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Contemporary Approach to Neurologic Prognostication of Coma After Cardiac Arrest

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Coma after cardiac arrest (CA) is an important cause of admission to the ICU. Prognosis of post-CA coma has significantly improved over the past decade, particularly because of aggressive postresuscitation care and the use of therapeutic targeted temperature management (TTM). TTM and sedatives used to maintain controlled cooling might delay neurologic reflexes and reduce the accuracy of clinical examination. In the early ICU phase, patients' good recovery may often be indistinguishable (based on neurologic examination alone) from patients who eventually will have a poor prognosis. Prognostication of post-CA coma, therefore, has evolved toward a multimodal approach that combines neurologic examination with EEG and evoked potentials. Blood biomarkers (eg, neuron-specific enolase [NSE] and soluble 100-β protein) are useful complements for coma prognostication; however, results vary among commercial laboratory assays, and applying one single cutoff level (eg, >33 μg/L for NSE) for poor prognostication is not recommended. Neuroimaging, mainly diffusion MRI, is emerging as a promising tool for prognostication, but its precise role needs further study before it can be widely used. This multimodal approach might reduce false-positive rates of poor prognosis, thereby providing optimal prognostication of comatose CA survivors. The aim of this review is to summarize studies and the principal tools presently available for outcome prediction and to describe a practical approach to the multimodal prognostication of coma after CA, with a particular focus on neuromonitoring tools. We also propose an algorithm for the optimal use of such multimodal tools during the early ICU phase of post-CA coma.

CHEST 2014; 146(5):1375-1386

ABBREVIATIONS: BIS = bispectral index; CA = cardiac arrest; CPC = Cerebral Performance Category; FPR = false-positive rate; MMN = mismatch negativity; NSE = neuron-specific enolase; S-100B = soluble 100-β protein; SSEP = somatosensory evoked potential; TTM = targeted temperature management

Coma after cardiac arrest (CA) is an important cause of ICU admission for acute brain injury. Over the past decade, the number of patients who survive a coma after CA has increased significantly.[1] Two major factors have contributed to outcome improvement: postresuscitation care (ie, the number of general supportive measures, including early coronary reperfusion, fluid resuscitation, adequate cerebral and systemic perfusion pressure, controlled sedation, glycemic control, that help to

Manuscript received March 3, 2014; revision accepted June 2, 2014.

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FUNDING/SUPPORT: This study was supported by the Swiss National Science Foundation through research grants to Drs Oddo [Grant 320030_138191] and Rossetti [Grant CR32I3_143780].

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DOI: 10.1378/chest.14-0523

protect a postanoxic brain against so-called secondary cerebral damage)[2] and the introduction[3,4] and clinical implementation[5,6] of targeted temperature management (TTM) with the use of induced cooling. According to the most recent studies, approximately 50% of patients experiencing coma after CA and treated with TTM survive with good long-term neurologic recovery.[7] Notwithstanding the recent controversy about the exact target temperature to adopt in this context (33°C vs 36°C),[7] TTM exerts significant neuroprotection and remains a mainstay of therapy for postanoxic coma.[8]

Despite these important advancements, at least one-half of patients will eventually have a poor prognosis. In the early phase following CA (approximately 72 h), and partly because of sedation and TTM, it is not always easy to clearly distinguish based on clinical examination alone patients with persistent coma who will have a poor prognosis from those who are transiently comatose but might subsequently awaken and eventually have a good recovery.[9] Adequate prognostication of neurologic outcome in the early phase following CA is, therefore, of great importance, particularly because it allows for targeting therapy intensity and appropriate allocation of resources.[10] Prognostication of patients with acute brain injury is a difficult task for clinicians and nurses involved in the care process as well as for family and society, who may be left with the potential burden of a long-term neurologic deficit. A major challenge is to reduce the uncertainty about outcome prediction. A new paradigm is being increasingly adopted that has switched from a standard approach primarily based on neurologic examination[11] to a more advanced multimodal approach that combines clinical examination with a series of additional tools, including EEG, evoked potentials, blood biomarkers, and neuroimaging, aimed at more precisely quantifying the severity of postanoxic brain damage and improving the accuracy of outcome prediction.

The aim of this review is to summarize the principal tools presently available for outcome prediction and to describe a practical approach to the multimodal prognostication of coma after CA, with a particular focus on neuromonitoring tools. We also propose an algorithm for the optimal use of such multimodal tools during the early ICU phase of postanoxic coma.

Available Tools for Coma Prognostication After CA

Outcome Assessment

Accuracy of coma prognostication can be defined as the false-positive rate (FPR = 1-specificity) to predict poor prognosis. The perfect prognosticator is one with 100% specificity that yields an FPR of 0 for poor prognosis. According to the Glasgow-Pittsburgh Cerebral Performance Categories (CPCs),[12] poor prognosis includes CPC 3 (severe disability, dependent in daily life activities), CPC 4 (persistent vegetative state), or CPC 5 (death). Good prognosis comprises CPC 1 (full recovery) and CPC 2 (moderate disability, allowing to return home and to be independent in daily life activities).

Neurologic Examination

Neurologic examination remains the first-line approach to initially assessing prognosis of comatose patients in general. In unconscious patients after CA, lack of motor response to painful stimulation better than extension (motor component of Glasgow coma scale ≤ 2) and absence of brain stem reflexes (including pupillary, corneal, and oculocephalic reactivity) at 72 h are classically associated with poor prognosis.[11]

Effect of Sedation and Hypothermia on Motor Response and Brain Stem Reflexes: Induced hypothermia reduces cytochrome P450-mediated clearance of the sedative and analgesic agents (eg, midazolam, fentanyl) commonly used during TTM.[13] In addition, some patients may have altered renal and hepatic function, which may further delay drug clearance. The combined effect of TTM and controlled sedation alters neurologic examination and may particularly delay reaction to painful stimuli,[14-16] thereby rendering clinical examination alone, particularly motor response (see next), less reliable and insufficiently accurate to predict prognosis in the early phase of coma after CA.

In a recent meta-analysis of 10 studies in patients treated with TTM to 33°C to 34°C after CA, Kamps et al[17] found that a motor response ≤ 2 on the Glasgow coma scale at 72 h (n = 811 patients) had an unacceptably high FPR of 21% on average (95% CI, 8%-43%). Brain stem responses had better accuracy, but absent corneal reflexes (n = 429 patients) yielded an average FPR of 2%. Bilaterally absent pupillary reactivity was available in 566 patients and had the lowest FPR to predict poor outcome. Brain stem and pupillary reflexes were performed at 48 to 72 h after CA in these studies.

Electrophysiologic Examinations

EEG: The utility of EEG in postanoxic coma is to help to improve accuracy of coma prognostication and to detect postanoxic status epilepticus.

Coma Prognostication: Using the dynamic response of the EEG background to nociceptive or auditory stimuli, EEG has been used for more than two decades to predict outcome of postanoxic coma.[18] With this approach, it is possible to analyze changes in amplitude and frequency of the EEG background and to distinguish between two main patterns: (1) reactive (ie, acceleration or slowing of the EEG recording upon a nociceptive or auditory stimulation) (Fig 1) vs (2) nonreactive (ie, no change of the EEG recording upon a nociceptive or auditory stimulation) (Fig 2). It is important to note that the lack of standardized tools to assess EEG reactivity (intensity of pain and the exact sites where to apply painful stimulation as well as the amount of sedation used) may affect reactivity. Therefore, EEG should be performed at least at two time points—during TTM and after TTM—in normothermic conditions and off sedation.

Additional spontaneous EEG findings are associated with poor prognosis, mainly a pattern of discontinuous EEG background (ie, $<$ 50% of the trace is suppressed) or of so-called spontaneous burst suppression (ie, $>$ 50% of the recording is suppressed)[19] (Fig 3). Growing clinical evidence from several single-center prospective studies has demonstrated that EEG performed after return to normothermia significantly improves the accuracy of coma prognostication after CA, particularly in patients treated with TTM.[14,15,20-24] On the basis of these studies, continuous and reactive EEG background is associated with good prognosis; conversely, discontinuous, unreactive EEG has a very high specificity for poor prognosis (with an FPR close to 0%).

Postanoxic Status Epilepticus: Postanoxic status epilepticus occurs in about one-third of comatose patients after CA and is generally considered a sign of poor prognosis.[25-29] EEG epileptic patterns or the occurrence of generalized periodic epileptiform discharges (Fig 4) are markers of diffuse severe postanoxic brain damage. When observed early during TTM and sedation (which both have intrinsic antiepileptic properties), such early seizures are almost 100% predictive of poor prognosis.[30] However, seizures do not necessarily correlate with bad outcome. Several studies observed that survival with good neurologic recovery is possible in a particular subset of patients who have late seizures (ie, after the rewarming phase following TTM and off sedation) and display favorable clinical (presence of brain stem reflexes) and electrophysiologic (continuous, reactive EEG background; preserved cortical somatosensory evoked potentials [SSEPs]) signs.[26,31,32] The underlying pathophysiology of these types of seizures is not completely understood and warrants further investigation. Interestingly, Rossetti et al[33] found no correlation between levels of neuron-specific enolase (NSE), a marker of neuronal injury, and postanoxic seizures. Seizures may be nonconvulsive (ie, only detectable on EEG) or convulsive, including myoclonus. Several forms of post-CA myoclonus exist, and there is still some confusion about precise terminology. It is important to distinguish myoclonic seizures and status epilepticus (myoclonus + EEG seizures) from reticular status myoclonus (myoclonus without EEG seizures, implying that the cerebral cortex is too impaired to generate electrographic epileptiform discharges). Reticular status myoclonus is a sign of severe global cortical and subcortical damage and is associated with early death.[31,32] Not all myoclonus is associated with poor neurologic outcome, and it is very difficult, if not impossible, to differentiate the various forms of myoclonus in such way to be certain that myoclonus is associated with poor recovery. Clinicians must be aware that acute postanoxic myoclonus is not necessarily a sign of no recovery in that the FPR of early myoclonus varies from 3%[15] to 10%[34] up to 12% according to the Prognosis after Postanoxic Coma II (PROPAC II) study.[35]

EEG Timing and Type of Monitoring: Early seizures during the first 12 to 24 h of TTM are almost invariably associated with an ominous prognosis. Furthermore, with respect to prognostication, too early a diagnosis ($<$ 12 h) of reactive vs nonreactive background may lead to false prognostication.[30] Whether to use intermittent vs continuous EEG monitoring is still a debated issue.[36] We found that standard intermittent EEG is comparable to continuous EEG for both prognostication (EEG reactivity) and seizure detection.[30] This finding has an important practical implication, especially for centers where EEG resources are limited. Repeated EEG, including testing of background reactivity, performed at least at two definite time points (eg, during TTM and after TTM, early following the rewarming phase and off sedation) represents a good compromise. Finally, although simplified four- to nine-channel EEG may be suitable for coma prognostication in adult patients,[22,23] it is not recommended for the detection of postanoxic seizures, where standard 19- to 21-channel EEG is preferred.[36]

Simplified EEG with the use of bispectral index (BIS) monitoring has also been studied as an alternative to standard EEG for coma prognostication after CA.[37,38] A BIS $>$ 45 at 24 h from CA provides a 63% sensitivity and 86% specificity for good prognosis.[39] These

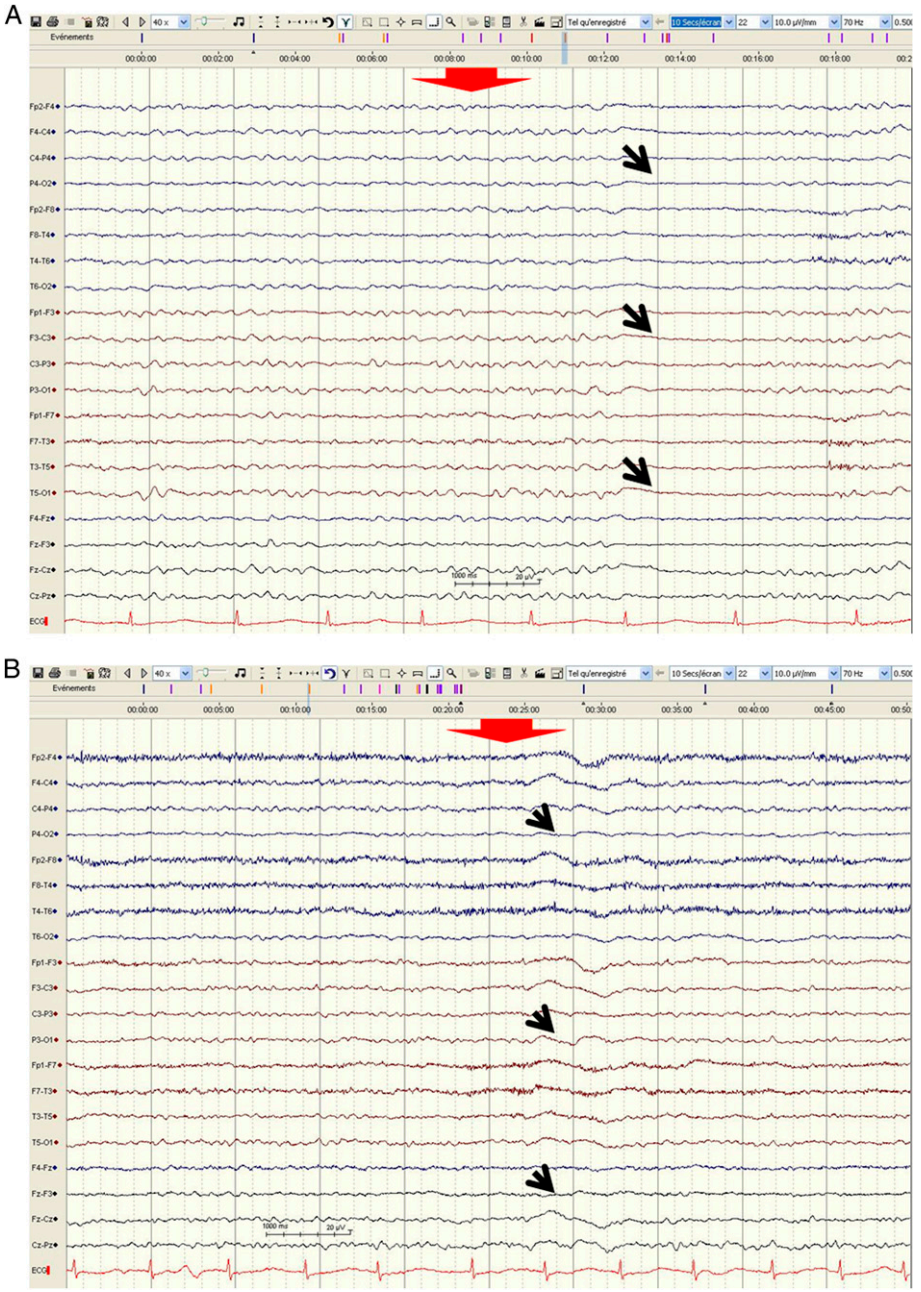

Figure 1 – *EEG showing a reactive background. Example of one illustrative comatose patient after cardiac arrest who will eventually have a good prognosis. A, Auditory stimulations (red arrow) during mild induced hypothermia and sedation show a diffuse attenuation (flattening) and acceleration of the EEG background (black arrows). B, After rewarming, in normothermic conditions and off sedation, transient diffuse EEG slowing (black arrows) is observed when calling the patient. Bipolar longitudinal montage, 10 μV/mm, 30 mm/s.*

methods, however, are not widely used, and further independent assessments are required before routine implementation of BIS monitoring.

Somatosensory Evoked Potentials: SSEPs involve the stimulation of bilateral median nerves and the recording of a cortical response, called the N20 peak. Examples of a normal and an abnormal (bilaterally absent) N20 response are illustrated in Figure 5. A bilaterally absent N20 response on SSEP is a robust predictor of poor prognosis. The predictive value of SSEP has been confirmed by several studies performed in patients treated with TTM.[14,15,40,41] Apart from exceptional cases,[42] bilateral absence of the N20 component at 48 to 72 h after CA is invariably associated with irreversible coma and poor prognosis. Two systematic reviews confirmed the value of SSEP in predicting poor prognosis after CA,[17,43] where bilateral absence of N20 response

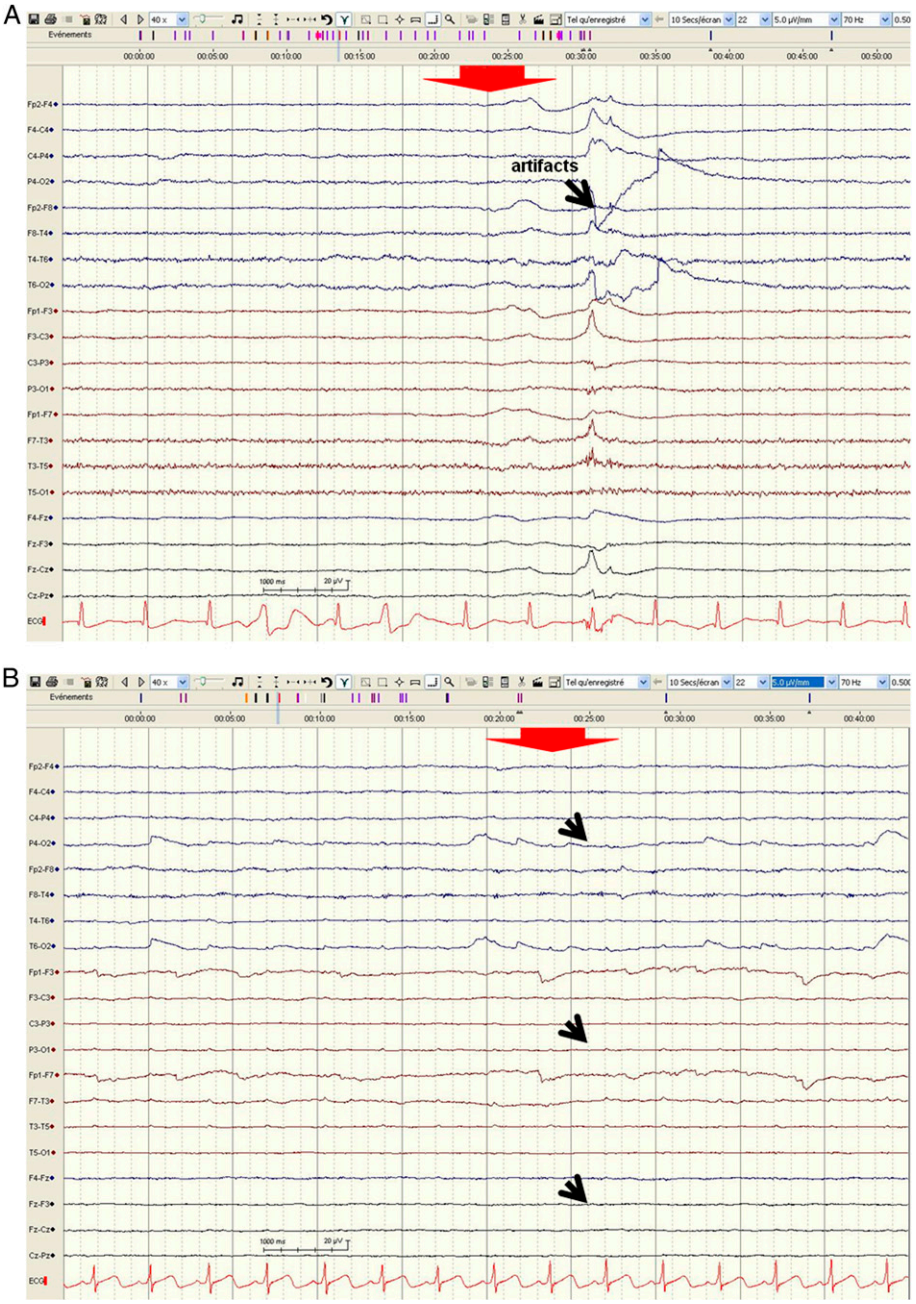

Figure 2 – *EEG showing nonreactive background. Example of one illustrative comatose patient after cardiac arrest who will eventually die. A and B, Painful stimulations to the chest (red arrow) during mild induced hypothermia and sedation (A) and in normothermic conditions after rewarming and off sedation (B) show the absence of a notable change in the EEG background apart from movement artifacts. Bipolar longitudinal montage, 5 μV/mm, 30 mm/s.*

had 100% specificity of poor prognosis (FPR of 0%). Similar to EEG reactivity,[30] SSEP N20 response does not appear to be influenced by mild hypothermic conditions.[41,44]

Blood Biomarkers

In the setting of post-CA coma, levels of NSE and soluble 100-β protein (S-100B) in patient serum have been the most widely studied markers.

Neuron-Specific Enolase: NSE is an intracellular enzyme present in neurons and other cells of neuroectodermal origin. It is a marker of neuronal injury, with an estimated half-life of approximately 24 h. Serum NSE levels are strongly correlated to the severity of cerebral damage after CA as assessed by postmortem brain autopsy[45] and appear to be the biomarker with highest prognostic value after CA and TTM.[46,47] Before the TTM era, serum NSE levels $>$ 33 μg/L 24 to 72 h after CA was

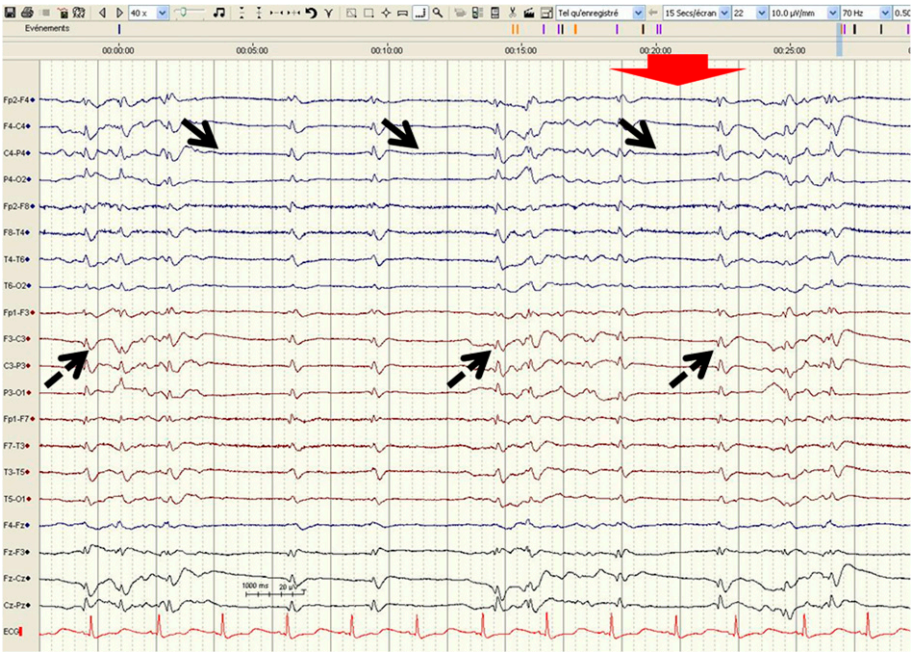

Figure 3 – *EEG showing spontaneous burst-suppression background with superimposed middle-voltage generalized periodic discharges. At 48 h following cardiac arrest, after rewarming from therapeutic hypothermia, and in normothermic conditions, a diffusely suppressed (flat) background (solid black arrows) alternates with irregular, diffuse electrical activity intermixed with generalized spikes (dashed black arrows). The EEG background shows no reactivity to auditory stimuli (red arrow). The patient had a poor outcome. Bipolar longitudinal montage, 10 μV/mm, 30 mm/s.*

strongly, although not invariably, associated with poor prognosis.[11,48] In patients treated with TTM, however, several studies have shown that applying one single cut-off level (> 33 μg/L in this specific setting) may be misleading. Much higher cutoff serum NSE values than 33 μg/L were necessary to reach an FPR of 0% in patients treated with TTM, with levels as high as 78.9 μg/L to predict a poor outcome with a specificity of 100%.[33,40,46,49,50] For example, in a cohort of 61 consecutive comatose patients after CA treated with TTM, we

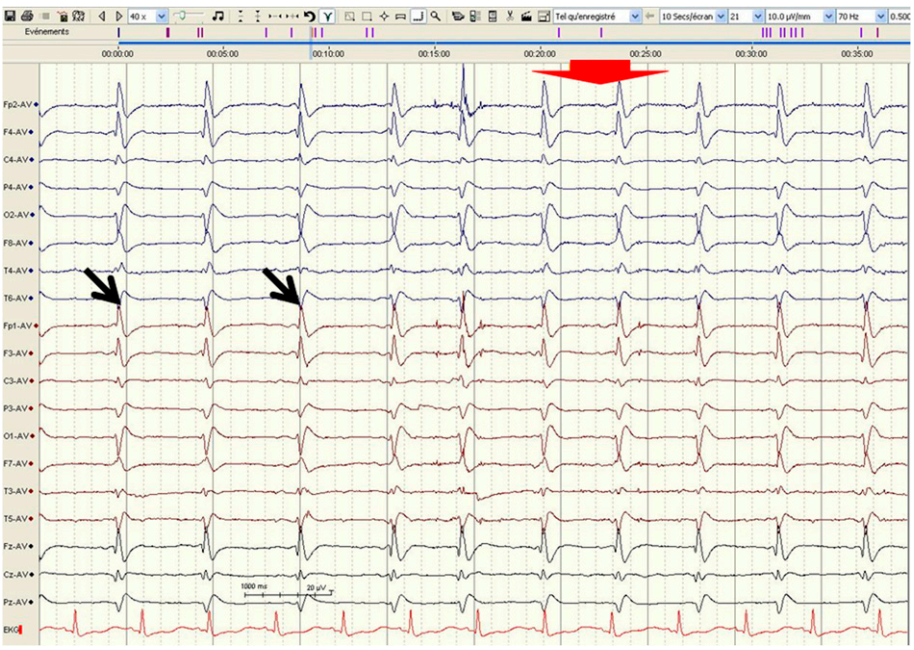

Figure 4 – *EEG showing generalized, high-voltage generalized periodic discharges. At 48 h after cardiac arrest, after rewarming from therapeutic hypothermia, and in normothermic conditions, generalized spikes occurring nearly every second (black arrows) are observed on a diffusely suppressed (flat) background unreactive to sound stimulation (red arrow). The patient did not recover. Bipolar longitudinal montage, 10 μV/mm, 30 mm/s.*

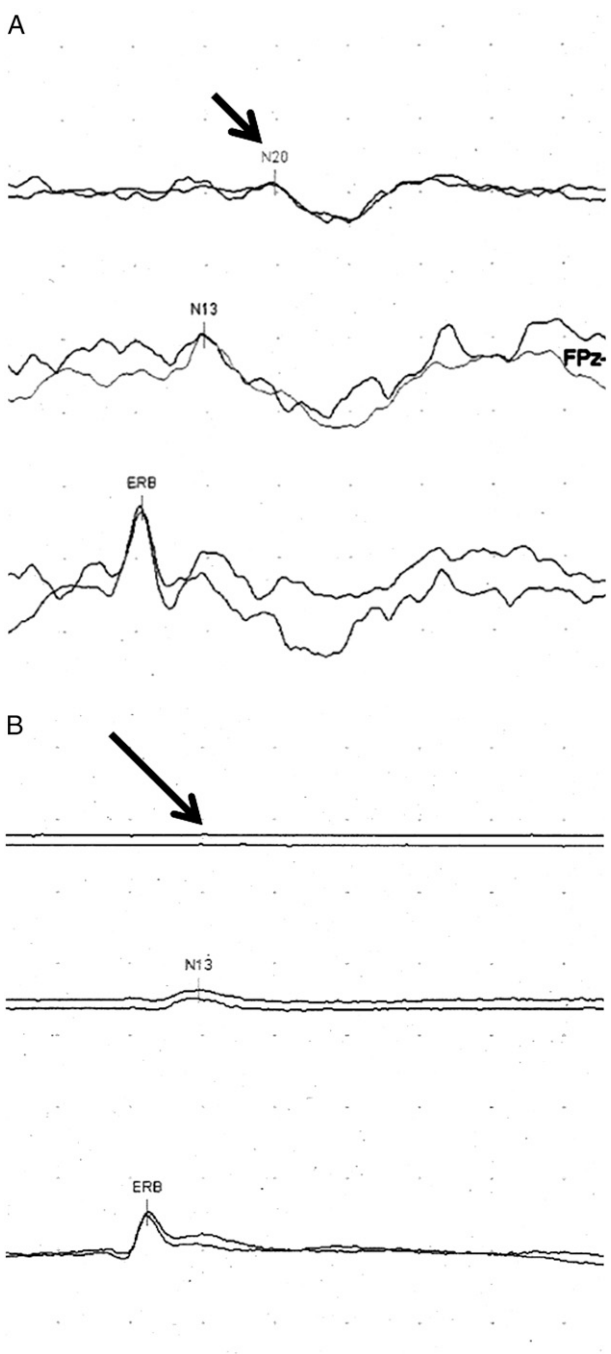

Figure 5 – *Somatosensory evoked potentials from two comatose patients after cardiac arrest recorded in normothermic conditions. A and B, The bottom lines show the electrical response after median nerve stimulation at the brachial plexus (ERB point), the middle lines show the upper cervical region (N13), and the upper lines show the contralateral parietal region (N20). Shown are examples of the presence (A), with arrow pointing to an upward and then downward deflection, and absence (B), with arrow pointing to a flat line, of N20 cortical response. FPz = frontopolar zero.*

found five who survived (three had a good neurologic recovery) despite peak serum NSE levels > 33 μg/L at 48 to 72 h.[33] Methodologic and sampling issues are important. Differences in the cutoff values for NSE levels may be due to the timing of blood sampling. Indeed, some authors considered a cutoff NSE level of > 57 μg/L 72 h after CA (specificity, 100%; sensitivity, 47%),[51] whereas others tested a cutoff of > 151 μg/L at 48 h (specificity, 100%; sensitivity, 23%).[52] Finally, variability in NSE values depends on the laboratory assay used and the way samples are transported (mainly that hemolysis may falsely elevate NSE levels).[49]

Soluble 100-β Protein: S-100B is a calcium-binding protein present in high concentration in astroglial cells. Elevated S-100B level is associated with brain cell apoptosis and worsening postanoxic brain injury.[53] Peak serum levels usually are observed during the first 24 h after CA; thus, S-100B levels may help to define prognosis earlier than NSE levels.[54] In studies prior to the TTM era, the level of S-100B 24 h after CA was significantly higher in patients with poor outcome. The best cutoff value was ≥ 0.5 μg/L, which yielded a specificity of 100% and a sensitivity of 75%.[55] In patients treated with TTM, an S-100B level of > 0.5 μg/L at 24 h had a specificity of 96% and a sensitivity of 62% for poor outcome.[56]

In a systematic review of 24 studies evaluating the prognostic value of NSE and S-100B, only five involved uniform application of a blood sampling schedule, with sampling intervals specified based on a set starting point.[57] Specificity, however, was not 100%, and it was difficult to assess the cutoff values and predictive accuracy for both biomarkers. At present, NSE or S-100B should not be used alone to decide withdrawal of therapy.

MRI

Few data are available regarding CT scan as a prognostic tool for coma after CA, but its prognostic value seems limited so far.[58] CT scan should only be used to rule out cerebral causes of CA (eg, hemorrhages).[59] With respect to coma prognostication, MRI appears to be the most promising tool to assess the severity of hypoxic-ischemic encephalopathy.[60] Diffusion-weighted imaging with the use of apparent diffusion coefficient maps is superior to conventional MRI in predicting prognosis and has been studied particularly in comatose patients post-CA treated with TTM.[61-64] Spatial and temporal differences in apparent diffusion coefficients may provide insight into mechanisms of hypoxic-ischemic brain injury and, hence, recovery.[62,64,65] Diffusion MRI provides high specificity (95%-100%) for poor prognosis; however, sensitivity seems to be generally very low (25%-30%).[63,66]

The ideal time window for prognostication using diffusion MRI is approximately 5 days after CA. In a comparison of MRI in this time window with neurologic examination at 3 days, diffusion MRI improved the sensitivity for predicting poor outcome by 38% while maintaining 100% specificity.[63] MRI is evolving as a tool for coma prognostication in CA survivors. Recent studies demonstrated the great potential of MRI by using cluster-based computerized image analysis.[67] Based on the available data, however, the quality of evidence is still insufficient to presently recommend MRI as a standard tool for prognostication of post-CA coma.[58]

Multimodality

The use of a multimodal approach for coma prognostication (ie, combining clinical examination with electrophysiology and biomarkers) has been widely recommended by reviews, meta-analyses, and guidelines.[1,9,43,59,68] This approach is supported by a number of clinical studies demonstrating that the combination of several prognosticators significantly improves the accuracy of outcome prediction. In a multicenter Dutch study of 391 patients treated with TTM, the combination of neurologic examination with SSEP and NSE yielded a very low FPR for poor prognosis within 72 h.[40] In a recent cohort study of 134 patients treated with TTM at our institution, the combination of neurologic examination with EEG reactivity and NSE provided the highest accuracy (area under the receiver operating characteristic curve, 0.89) for coma prognostication at 48 h.[34] Whether to use SSEP or EEG probably depends on local availability and expertise, but there is undoubtedly a growing body of evidence demonstrating that electrophysiologic tools warrant ICU implementation to optimize coma prognostication after CA. The added value of biomarkers such as NSE has also been demonstrated in these studies. A study by Kim et al[69] showed that when combining diffusion MRI with serum NSE, MRI-based predictions identified an additional five patients with poor outcome out of 14 with 48-h NSE levels <78.9 μg/L, further supporting the use of a multimodal approach for the prognostication of comatose patients after CA.

The Issue of Time: How Long Should We Wait to Prognosticate?

Time delay in coma prognostication and potential withdrawal of intensive care is an important issue. Guidelines generally recommend at least 72 h after CA before making decisions.[1,11] We believe that this time is arbitrary. In some circumstances, 72 h after CA may not be enough because of delayed coma, residual sedation, or the appearance of late seizures after rewarming. Based on a multimodal approach for coma prognostication, the presence of favorable signs will determine interventions. For example, the presence of EEG reactivity (even during TTM) indicates that the patient has a relatively high chance of regaining consciousness; therefore, continuation of intensive therapy is warranted beyond 72 h. On the contrary, absence of EEG reactivity and SSEP after return of normothermia can trigger treatment withdrawal within 72 h. Ultimately, the best strategy is the integration of various signs (clinical examination, EEG, SSEP, blood biomarkers) into a multimodal approach (Fig 6). This might mean that for some patients, more time is needed, and if doubts about prognostication persist, some additional days of observation and transfer to facilities that can provide full electrophysiologic examinations are indicated.

Future Perspectives and Challenges

Improving the Prediction of Good Recovery

Automated EEG Analysis: An important limitation of the present approach and of many prognosticators (including neurologic examination, SSEP, NSE, and MRI) is that they are generally very good in predicting poor prognosis (ie, they have high specificity) but they are insufficient in predicting which comatose patient will have good recovery. For example, absent pupillary reactivity and bilaterally absent N20 on SSEP have very high accuracy in predicting poor prognosis, but when they are present, their accuracy in predicting awakening with good recovery is no more than 50%.[17] For patients in such a gray zone of uncertain prognosis, this group repeatedly found that the presence of EEG background reactivity is approximately 80% to 85% predictive of good recovery in the early phase (24-48 h, even during TTM) after CA.[15,34,70] Adequate identification of EEG reactivity, however, lacks a standardized approach. The use of automated analysis of EEG background reactivity is promising and has been shown to be as accurate as the visual analysis of EEG.[71]

Auditory Evoked Potentials: Evoked potentials measure changes in neuronal activity induced by sensory stimuli and record the automated, early cortical response to somatosensory or auditory stimulation.[72] They may also record the active reaction of the cortex to these stimuli (ie, cognitive evoked potentials, including the mismatch negativity [MMN]).[73] The MMN is a component of the event-related potential to a deviant

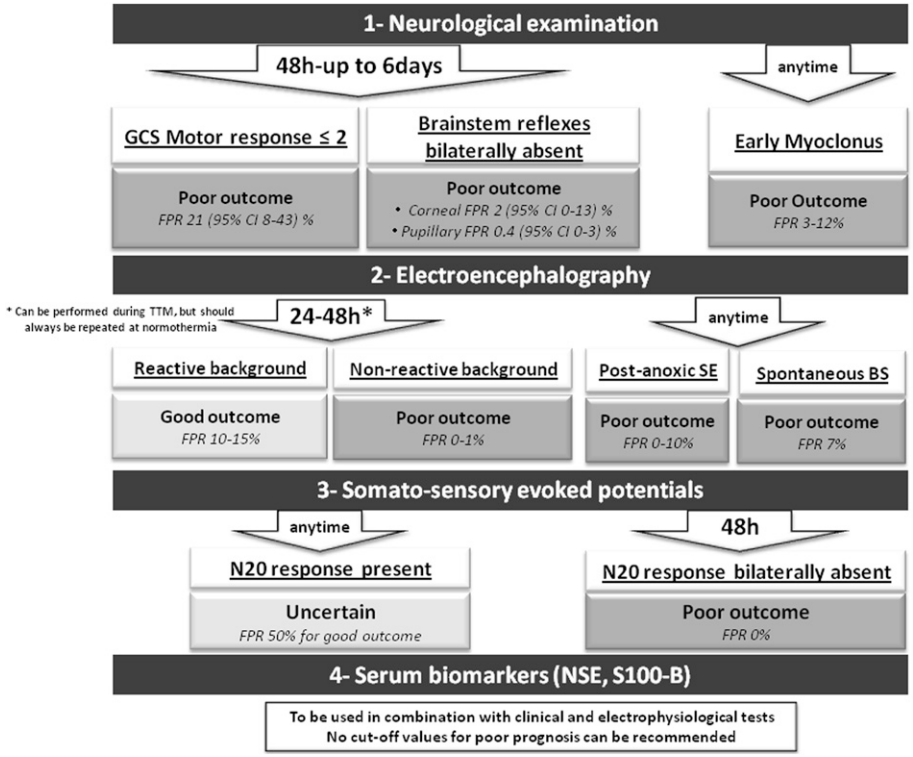

Figure 6 – *Practical algorithm for coma prognostication after cardiac arrest in adult patients treated with TTM. Clinical examination is the first step for coma prognostication, but the FPR for poor prognosis is > 0%, particularly for motor response. EEG and somatosensory evoked potential (SSEP) (used alone or in combination, depending on local availability and expertise) are essential to improve prognostic accuracy. A nonreactive EEG background and bilaterally absent N20 cortical response on SSEP both have very low FPR (close to 0) for poor prognosis. A continuous, reactive EEG background also has a high specificity (80%-85%) for good neurologic recovery. Blood biomarkers (NSE or S100-B) are useful complements to prognostication. BS = burst suppression; FPR = false-positive rate; GCS = Glasgow coma scale; NSE = neuron-specific enolase; S100-B = soluble 100-β protein; SE = status epilepticus; TTM = targeted temperature management.*

stimulus in a sequence of standard stimuli. In the case of auditory stimuli, the MMN occurs after an infrequent change in a repetitive sequence of sounds. The deviant sound can differ from the standards in one or more perceptual features, such as pitch, duration, and loudness. Fischer et al[74] measured MMN in comatose patients after CA not treated with TTM. When performed after the acute period (on average at 10 days from CA), all patients in whom MMN was present awoke (100% specificity). MMN was superior to SSEP for the prediction of awakening and had the best specificity and positive predictive value for good recovery. This group recently focused on the prognostic value of MMN in the early phase of acute coma (< 72 h) while using automated EEG analysis of auditory discrimination in 30 comatose patients after CA treated with TTM.[75] Evoked potentials were performed at two time points. We observed that all patients who displayed a progression of auditory discrimination between the first (TTM period, 33°C, < 24 h from CA) and the second (post-TTM period, 37°C, 48 h from CA) EEG recording awoke and had a good recovery (100% specificity for good prognosis). These findings are promising and suggest that automated EEG analysis might have a great potential for accurately predicting awakening from postanoxic coma in the early ICU phase.

Potential Biomarkers of the Future

The field of biomarkers of acute brain injury is evolving. Over recent years, many potential candidates have been identified, which can be sampled from both blood and cerebrospinal fluid and may help to quantify the extent of brain damage in several acute cerebral conditions.[76] In comatose patients after CA, plasma neurofilament heavy chain is an interesting molecule with potential in prognostication.[77] Other brain biomarkers such as serum glial fibrillary acidic protein, brain-derived neurotrophic factor, and tau protein are also promising,[78-80] but more data are needed before these can be introduced in clinical practice. Neurofilament heavy chain or total tau-protein sampling from cerebrospinal fluid may further improve coma prognostication after CA[81] but at the expense of added invasiveness and increased risk of complications (eg, bleeding), particularly in patients with cardiac causes of CA who receive antiplatelet agents or anticoagulants. Finally, ischemia-reperfusion syndrome after CA shares some of the pathophysiologic mechanisms of the sepsis syndrome,[82] and several studies have found early elevation (within 48 h) of serum procalcitonin (a marker of sepsis syndrome severity) to be associated with mortality after CA and TTM.[83-86]

Conclusions

Prognostication of coma after CA in the era of TTM requires a multimodal approach. Clinical examination remains the first step. TTM and sedation used for early neuroprotection in comatose patients after CA alter neurologic reflexes and might delay recovery of motor responses up to 5 to 6 days. In this setting, neurologic examination alone may become less reliable in the early ICU phase. Reactivity on EEG to painful and auditory stimulation and N20 response on SSEP are not significantly influenced by TTM and sedation and in combination with clinical examination, significantly improve prognostic accuracy. Serum biomarkers, mainly NSE and S-100B, are helpful for outcome assessment. Levels of both biomarkers, however, are influenced by TTM, and no single cutoff provides sufficient prognostic accuracy; therefore, these parameters are only useful in combination with clinical examination and electrophysiologic tools. Diffusion-weighted MRI may provide further insight into the mechanisms of hypoxic-ischemic encephalopathy and could be an additional prognostic tool, especially in predicting long-term neurologic deficits among CA survivors. Automated EEG analysis of background reactivity and auditory evoked potentials hold great promise in identifying patients in the early ICU phase who will have a favorable recovery from postanoxic coma.

Acknowledgments

Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

References

1. Peberdy MA, Callaway CW, Neumar RW, et al; American Heart Association. Part 9: post-cardiac arrest care: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2010;122(18)(suppl 3): S768-S786.
2. Nolan JP, Soar J. Postresuscitation care: entering a new era. *Curr Opin Crit Care*. 2010;16(3):216-222.
3. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002;346(8):557-563.
4. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. 2002;346(8):549-556.
5. Bouwes A, Kuiper MA, Hijdra A, Horn J. Induced hypothermia and determination of neurological outcome after CPR in ICUs in the Netherlands: results of a survey. *Resuscitation*. 2010;81(4):393-397.
6. Oddo M, Schaller MD, Feihl F, Ribordy V, Liaudet L. From evidence to clinical practice: effective implementation of therapeutic hypothermia to improve patient outcome after cardiac arrest. *Crit Care Med*. 2006;34(7):1865-1873.
7. Nielsen N, Wetterslev J, Cronberg T, et al; TTM Trial Investigators. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med*. 2013;369(23):2197-2206.
8. Rittenberger JC, Callaway CW. Temperature management and modern post-cardiac arrest care. *N Engl J Med*. 2013;369(23): 2262-2263.
9. Cronberg T, Brizzi M, Liedholm LJ, et al. Neurological prognostication after cardiac arrest–recommendations from the Swedish Resuscitation Council. *Resuscitation*. 2013;84(7):867-872.
10. Kurz MC. For whom the bell tolls…. *Resuscitation*. 2011;82(11): 1371-1372.
11. Wijdicks EF, Hijdra A, Young GB, Bassetti CL, Wiebe S; Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2006;67(2): 203-210.
12. Phelps R, Dumas F, Maynard C, Silver J, Rea T. Cerebral Performance Category and long-term prognosis following out-of-hospital cardiac arrest. *Crit Care Med*. 2013;41(5):1252-1257.
13. Tortorici MA, Kochanek PM, Poloyac SM. Effects of hypothermia on drug disposition, metabolism, and response: a focus of hypothermia-mediated alterations on the cytochrome P450 enzyme system. *Crit Care Med*. 2007;35(9):2196-2204.
14. Fugate JE, Wijdicks EF, Mandrekar J, et al. Predictors of neurologic outcome in hypothermia after cardiac arrest. *Ann Neurol*. 2010; 68(6):907-914.
15. Rossetti AO, Oddo M, Logroscino G, Kaplan PW. Prognostication after cardiac arrest and hypothermia: a prospective study. *Ann Neurol*. 2010;67(3):301-307.
16. Samaniego EA, Mlynash M, Caulfield AF, Eyngorn I, Wijman CA. Sedation confounds outcome prediction in cardiac arrest survivors treated with hypothermia. *Neurocrit Care*. 2011;15(1):113-119.
17. Kamps MJ, Horn J, Oddo M, et al. Prognostication of neurologic outcome in cardiac arrest patients after mild therapeutic hypothermia: a meta-analysis of the current literature. *Intensive Care Med*. 2013;39(10):1671-1682.
18. Synek VM. Value of a revised EEG coma scale for prognosis after cerebral anoxia and diffuse head injury. *Clin Electroencephalogr*. 1990;21(1):25-30.
19. Hirsch LJ, LaRoche SM, Gaspard N, et al. American Clinical Neurophysiology Society's standardized critical care EEG terminology: 2012 version. *J Clin Neurophysiol*. 2013;30(1):1-27.
20. Cloostermans MC, van Meulen FB, Eertman CJ, Hom HW, van Putten MJ. Continuous electroencephalography monitoring for early prediction of neurological outcome in postanoxic patients after cardiac arrest: a prospective cohort study. *Crit Care Med*. 2012;40(10):2867-2875.
21. Crepeau AZ, Rabinstein AA, Fugate JE, et al. Continuous EEG in therapeutic hypothermia after cardiac arrest: prognostic and clinical value. *Neurology*. 2013;80(4):339-344.
22. Rundgren M, Rosén I, Friberg H. Amplitude-integrated EEG (aEEG) predicts outcome after cardiac arrest and induced hypothermia. *Intensive Care Med*. 2006;32(6):836-842.
23. Rundgren M, Westhall E, Cronberg T, Rosén I, Friberg H. Continuous amplitude-integrated electroencephalogram predicts outcome in hypothermia-treated cardiac arrest patients. *Crit Care Med*. 2010;38(9):1838-1844.
24. Thenayan EA, Savard M, Sharpe MD, Norton L, Young B. Electroencephalogram for prognosis after cardiac arrest. *J Crit Care*. 2010; 25(2):300-304.
25. Legriel S, Bruneel F, Sediri H, et al. Early EEG monitoring for detecting postanoxic status epilepticus during therapeutic hypothermia: a pilot study. *Neurocrit Care*. 2009;11(3):338-344.
26. Legriel S, Hilly-Ginoux J, Resche-Rigon M, et al. Prognostic value of electrographic postanoxic status epilepticus in comatose cardiac-arrest survivors in the therapeutic hypothermia era. *Resuscitation*. 2013;84(3):343-350.
27. Nielsen N, Sunde K, Hovdenes J, et al; Hypothermia Network. Adverse events and their relation to mortality in out-of-hospital

cardiac arrest patients treated with therapeutic hypothermia. *Crit Care Med*. 2011;39(1):57-64.

28. Rittenberger JC, Popescu A, Brenner RP, Guyette FX, Callaway CW. Frequency and timing of nonconvulsive status epilepticus in comatose post-cardiac arrest subjects treated with hypothermia. *Neurocrit Care*. 2012;16(1):114-122.
29. Rossetti AO, Logroscino G, Liaudet L, et al. Status epilepticus: an independent outcome predictor after cerebral anoxia. *Neurology*. 2007;69(3):255-260.
30. Alvarez V, Sierra-Marcos A, Oddo M, Rossetti AO. Yield of intermittent versus continuous EEG in comatose survivors of cardiac arrest treated with hypothermia. *Crit Care*. 2013;17(5):R190.
31. Lucas JM, Cocchi MN, Salciccioli J, et al. Neurologic recovery after therapeutic hypothermia in patients with post-cardiac arrest myoclonus. *Resuscitation*. 2012;83(2):265-269.
32. Rossetti AO, Oddo M, Liaudet L, Kaplan PW. Predictors of awakening from postanoxic status epilepticus after therapeutic hypothermia. *Neurology*. 2009;72(8):744-749.
33. Rossetti AO, Carrera E, Oddo M. Early EEG correlates of neuronal injury after brain anoxia. *Neurology*. 2012;78(11):796-802.
34. Oddo M, Rossetti AO. Early multimodal outcome prediction after cardiac arrest in patients treated with hypothermia. *Crit Care Med*. 2014;42(6):1340-1347.
35. Bouwes A, van Poppelen D, Koelman JH, et al. Acute posthypoxic myoclonus after cardiopulmonary resuscitation. *BMC Neurol*. 2012;12:63.
36. Claassen J, Taccone FS, Horn P, Holtkamp M, Stocchetti N, Oddo M; Neurointensive Care Section of the European Society of Intensive Care Medicine. Recommendations on the use of EEG monitoring in critically ill patients: consensus statement from the neurointensive care section of the ESICM. *Intensive Care Med*. 2013;39(8): 1337-1351.
37. Riker RR, Stone PC Jr, May T, McCrum B, Fraser GL, Seder D. Initial bispectral index may identify patients who will awaken during therapeutic hypothermia after cardiac arrest: a retrospective pilot study. *Resuscitation*. 2013;84(6):794-797.
38. Seder DB, Fraser GL, Robbins T, Libby L, Riker RR. The bispectral index and suppression ratio are very early predictors of neurological outcome during therapeutic hypothermia after cardiac arrest. *Intensive Care Med*. 2010;36(2):281-288.
39. Leary M, Fried DA, Gaieski DF, et al. Neurologic prognostication and bispectral index monitoring after resuscitation from cardiac arrest. *Resuscitation*. 2010;81(9):1133-1137.
40. Bouwes A, Binnekade JM, Kuiper MA, et al. Prognosis of coma after therapeutic hypothermia: a prospective cohort study. *Ann Neurol*. 2012;71(2):206-212.
41. Bouwes A, Binnekade JM, Zandstra DF, et al. Somatosensory evoked potentials during mild hypothermia after cardiopulmonary resuscitation. *Neurology*. 2009;73(18):1457-1461.
42. Leithner C, Ploner CJ, Hasper D, Storm C. Does hypothermia influence the predictive value of bilateral absent N20 after cardiac arrest? *Neurology*. 2010;74(12):965-969.
43. Sandroni C, Cavallaro F, Callaway CW, et al. Predictors of poor neurological outcome in adult comatose survivors of cardiac arrest: a systematic review and meta-analysis. Part 1: patients not treated with therapeutic hypothermia. *Resuscitation*. 2013;84(10): 1310-1323.
44. Tiainen M, Kovala TT, Takkunen OS, Roine RO. Somatosensory and brainstem auditory evoked potentials in cardiac arrest patients treated with hypothermia. *Crit Care Med*. 2005;33(8):1736-1740.
45. Bjorklund E, Lindberg E, Rundgren M, Cronberg T, Friberg H, Englund E. Ischaemic brain damage after cardiac arrest and induced hypothermia–a systematic description of selective eosinophilic neuronal death. A neuropathologic study of 23 patients. *Resuscitation*. 2014;85(4):527-532.
46. Cronberg T, Rundgren M, Westhall E, et al. Neuron-specific enolase correlates with other prognostic markers after cardiac arrest. *Neurology*. 2011;77(7):623-630.
47. Oksanen T, Tiainen M, Skrifvars MB, et al. Predictive power of serum NSE and OHCA score regarding 6-month neurologic outcome after out-of-hospital ventricular fibrillation and therapeutic hypothermia. *Resuscitation*. 2009;80(2):165-170.
48. Zandbergen EG, Hijdra A, Koelman JH, et al; PROPAC Study Group. Prediction of poor outcome within the first 3 days of postanoxic coma. *Neurology*. 2006;66(1):62-68.
49. Mlynash M, Buckwalter MS, Okada A, et al. Serum neuron-specific enolase levels from the same patients differ between laboratories: assessment of a prospective post-cardiac arrest cohort. *Neurocrit Care*. 2013;19(2):161-166.
50. Steffen IG, Hasper D, Ploner CJ, et al. Mild therapeutic hypothermia alters neuron specific enolase as an outcome predictor after resuscitation: 97 prospective hypothermia patients compared to 133 historical non-hypothermia patients. *Crit Care*. 2010;14(2):R69.
51. Storm C, Nee J, Jörres A, Leithner C, Hasper D, Ploner CJ. Serial measurement of neuron specific enolase improves prognostication in cardiac arrest patients treated with hypothermia: a prospective study. *Scand J Trauma Resusc Emerg Med*. 2012;20:6.
52. Zellner T, Gärtner R, Schopohl J, Angstwurm M. NSE and S-100B are not sufficiently predictive of neurologic outcome after therapeutic hypothermia for cardiac arrest. *Resuscitation*. 2013;84(10):1382-1386.
53. Böttiger BW, Möbes S, Glätzer R, et al. Astroglial protein S-100 is an early and sensitive marker of hypoxic brain damage and outcome after cardiac arrest in humans. *Circulation*. 2001;103(22):2694-2698.
54. Shinozaki K, Oda S, Sadahiro T, et al. Serum S-100B is superior to neuron-specific enolase as an early prognostic biomarker for neurological outcome following cardiopulmonary resuscitation. *Resuscitation*. 2009;80(8):870-875.
55. Zingler VC, Krumm B, Bertsch T, Fassbender K, Pohlmann-Eden B. Early prediction of neurological outcome after cardiopulmonary resuscitation: a multimodal approach combining neurobiochemical and electrophysiological investigations may provide high prognostic certainty in patients after cardiac arrest. *Eur Neurol*. 2003;49(2):79-84.
56. Rundgren M, Karlsson T, Nielsen N, Cronberg T, Johnsson P, Friberg H. Neuron specific enolase and S-100B as predictors of outcome after cardiac arrest and induced hypothermia. *Resuscitation*. 2009;80(7):784-789.
57. Shinozaki K, Oda S, Sadahiro T, et al. S-100B and neuron-specific enolase as predictors of neurological outcome in patients after cardiac arrest and return of spontaneous circulation: a systematic review. *Crit Care*. 2009;13(4):R121.
58. Hahn DK, Geocadin RG, Greer DM. Quality of evidence in studies evaluating neuroimaging for neurologic prognostication in adult patients resuscitated from cardiac arrest. *Resuscitation*. 2014;85(2): 165-172.
59. Taccone FS, Cronberg T, Friberg H, et al. How to assess prognosis after cardiac arrest and therapeutic hypothermia. *Crit Care*. 2014;18(1):202.
60. Els T, Kassubek J, Kubalek R, Klisch J. Diffusion-weighted MRI during early global cerebral hypoxia: a predictor for clinical outcome? *Acta Neurol Scand*. 2004;110(6):361-367.
61. Choi SP, Park KN, Park HK, et al. Diffusion-weighted magnetic resonance imaging for predicting the clinical outcome of comatose survivors after cardiac arrest: a cohort study. *Crit Care*. 2010; 14(1):R17.
62. Mlynash M, Campbell DM, Leproust EM, et al. Temporal and spatial profile of brain diffusion-weighted MRI after cardiac arrest. *Stroke*. 2010;41(8):1665-1672.
63. Wijman CA, Mlynash M, Caulfield AF, et al. Prognostic value of brain diffusion-weighted imaging after cardiac arrest. *Ann Neurol*. 2009;65(4):394-402.
64. Wu O, Sorensen AG, Benner T, Singhal AB, Furie KL, Greer DM. Comatose patients with cardiac arrest: predicting clinical outcome with diffusion-weighted MR imaging. *Radiology*. 2009;252(1): 173-181.
65. Greer D, Scripko P, Bartscher J, et al. Clinical MRI interpretation for outcome prediction in cardiac arrest. *Neurocrit Care*. 2012;17(2):240-244.
66. Greer DM, Scripko PD, Wu O, et al. Hippocampal magnetic resonance imaging abnormalities in cardiac arrest are associated with poor outcome. *J Stroke Cerebrovasc Dis*. 2013;22(7):899-905.

67. Kim J, Kim K, Hong S, et al. Low apparent diffusion coefficient cluster-based analysis of diffusion-weighted MRI for prognostication of out-of-hospital cardiac arrest survivors. *Resuscitation*. 2013; 84(10):1393-1399.

68. Oddo M, Rossetti AO. Predicting neurological outcome after cardiac arrest. *Curr Opin Crit Care*. 2011;17(3):254-259.

69. Kim J, Choi BS, Kim K, et al. Prognostic performance of diffusion-weighted MRI combined with NSE in comatose cardiac arrest survivors treated with mild hypothermia. *Neurocrit Care*. 2012;17(3):412-420.

70. Rossetti AO, Urbano LA, Delodder F, Kaplan PW, Oddo M. Prognostic value of continuous EEG monitoring during therapeutic hypothermia after cardiac arrest. *Crit Care*. 2010;14(5):R173.

71. Noirhomme Q, Lehembre R, Lugo ZdelR, et al. Automated analysis of background EEG and reactivity during therapeutic hypothermia in comatose patients after cardiac arrest. *Clin EEG Neurosci*. 2014; 45(1):6-13.

72. Vanhaudenhuyse A, Laureys S, Perrin F. Cognitive event-related potentials in comatose and post-comatose states. *Neurocrit Care*. 2008;8(2):262-270.

73. Duncan CC, Barry RJ, Connolly JF, et al. Event-related potentials in clinical research: guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. *Clin Neurophysiol*. 2009;120(11):1883-1908.

74. Fischer C, Luauté J, Némoz C, Morlet D, Kirkorian G, Mauguière F. Improved prediction of awakening or nonawakening from severe anoxic coma using tree-based classification analysis. *Crit Care Med*. 2006;34(5):1520-1524.

75. Tzovara A, Rossetti AO, Spierer L, et al. Progression of auditory discrimination based on neural decoding predicts awakening from coma. *Brain*. 2013;136(pt 1):81-89.

76. Zetterberg H, Smith DH, Blennow K. Biomarkers of mild traumatic brain injury in cerebrospinal fluid and blood. *Nat Rev Neurol*. 2013;9(4):201-210.

77. Rundgren M, Friberg H, Cronberg T, Romner B, Petzold A. Serial soluble neurofilament heavy chain in plasma as a marker of brain injury after cardiac arrest. *Crit Care*. 2012;16(2):R45.

78. Kaneko T, Kasaoka S, Miyauchi T, et al. Serum glial fibrillary acidic protein as a predictive biomarker of neurological outcome after cardiac arrest. *Resuscitation*. 2009;80(7):790-794.

79. Mörtberg E, Zetterberg H, Nordmark J, et al. Plasma tau protein in comatose patients after cardiac arrest treated with therapeutic hypothermia. *Acta Anaesthesiol Scand*. 2011;55(9):1132-1138.

80. Mörtberg E, Zetterberg H, Nordmark J, Blennow K, Rosengren L, Rubertsson S. S-100B is superior to NSE, BDNF and GFAP in predicting outcome of resuscitation from cardiac arrest with hypothermia treatment. *Resuscitation*. 2011;82(1):26-31.

81. Rosén C, Rosén H, Andreasson U, et al. Cerebrospinal fluid biomarkers in cardiac arrest survivors. *Resuscitation*. 2014;85(2): 227-232.

82. Adrie C, Laurent I, Monchi M, Cariou A, Dhainaou JF, Spaulding C. Postresuscitation disease after cardiac arrest: a sepsis-like syndrome? *Curr Opin Crit Care*. 2004;10(3):208-212.

83. Annborn M, Dankiewicz J, Erlinge D, et al. Procalcitonin after cardiac arrest - an indicator of severity of illness, ischemia-reperfusion injury and outcome. *Resuscitation*. 2013;84(6):782-787.

84. Engel H, Ben Hamouda N, Portmann K, et al. Serum procalcitonin as a marker of post-cardiac arrest syndrome and long-term neurological recovery, but not of early-onset infections, in comatose post-anoxic patients treated with therapeutic hypothermia. *Resuscitation*. 2013;84(6):776-781.

85. Hayashida H, Kaneko T, Kasaoka S, et al. Comparison of the predictability of neurological outcome by serum procalcitonin and glial fibrillary acidic protein in postcardiac-arrest patients. *Neurocrit Care*. 2010;12(2):252-257.

86. Stammet P, Devaux Y, Azuaje F, et al. Assessment of procalcitonin to predict outcome in hypothermia-treated patients after cardiac arrest. *Crit Care Res Pract*. 2011;2011:631062.