by the bilateral absence of SSEPs (N20 response) within 1–3 days", which they believed to be the most valuable laboratory test at that time (Wijdicks et al., 2006). Over a decade later though there is still some confusion and lingering concern that SSEPs may be difficult to perform or interpret on the Intensive Care Unit (ICU), and may be confounded by newer standards of care such as sedation and therapeutic hypothermia (Horn and Tjepkema-Cloostermans, 2017). Indeed the landmark study of Wijdicks pointed out at the time that studies had not systematically addressed the role of these two confounders. Furthermore, case reports have worryingly identified a few comatose patients who have survived with bilater-

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ally absent SSEPs (N20 responses); although typically false positive predictions have occurred in children under 10 years, after traumatic brain injury, or in studies performed in the first 24–48 h of coma onset (for a review see Kane and Oware, 2015).

Clearly, there is foundation for the fear that an adverse test result will lead to premature withdrawal of life-sustaining treatment (WLST), thereby producing a 'self-fulfilling prophecy' of death. At the same time, there is concern amongst the general population of survival with a severe permanent brain injury, and in 1989 the AAN issued a statement that life-sustaining treatment "provides no benefit to patients in a persistent vegetative state" (American Academy of Neurology, 1989). We need to put in place guardrails against potential miscarriages of neurological prognosis, as the evidence now suggests that the commonest cause of death in these patients is the WLST itself (Sandroni and Taccone, 2016). Recently the European Resuscitation Council (ERC) and the European Society of Intensive Care Medicine (ESICM) issued guidelines for multimodal prognostication in comatose survivors of CA (Sandroni et al., 2014). Clinical signs can lack sensitivity, be unreliable and even overly pessimistic in the modern era of intensive care treatment, which includes use of sedation, neuromuscular blocking drugs and targeted temperature management. These authors therefore recommend that adequate time should be given for the return of consciousness and to avoid interference from the residual effects of sedation and/or neuromuscular blocking drugs (i.e. $\geq$72 h after return of spontaneous circulation, ROSC). Major confounders such as hypothermia, severe hypotension, hypoglycemia, intracerebral haemorrhage, and metabolic or respiratory derangements should be excluded. Absent or extensor motor response, bilateral absence of either pupillary and corneal reflexes or N20 wave of SSEP were identified, after 72 h post-ROSC, as the most robust predictors of a poor neurological outcome (defined as cerebral performance category (CPC) $\geq$3). Early status myoclonus epilepticus, elevated serum levels of neuron specific enolase (NSE), unreactive malignant EEG patterns after rewarming, and neuroimaging signs of post-anoxic brain injury were identified as useful but less robust predictors. Randomized blinded multicenter trials of these predictors may address our knowledge gaps and help to develop an outcome prediction algorithm, but would be difficult to perform logistically and also potentially unethical. These recommendations should therefore act as a clarion call for neurologists and clinical neurophysiologists to lead the robust independent electrophysiological assessment of adult comatose post CA patients. There is some indication that the critical care teams either do not fully appreciate the significance of the SSEP findings, or do not sufficiently use the test for other reasons (Robinson et al., 2016). Furthermore the actual decision-making process that connects neuroprognostication and WLST has received little attention (Geocadin et al., 2006). So the question now is not if, but how we should convey this information to our clinical colleagues managing this group of patients on the ICU. Dr. Kane and Professor Robinson are entirely agreed that a SSEP is the current gold standard of electrophysiological assessment, but differ in how this information should be assimilated and reported.

## 2. Dr Nick Kane's position

Outcome prediction ideally should not be performed in isolation with single measures, nor too soon after CA, in order to prevent inappropriate withdrawal of treatment; at the same time as preventing ongoing futile life support in a patient with absent SSEPs and/or EEG evidence of on-going intractable myoclonic status epilepticus. The patient's clinical history and neurological examination form the cornerstone of neuroprognostication but, as with laboratory tests, can have appreciable false negative and positive rates, such that they cannot be relied upon alone (Perman et al., 2012). Similarly co-morbidity, serological measures of blood glucose and pH, and body temperature are significantly associated with mortality, but should not be used as isolated indices in individuals when predicting likely outcome (Nolan et al., 2007).

Sandroni et al. (2013a,b) undertook a systematic review and meta-analysis of predictors of poor neurological outcome in adult comatose survivors of CA, either not treated (part 1, i.e. normothermic) or treated with induced hypothermia (part 2, i.e. cooled). Respectively, they found that the presence of myoclonus, absence of pupillary reflexes, bilateral absence of N20 SSEP, and low EEG voltage in the normothermic group (part 1); and bilateral absence of N20 SSEP, a non-reactive EEG after rewarming, or a combination of absent ocular (pupillary light and corneal) reflexes and motor score $\geq$2 after rewarming in the cooled group (part 2), to be the predictors with highest specificity and precision (i.e. 0% false positive rates). These authors point out the limitations of the published evidence, in particular the lack of blinding of the treating teams from test results with subsequent potential for self-fulfilling prophesies; but also the low quality, inconsistent timing of outcome measurements, lack of reproducibility and validation, with consequent risk of bias. In the absence of a single reliable indicator Taccone and fellow experts in the field (2014) eloquently outlined the rationale for and practical approach to a multimodal prognostic decision-making process; using neurological examination, electrophysiology (EEG and SSEPs), neuroimaging (MRI) and biomarkers (NSE and S-100β protein).

Whilst not discounting neuroimaging and biomarkers, the best available validated evidence currently points towards an electroclinical assessment. Such an approach was adopted by Rossetti et al. (2010) in a prospective study of 111 consecutive comatose survivors (>16 years of age) of CA treated with hypothermia; during which they also quantified the alarming false positive mortality predictions of three clinical variables (incomplete brainstem reflexes, myoclonus and absent motor response to pain). However, they found that the presence of at least 2 independent predictors out of 4 (incomplete brainstem reflexes, myoclonus, unreactive EEG and absent cortical SSEPs) accurately predicted poor long-term neurological recovery, with a positive predictive value of 1.00. A multicenter prospective cohort study of 391 adults using somewhat similar methodology, but no analysis of EEG, concluded that poor outcomes can be reliably predicted by testing brainstem reflexes and SSEPs at 72 h, but not the motor score or NSE (Bouwes et al., 2012). At the time of the landmark review of Wijdicks et al. (2006) there was insufficient evidence to recommend EEG for prognostication, but we now know that certain subcategories may be highly predictive of poor outcome, such as burst-suppression or low voltage EEG (Sivaraju et al., 2015).

A recent two-center prospective investigation of early continuous EEG recording in 277 consecutive comatose patients after CA treated with hypothermia, classified EEG as unfavorable (isoelectric, low voltage, burst-suppression with identical bursts), intermediate (evolving seizures, generalized periodic discharges, or burst-suppression without identical bursts) or favorable (continuous patterns) at 12, 24, 48 and 72 h, and dichotomized outcome as good or poor (Hofmeijer et al., 2015). They found that not only was an unfavorable EEG a good predictor of poor outcome, but also that favorable EEG patterns (i.e. continuous 'reactive' physiological rhythms) were strongly associated with good outcomes. The principal rationale for EEG recording after CA is to detect post-anoxic status epilepticus, which may be 'subtle' or even non-convulsive, potentially causing secondary neuronal injury and therefore requiring therapeutic management (Young, 2009). In a prospective study of 106 comatose CA adults treated with hypothermia, Legriel et al. (2013) identified 31% with post-anoxic status epilepticus, and

found it to be independently associated with a poor outcome, although not invariably fatal. A retrospective EEG analysis of 364 adult CA patients treated with targeted temperature management (TTM) also identified survivors with unfavorable or malignant EEG patterns (including generalized periodic discharges and burst suppression), some of which could be attributable to the effects of sedation (Amorim et al., 2015). These observations underscore the fact that EEG is sensitive to sedation and/or hypothermia, such that EEG alone cannot provide certainty of poor prognosis. Nonetheless EEG is the electrical output of the cerebral cortex, which is selectively vulnerable to hypoxic-ischemic brain injury, as well as the site of higher human cognitive functions. SSEPs on the other hand are a marker of the integrity of the dorsal column-lemniscal pathway and output predominantly of the primary somatosensory cortex, and thus together they provide complementary information that can help refine prognostic predictions. Both of these non-invasive tests can be performed at the patient bedside on ICU, with excellent safety profiles.

## 3. Prof. Larry Robinson's position

For the prediction of non-awakening from coma, we need exceedingly robust and reliable tests that can be easily communicated to our critical care colleagues. The bilateral absence of the N20 cortical response on median nerve somatosensory evoked potentials is an example of such a test. When a patient in coma after cardiac arrest has bilaterally absent responses, there is an exceedingly low chance that a patient will awaken, with an estimated false positive rate of <0.5% (Sandroni et al., 2014). Even with a very rare false positive result in these patients, the likelihood of a *good* outcome is still low. While we do not have much outcome information on the very rare patient who does awaken in the setting of *absent* responses, we do know that the majority of those who awaken with *abnormal* response remain in the severe disability category on the Glasgow outcome scale (Robinson et al., 2003) – still not a good outcome, even if they technically awaken.

Thus outcomes associated with absent N20 responses meet the definition of medical futility, which can be defined as <1% chance of a good outcome (Schneiderman et al., 1990), or the very low likelihood that physiologic benefits would results from treatment (Kasman, 2004). This should be sufficient information to discuss discontinuing life support with the family.

Of course, as Dr. Kane indicates, these tests need to be taken in a clinical context, which I believe they already are. First, the test is not usually ordered unless the patient is in coma due to a cardiac arrest, and the treating clinicians are concerned enough about a poor prognosis that they are considering having a discussion with the family about discontinuing life support. In fact, because of this pre-selection, just having the evoked potential team walk in the room establishes a high pre-test probability of a poor outcome. Even with a *normal* SSEP response in these patients, only about half will ultimately have an outcome better than severe disability on the Glasgow Outcome Scale (Robinson et al., 2003). Moreover, any subsequent decision-making based on the test results takes into account the most current patient status. We would not expect, for example, to see a replay of the Monty Python scene where clinicians are disconnecting life support from a patient who is telling them they are not comatose (Jones and Gilliam, 1975), no matter what the electrophysiological results might be.

Nevertheless, the recent Sandroni and Taccone (2016) article brings up 2 important questions that deal directly with how neurophysiologists can best support our critical care colleagues in treating their comatose patients after CA: (1) Do we somehow combine various tests, and (2) How do we communicate results?

Combining multiple tests such as clinical findings, SSEP, EEG, biochemical markers, imaging and other tests may be appealing, but it is not a simple matter. Typically, one would use a recursive partitioning approach (Strobl et al., 2009) – for example: if SSEPs are abnormal, and EEG shows myoclonus, and brainstem reflexes are absent, then the patient will not awaken. While it is appealing to try to combine results in this way, there are significant statistical challenges in doing so. First this approach does not work well for continuous variables. So, for example, one could dichotomize SSEP amplitudes as normal or abnormal, but one could not enter amplitude values in μV into the model. In addition, one needs much larger sample sizes of research subjects for acceptable reliability, so that we have sufficiently large samples of people with different outcomes on each test entered into the model. We would need several large studies that result in similar models, to achieve confidence in using such a model. Finally, there is the risk of "overfitting" the data. Overfitting occurs, particularly with complex models, when there are few patients compared to the number of parameters – these models then partially reflect random error or noise rather than underlying associations. Given these sources of unreliability, there are advantages of utilizing a single robust reliable test (presence or absence of the N20), rather than a more complex, but less reliable multi-modal model.

Communicating the results of testing to our critical care colleagues is another important challenge that raises a number of questions. Should we provide a percentage chance of awakening with 95% confidence intervals, based upon prior literature? Or should we provide qualitative statements? Given that patients and families have more frequent access to medical records, how will families interpret these statements? Will they hope or believe that their loved one will be the 0.1% exception to the rule?

In my setting in Toronto, this question generated considerable discussion and collaborative drafting of interpretative statements. Ultimately, the critical care team preferred qualitative statements, so that the conversation with the family could be couched in terms that are meaningful to the family. So, for example, our statement for absent responses is: "Bilaterally absent median SSEP responses were noted. In patients with hypoxic ischemic encephalopathy, bilaterally absent responses indicate a very poor prognosis (very high certainty of non-awakening or non-return of consciousness), including in the setting of targeted temperature management (therapeutic hypothermia)." For those with normal responses, but still in coma, we use "Normal SSEP study. In patients in coma for 72 h due to hypoxic ischemic encephalopathy, this indicates a moderate chance of awakening. Of those who awaken, a sizeable minority will have severe disability."

I believe the most critical aspect of this work may be to have ongoing discussions between critical care physicians and neurophysiologists, so there is a common understanding of the role that electrophysiology should play in outcome prediction. In my setting, it is preferred to use a simple and robust test followed by qualitative statements. But I encourage readers to engage in a meaningful discussion with critical care colleagues at their own institution to determine what works for their setting.

## 4. Dr. Nick Kane's response

Whilst I admire Professor Robinson's pragmatic 'single test' approach, in Bristol we have accepted the uncertainty around multimodal neuroprognostication, and feel that additional predictors can increase or decrease the confidence of predictions. We perform a combined electrophysiological (EEG and SSEP) assessment $\geq$72 h after ROSC, when the patient has been returned to normothermia and ideally with a little sedation as humanely possible. As in Toronto, we typically use qualitative descriptions when

communicating with our ICU colleagues but avoid certitude; we aim to 'triage' into either poor neurological prognosis (bilateral absent N20s and a malignant EEG pattern), indeterminate prognosis (if N20 is uni- or bilaterally present and the EEG a malignant or intermediate pattern), or favorable neurological prognosis (N20s present bilaterally and a continuous EEG pattern with some normal voltage physiological oscillations ± reactivity to external stimulation). Nevertheless even with the most favorable electrophysiological picture the mortality is ~50%, in part due to cardiac death and/or a decision to WLST on other grounds. The drawback of this approach is that about a third of our patients have an indeterminate electrophysiological prognostic prediction, which may delay decision-making, although other clinical and investigative findings may be instructive. However, this informed approach allows a more open collaborative dialogue and shared decision-making with the patient's relatives, which is followed by a 24 h 'cooling-off' period before WLST.

## 5. Prof. Larry Robinson's response

Dr. Kane brings up some good points and, as he points out, unfortunately the prognosis is generally unfavorable for this patient group as a whole. It would be interesting, as we accumulate more data over time, to have an approach in which we have a pre-test probability of awakening that is then moved up or down using odds ratios as we do each test. We, and our critical care colleagues, likely already do this clinically, in our minds, in a qualitative fashion as we review each test and serially examine the patient. I don't believe we have the data yet, but perhaps, at some point in the future, we could move this to a quantitative approach.

## 6. Comment from Professor Jerry Nolan

My intensive care colleagues and I implemented locally the ERC-ESICM guidelines on prognostication in comatose survivors of cardiac arrest soon after their publication in 2014 (Sandroni et al., 2014). Data from several centres around the world indicate that WLST decisions in comatose post-cardiac arrest patients have been made far too early (Elmer et al., 2016; Paul et al., 2016). Although recent data from the UK show that the time to WLST decisions in these patients is lengthening, such decisions are made at less than 2 days after admission to an intensive care unit (ICU) in 25% of cases (Nolan et al., 2016).

Having adopted the ERC-ESICM prognostication guidelines we have implemented multimodal prognostication. After 24 h of TTM at 36 °C (changed from 33 °C following the TTM study (Nielsen et al., 2013) we rewarm the patient slowly to 37 °C and then stop all sedative drugs (typically propofol and alfentanil). Patients undergo daily clinical neurological examination and serum NSE values are measured at 24, 48 and 72 h. During this time, if there is any clinical evidence of seizures we request an EEG and start anticonvulsant treatment as appropriate.

Post-cardiac arrest patients who remain comatose and have a Glasgow Motor Score of 1 or 2 at 72 after ROSC will enter the ERC-ESICM algorithm (Sandroni et al., 2014). At this time, the combination of no pupillary light reflex (PLR) and corneal reflexes (CR) indicates a poor neurological outcome (CPC 3–5) with a false positive rate of 0% (95% CI 0–8%), but the sensitivity is just 15% (95% CI 7–26%), indicating that the majority of patients who will eventually have a poor outcome will not display the combination of absent PLR and CRs (Bisschops et al., 2011). For this reason, assuming we have allowed sufficient time for sedative drugs to clear (we generally allow at least 24 h after infusing propofol and alfentanil), we would usually request an EEG and SSEPs at 72 h in those post-cardiac arrest patients who remain comatose. If N20 responses are reported to be absent bilaterally, we would discuss with the patient's relatives, involve a second intensive care consultant, and usually decide to WLST. However, in most cases the SSEPs are present and we would then wait at least another 24 h and evaluate the qualitative report on the EEG provided by Dr. Kane. This report would form just one of several prognostication tests that we evaluate and, as indicated by the ERC-ESICM algorithm, if two or more of these tests indicated a likely poor outcome we would decide to WLST. We would repeat the clinical examination looking for any evidence of neurological improvement. Many patients admitted to the ICU would have received a brain computed tomography (CT) scan just before admission (to rule out an intracranial cause of cardiac arrest) but, in any case, a patient remaining comatose after 3 days would generally have a repeat CT brain scan. Obvious loss of grey-white differentiation would suggest a poor prognosis but in our experience radiologists usually provide only a subjective evaluation of the grey-white differentiation and do not provide an objective measurement of the grey matter to white matter ratio (Lee et al., 2015). We would also evaluate the serum NSE values measured at 24, 48 and 72 h (Stammet et al., 2015; Streitberger et al., 2017). The ERC-ESICM guidelines do not recommend a specific NSE threshold for prediction of a poor outcome but a recent study of over 1000 patients indicates that, a value of 90 μg/L in the first three days after ROSC was associated with 'almost' no false positives (Streitberger et al., 2017). Increasing serum NSE values between 24 and 48 h may also be associated with a poor prognosis (Stammet et al., 2015) although this has been challenged recently (Wiberg et al., 2017). By assimilating the data obtained from clinical examination, neurophysiological tests, biomarkers and imaging we would discuss with the intensive care team and with the patient's relatives and decide to either WLST or continue intensive care treatment and re-evaluate daily.

In my view, this multimodal approach has improved the confidence of clinicians in making prognostication decisions but there also objective data indicating that this strategy improves the accuracy of prognostication in post-cardiac arrest patients (Youn et al., 2016). Significant challenges remain and in my experience one of the most common and problematic is the patient with hypoxic-ischaemic brain injury and intractable status epilepticus. The seizures are often resistant to treatment, despite multiple anti-epileptic drugs, and we now know that although most will have a poor outcome, some have a good outcome despite status myoclonus (Seder et al., 2015; Reynolds and Claassen, 2017).

## Conflict of interest statement

Dr. Kane and Professor Robinson have no conflict of interest, financial or otherwise, to declare. Professor Nolan is Chair of the European Resuscitation Council and is a co-author of the ERC-ESICM guidelines on prognostication in comatose survivors of cardiac arrest.

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