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Neuroprotective strategies and neuroprognostication after cardiac arrest

Fabio Silvio Taccone, MD, PhD, Associate Professor *, Ilaria Alice Crippa, MD, Fellow in Anesthesiology and Intensive Care, Antonio Maria Dell'Anna, MD, Fellow in Anesthesiology and Intensive Care, Sabino Scolletta, MD, Associate Professor

Department of Intensive Care, Erasme Hospital, Université Libre de Bruxelles (ULB), Route de Lennik 808, 1070 Brussels, Belgium

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Neurocognitive disturbances are common among survivors of cardiac arrest (CA). Although initial management of CA, including bystander cardiopulmonary resuscitation, optimal chest compression, and early defibrillation, has been implemented continuously over the last years, few therapeutic interventions are available to minimize or attenuate the extent of brain injury occurring after the return of spontaneous circulation. In this review, we discuss several promising drugs that could provide some potential benefits for neurological recovery after CA. Most of these drugs have been investigated exclusively in experimental CA models and only limited clinical data are available. Further research, which also considers combined neuroprotective strategies that target multiple pathways involved in the pathophysiology of postanoxic brain injury, is certainly needed to demonstrate the effectiveness of these interventions in this setting. Moreover, the evaluation of neurological prognosis of comatose patients after CA remains an important challenge that requires the accurate use of several tools. As most patients with CA are currently treated with targeted temperature management (TTM), combined with sedative drug therapy, especially during the hypothermic phase, the reliability of neurological examination in evaluating these patients is delayed to 72–96 h after admission. Thus, additional tests,

* Corresponding author. Tel.: +32 25555587; Fax: +32 25554698.
E-mail address: ftaccone@ulb.ac.be (F.S. Taccone).

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including electrophysiological examinations, brain imaging and biomarkers, have been largely implemented to evaluate earlier the extent of brain damage in these patients.

Introduction

Cardiac arrest (CA) is a common event, affecting >350,000 individuals in the United States and 275,000 in Europe every year [1,2]. Despite improvements in short- and long-term survival rates and neurological outcomes over the recent years [3,4], sudden CA remains an important cause of morbidity and mortality, representing the third leading cause of death in the United States [5].

The overall outcome has largely improved over the years due to better emergency care, including early and correctly administered cardiopulmonary resuscitation (CPR), bystander CPR, early defibrillation for shockable rhythms, and wider implementation of post-resuscitation care bundles [6,7]. Nevertheless, persistent postanoxic coma remains the leading cause of death among those who survived CA [8]. In particular, the occurrence of hypoxic–ischemic encephalopathy (HIE) after CA was recently integrated in the so-called "post-resuscitation syndrome", which is characterized by post-anoxic brain injury, cardiovascular impairment, and a systemic inflammatory response following the ischemia/reperfusion process [9], potentially contributing to enhanced HIE.

Clinicians must consider two important issues when managing a patient with HIE. First, the pathogenesis of HIE is complex and multifactorial (Fig. 1), making it unlikely that one therapy alone will effectively prevent or "cure" this complication. Different interventions have been evaluated in experimental models and clinical trials in this setting, although the results have been disappointing or difficult to interpret. Second, the assessment of neurological recovery in such patients is challenging, and a reliable and early method for predicting the outcome in those who remain comatose is warranted.

Thus, the aim of this review is to describe the therapies that can potentially attenuate brain injury and promote neurological recovery in comatose survivors of CA, in particular different promising drugs that are currently undergoing early clinical testing. In addition, we discuss how multimodal neurological monitoring should be used to assess the prognosis in this patient population.

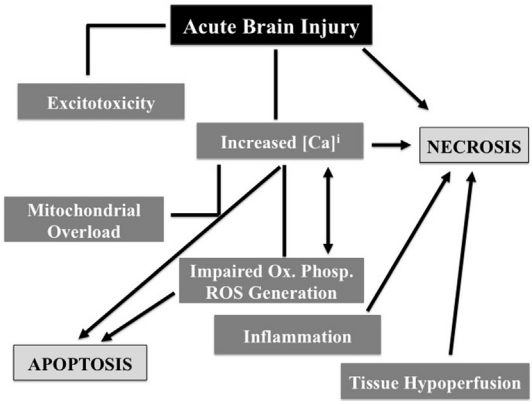

Fig. 1. A schematic summary of the main mechanisms implicated in postanoxic brain injury. Ox. Phosp. = oxidative phosphorylation; $[Ca]^i$ = intracellular calcium concentrations.

General neuroprotection

Various insults can aggravate the initial postanoxic brain damage, and preventing or minimizing such insults represents a form of brain protection. In the setting of HIE, brain injury can be enhanced by excessive oxygen administration, which may potentially increase the reperfusion injury or significantly reduce the carbon dioxide or arterial pressure levels, resulting in brain hypoperfusion, whereas disturbances in glucose concentrations and seizure occurrence can produce significant changes in brain metabolism and alterations in cell function [10].

Neuroprotective drugs

Over the past few years, there has been increasing interest in alternative strategies that could promote brain protection immediately after return of spontaneous circulation (ROSC). Among the tested interventions, inhaled noble gases, nitric oxide, erythropoietin (EPO), magnesium, calcium antagonists, steroids, and cyclosporine have shown promising applications (Fig. 2).

Noble gases

Noble gases, particularly xenon and argon, are known to have some neuroprotective effects in vitro by the attenuation of glutamate-induced cerebral damage and by activating the γ-amino butyric acid (GABA) receptors; further, they have been tested in animal models of CA [11,12]. A combination of oxygen and xenon as an inhaled mixture has been shown to reduce the extent of neurological damage after ischemia due to CA [13]. In a porcine model of CA, Fries et al. randomized pigs to receive targeted temperature management (TTM) or TTM plus inhaled oxygen and xenon (FiXe = 70%, FiO_2 = 30%). Xenon-treated animals had significantly improved functional neurological recovery and reduced myocardial dysfunction [14]. Arola et al. performed a similar comparison in humans, randomizing patients surviving out-of-hospital CA (OHCA) to receive either TTM (target temperature of 33 °C) or TTM plus inhaled xenon. The authors reported improved cardiovascular function in the xenon group, with no adverse effects; unfortunately, the neurological outcomes were not assessed in this study [15].

Argon has also been tested as a cheaper alternative to xenon. One hour after successful CPR, Brucken et al. randomized Sprague–Dawley rats to ventilation with 30% oxygen plus 70% argon ($n = 7$) or 30% oxygen alone ($n = 7$). Argon-treated animals showed a significant reduction in histopathological damage of the neocortex and hippocampus, and a marked improvement in functional neurological

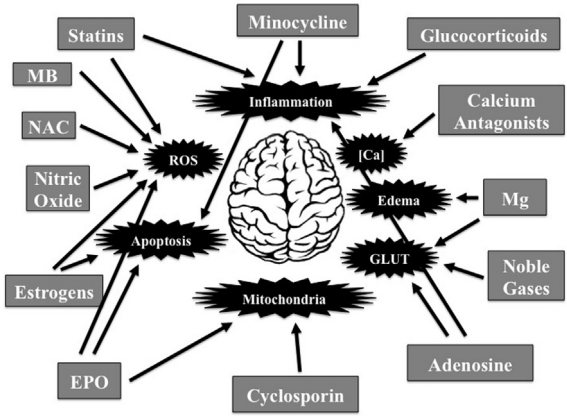

Fig. 2. A summary of potential neuroprotective interventions for postanoxic brain injury and their respective targets. GLUT = glutamate; [Ca] = intracellular calcium; ROS = reactive oxygen species; Mg = magnesium; MB = methylene blue; NAC = N-acetyl cysteine; EPO = erythropoietin.

recovery [16]. Similarly, in a porcine model of CA due to acute myocardial infarction after occlusion of the left anterior descending coronary artery [17], animals that received argon and oxygen ventilation had a better neurological outcome at 72 h (neurological alertness score: 100 vs. 79, $p < 0.01$; neurological deficit: 0 vs. 29, $p < 0.05$) than controls did. The serum levels of neuron-specific enolase (NSE), a biomarker of postanoxic brain injury, did not increase significantly in the argon group and histological brain injury was less extensive. In another study, Brucken et al. [18] investigated whether a delayed administration of argon (70% at different time points after ROSC) would still provide some neuroprotective effects in a murine model of CA. The authors found that argon-treated animals showed a significant improvement in the neurological deficit and a reduction in cortical brain damage when compared with controls, even when argon administration was delayed for 3 h after arrest.

Nitric oxide

Nitric oxide (NO) inhibits reactive oxygen species (ROS)-producing enzymes and directly scavenges ROS, thus potentially reducing the extent of postanoxic injury. The effects of NO are mediated via the soluble guanylate cyclase (sGC)—cyclic guanosine monophosphate (cGMP) pathway and other complex intracellular pathways [19]. Other potentially beneficial effects of NO are direct vasodilation of the coronary arteries, which could improve cardiac function in this setting. Experimental models have suggested a protective role of NO in cardiac and neurological function after CA [20,21]. To limit the systemic hypotension induced by NO, inhaled NO (iNO) at 40 ppm was administered for 23 h after ROSC in a murine model of CA: treated animals showed improved cardiac and neurological recovery [22]. Interestingly, TTM may activate NO pathways, especially in the heart, so that a combination of these two therapeutic strategies may be of greater benefit in treating postanoxic injury [23]. No studies have tested the effects of NO-donor agents in patients with postanoxic injury [24], while preliminary data show that low-dose nitrite infusion in CA survivors did not cause hypotension or methemoglobinemia [25], but it was not associated with any improvement in outcome.

Erythropoietin

EPO has several cellular effects in addition to its role in the regulation of erythropoiesis. In particular, because of its antiapoptotic, anti-inflammatory, and antioxidant properties, EPO plays a role in neuroprotection and cardioprotection [26]. High-dose EPO administration during CPR in a swine model of ventricular fibrillation (VF) reduced post-resuscitation myocardial dysfunction and promoted hemodynamic stability [27]. However, in a rat model of CA, postischemic EPO administration was not associated with beneficial effects on selective neuronal damage, but it did significantly improve memory function [28]. Finally, in a rat model of CA, survival to 72 h was significantly improved in animals that received pre-CA EPO compared with those that did not [29]. The effects of EPO administration have been evaluated in two clinical studies. In the first, patients received 90,000 UI of EPO during CPR [30]. The EPO group had higher rates of ROSC (92% vs. 53%, $p = 0.006$), 24-h survival (83% vs. 47%, $p = 0.008$), and hospital survival (54% vs. 20%, $p = 0.011$) than a historical control group. In the second [31], EPO therapy (five injections of 40,000 IU intravenously within 48 h) was associated with a trend towards greater 28-day survival (55% vs. 47%) and full neurological recovery (55% vs. 38%) compared with a historical cohort. In a randomized clinical trial presented at the 2014 European Society of Intensive Care Medicine (ESICM) Congress (Cariou et al., EPO-ACR 02 study, NCT00999583), the early administration of EPO did not improve mortality and neurological recovery in a large cohort of comatose CA survivors.

Statins

Statins inhibit 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase), which is involved in the synthesis of cholesterol. However, several other effects, including anti-inflammatory and antioxidant properties, immunomodulation, antithrombotic effects, and protection of the endothelial function, have been described [32]. In patients with subarachnoid hemorrhage, the administration of statins may reduce the incidence of cerebral vasospasm, delayed neurological deficit, and mortality

[33]. Patients receiving long-term treatment with statins also had a reduced risk of ventricular tachyarrhythmia or CA, compared with untreated patients [34]. Nevertheless, there are no specific data yet on the effects of statins on experimental and/or clinical HIE.

Magnesium and lamotrigine

Magnesium (Mg) exhibits beneficial effects on the brain via different mechanisms, such as inhibition of glutamate release and glutamate N-methyl-D-aspartate (NMDA) receptors, protection of blood–brain barrier (BBB) integrity, and reduction of brain edema [35]. Magnesium depletion may have detrimental effects in patients with HIE. Indeed, low Mg levels were associated with a reduced ROSC rate and poor outcome in a small cohort of patients with CA [36]. In one retrospective study, CA patients treated with TTM showed increased renal excretion of Mg [37], even if no particular detrimental effects of hypomagnesemia were observed. Prehospital administration of Mg (2 g) showed favorable trends toward better neurological recovery in resuscitated patients with CA (47% vs. 37% in the placebo group) [38]. In addition, no adverse effect of prehospital administration of Mg therapy was noted. In another study evaluating only in-hospital CA, patients treated with Mg during CPR had a similar proportion of ROSC (54% vs. 60%, $p = 0.44$) to the placebo group, as with survival to 24 h (43% vs. 50%, $p = 0.41$) and hospital discharge (21% vs. 21%, $p = 0.98$) [39]. Importantly, lamotrigine is alternatively used to reduce glutamate excitotoxicity, which has shown promising neuroprotective effects in animal models of brain ischemia using bilateral cerebral artery occlusion [40]. Similar neuroprotection was also found in a murine model of CA, where lamotrigine significantly improved the number of viable neurons compared with the placebo group 3 weeks after the anoxic injury [41]. No clinical data are currently available on comatose patients with CA for this drug.

Calcium antagonists

The role of increased intracellular levels of calcium in neurotoxicity, specifically in mediating the process of apoptosis, indicates that calcium antagonist agents may have beneficial effects in acute brain injury, such as subarachnoid hemorrhage [42]. In a canine model of CA, intravenous nicardipine maintained constant cerebral blood flow (CBF) at the pre-arrest level, thus preventing the hypoperfusion phase observed in the control group [43]. Lidoflazine, another calcium antagonist, could ameliorate late postischemic neurologic deficits in animal models of prolonged VF [44]. Nevertheless, in a large randomized clinical trial including OHCA ($n = 520$), lidoflazine therapy did not improve the mortality rate (82% vs. 83%) or the proportion of survivors with good neurological outcome (15% vs. 13%) when compared with placebo [45]. Similarly, nimodipine administration was associated with better cerebral oxygenation and neuronal activity in an experimental model of CA [46,47]. In the clinical setting, nimodipine therapy was associated with a significant reduction in intracranial pressure after CA when compared with untreated patients [48]. In a randomized clinical trial on OHCA ($n = 155$), nimodipine injection administered immediately after ROSC did not improve the 1-year survival rate (40% vs. 36%) compared with the placebo. Subgroup analyses showed that nimodipine could significantly reduce the occurrence of recurrent VF, resulting in improved survival among patients who required prolonged resuscitation attempts (i.e., >10 min; 47% vs. 8%) [49].

Minocycline

Minocycline is a broad-spectrum tetracycline antibiotic with excellent penetration into cerebral tissues, due to its lipid-soluble structure. This drug has shown anti-inflammatory and antiapoptotic properties, as well as neuroprotective effects on the BBB and white matter [50]. In a mice model of CA, microglial activation and neuronal death in the hippocampus 24 h after arrest could be significantly decreased by minocycline administration [51]. In addition, minocycline could attenuate neuroinflammation, as reflected by the brain tissue levels of tumor necrosis factor alpha (TNF-α), after hypothermic CA in rats [52]. However, no human data are available.

Cyclosporine

The use of Cyclosporine A (CsA) was recently proposed in the early phase after cerebral damage for its ability to preserve mitochondrial integrity in experimental brain injury models. In particular, cerebral ischemia–reperfusion injury is associated with the opening of the mitochondrial permeability transition pore (MPTP), which increases the permeability of the mitochondrial membrane to several molecules, eventually leading to mitochondrial swelling and cell death [53]. Effective therapy of brain injury with CsA can be achieved by closure of the MPTP, which is mediated by the interaction of CsA with a protein that regulates the opening of MPTP, called cyclophilin-D. In an animal model of hypothermic circulatory arrest, pigs treated with CsA (5 mg/kg) had a significantly lower intracranial pressure at reperfusion and rewarming, more rapid electroencephalographic recovery, and better neurological function than in the placebo group [54]. In another experimental model, early CsA administration (5 mg/kg) significantly improved short-term survival and post-resuscitation cardiac function [55]. Importantly, these effects were observed when CsA was administered at the onset of resuscitation, whereas no benefit was reported for late therapy (e.g., the reperfusion phase) [56]. In another study, CsA therapy reduced the number of apoptotic neurons and improved neurological recovery after CA in rats [57]. A randomized clinical trial (Cyclosporine A in Cardiac Arrest; CYRUS, NCT01595958), which has been recently completed, will provide important data on the potential effectiveness of CsA administration after OHCA on organ dysfunction after CA due to non-shockable rhythms.

Free radical scavengers

Methylene blue has been investigated as an antioxidant therapy after postanoxic injury. In a porcine model of prolonged CA, methylene blue increased short-term survival and decreased plasma inflammatory markers (8-isoprostane-prostaglandin F2α and 15-keto-dihydro-prostaglandin F2α) or biomarkers of brain injury (S100-B) [58]. In another animal study, methylene blue infusion administered during CPR significantly prevented the disruption of the BBB observed during the reperfusion phase [59]. Moreover, administration of methylene blue during resuscitation provided additional short-term neuroprotective effects on TTM when pigs were exposed to 12 min of untreated CA and 8 min of CPR [60]. N-acetylcysteine (NAC) prevents depletion of glutathione after experimental reperfusion injury, providing cellular protection against free radical overload [61]. However, NAC (150 mg/kg) failed to show any benefits in a canine model of global brain ischemia secondary to 10 min of untreated CA [62].

Anti-inflammatory agents

Glucocorticoids have potent anti-inflammatory effects with potential benefits in the early post-resuscitation period. Several studies have shown that after an anoxic injury, activation of the hypothalamic–pituitary–adrenal axis, as suggested by the increased levels of circulating cortisol, is followed by an inadequate response of the adrenal gland (e.g., adrenal insufficiency), thus resulting in low cortisol concentrations [63]. This adrenal dysfunction was more important in patients who required prolonged resuscitation attempts [64]. As low cortisol levels were also associated with an increased risk of poor outcome, administration of glucocorticoids has been considered as a valuable therapeutic option in this setting. In a randomized double-blind study ($n = 268$), patients with in-hospital CA who received vasopressin and methylprednisolone (40 mg) during CPR followed by hydrocortisone (50 mg q6h) after ROSC in addition to epinephrine showed improved survival to hospital discharge with favorable neurological status, when compared with epinephrine alone ($p = 0.02$) [65]. Glucocorticoids also have antioxidant and antiapoptotic properties that may contribute to preserving the integrity of neuron cells after ischemia–reperfusion [66]. However, some clinical studies reported no beneficial effect of glucocorticoids on neurological recovery following CA [67,68]. These findings may be explained by some potential detrimental effects of glucocorticoids on the brain, such as enhanced hypoxia-induced apoptosis, increased neuronal vulnerability to ischemia, and the alteration of synaptic transmission [69]. As an alternative to glucocorticoids, estrogens can bind to two nuclear receptors and provide significant neuroprotective effects [70]. In animal models of CA, different dosages of estrogen

given after ROSC provided some evidence of neuroprotection in the rostral and caudal caudo-putamen regions, but no effects in the hippocampal CA1 region [71–73].

Adenosine

Adenosine reduces the release of excitotoxic neurotransmitters, induces vasorelaxation, and exerts some anti-inflammatory and antioxidant effects [74]. Apart from some studies that combined adenosine with ischemic preconditioning, only one experimental study evaluated this drug as the sole neuroprotective intervention in the setting of CA; in a rat model, adenosine therapy (7.2 mg/kg) administered after ROSC was associated with a transient hypothermia, an increased postischemic brain blood flow, and reduced brain edema and neuronal loss in the hippocampus when compared with the control group [75]. As adenosine receptor (AR)-1 inhibition also results in major cardiovascular complications (e.g., bradycardia and hypotension), which may weaken its beneficial cerebral effects [76], selective activation of AR-2A and AR-3 may offer a possible treatment for brain disorders with similar efficacy and reduced adverse events. Future studies should explore the effects of these selective adenosine ligands in the setting of postanoxic brain injury.

Neuroprognostication after CA

After hospital admission following CA, comorbid diseases and circumstances related to initial resuscitation (i.e., no-flow time, duration of CPR, initial rhythm, or lactate levels) are strongly related to short-term survival; however, patients who may subsequently recover an intact neurological function cannot be accurately identified [77]. The best tool to evaluate brain recovery in such patients is repeated neurological examination. Nevertheless, as most patients with CA are currently treated with TTM, which requires the concomitant administration of sedative drugs, the reliability of neurological examination may be affected significantly [78]. Thus, the optimal approach to examining comatose patients who survived an anoxic injury is to combine different available tools in a multimodal approach, including neurological examination, for improving the quality of prognosis prediction.

How is brain function assessed during the first day from arrest?

The initial evaluation of these patients should include a complete neurological examination, in particular to evaluate the motor response and the presence of pupillary and corneal reflexes. In patients not treated with TTM, a persistent poor motor response (e.g., absent or extension to pain) associated with a bilateral lack of pupillary and/or corneal reflexes have been associated with poor prognosis [79]. In addition, the presence of status myoclonus in the first day from CA was a strong predictor of irreversible brain damage in this setting [80]. In patients treated with TTM, the natural course of neurological recovery is altered; myoclonus is abolished because sedative and neuromuscular blocking agents are used and >30% of survivors with intact neurological function will awake >72 h after arrest [81]. As such, early assessment of poor prognosis based only on clinical examination should not be used when implementing TTM. The exception, however, is a minority of patients with dilated and unreactive pupils, absent spontaneous breathing, and gag and cough reflexes, which may suggest a neuroradiological investigation to detect a neurological cause of CA (e.g., massive subarachnoid hemorrhage) or brain death [82].

In patients undergoing TTM, an electroencephalogram (EEG) monitoring should be considered immediately after hospital admission. The following three findings must be analyzed from the EEG: (a) presence of seizures, (b) EEG background, and (c) EEG reactivity. Early postanoxic seizures occur in 10–20% of patients and, when detected during TTM and sedatives administration, are associated with poor outcome [83]. In addition, postanoxic status epilepticus was an independent predictor of poor neurological outcome in this setting [84]. It remains unclear whether early epileptic patterns in these patients represent a condition treatable by an antiepileptic drug with improved outcome or whether they can be regarded as an expression of severe ischemic damage, which cannot be successfully treated with antiepileptic drugs. An ongoing randomized clinical trial will attempt to estimate the effects of medical treatment of postanoxic status epilepticus on the neurological outcome of CA (TELSTAR study,

NCT02056236). The EEG background is currently considered as "malignant" (e.g., burst or generalized suppression, flat or discontinuous EEG, alpha-coma) or benign (e.g., "continuous") [85]. The remaining patterns, including a generalized slowing activity, generalized alpha–theta frequencies, or the presence of epileptiform discharges, are considered to be of unknown outcome. In one study, malignant EEG patterns reliably predicted unfavorable outcome in 81% of patients; however, patients with "benign" or "uncertain" EEG findings had an uncertain prognosis, with >50% of patients eventually presenting a persistent vegetative state or various degrees of motor or cognitive impairment [86]. More recently, Rundgren et al. showed that an initial burst suppression EEG pattern was associated with poor outcome, whereas an initial flat pattern had no prognostic value, as some patients may show EEG background improvement with neurological recovery in a later phase. A continuous EEG background was markedly associated with good neurological outcome [87]. Importantly, an early burst suppression could also be misleading during prognosis as it was observed in 16% of CA survivors, particularly when some particular sedatives, such as propofol, were used [85]. Dynamic changes of EEG (e.g., "reactive" or "nonreactive" cerebral reactivity) are defined as the absence/presence of any reproducible change in EEG amplitude or frequency when the patient is stimulated. Absent EEG reactivity was significantly associated with in-hospital mortality after CA [83]. In addition, the EEG reactivity had a better predictive value of neurological outcome than malignant/benign EEG patterns [88]. Conversely, a reactive EEG background is often associated with good recovery [83]. Although the use of EEG appears to be mandatory in this setting, some significant concerns need to be considered when monitoring CA patients. First, EEG patterns and reactivity still cannot distinguish patients presenting neurological recovery or persistent brain damage with a small percentage of false-positive rate (FPR; e.g., the proportion of patients identified as having a poor outcome and eventually presenting neurological recovery); the study cohorts were relatively limited and findings validated only within few study groups. Moreover, there is no general agreement on patterns/reactivity definitions among centers, which would significantly reduce the wide generalizability of these results.

Together with the initial clinical examination and EEG monitoring, the measurement of biomarkers of brain injury may be beneficial and should be initiated after hospital admission. NSE is the most studied biomarker for prognostication of neurological outcome after CA; although values above 33 ng/ml were highly predictive of poor outcome in comatose patients not treated with TTM [79,80], the relevance of these cutoff values has been recently questioned due to the lack of a standardized methodology and uncertainties about the influence of TTM [89,90]. In a large prospective cohort, NSE was higher in non-survivors than survivors [91]. With regard to the first days after CA, the NSE cutoff value with an FPR of 2% to predict poor outcome was 66 ng/ml 24 h after arrest. An alternative to NSE is the S-100B protein, which is produced by glial cells. High concentrations of S-100B have also been found in patients remaining comatose after CA; however, the cutoff values for predicting poor outcome ranged from 0.2 to 1.5 mg/l [92,93]. Some studies have compared the predictive values of NSE and S-100B, yielding conflicting results [94,95]. Even if S-100B has a shorter half-life and could be potentially more sensitive in detecting extended brain damage in the early phase after a hypoxic injury, most of the existing data are related to NSE, which remains the "gold-standard" biomarkers in this setting.

Some authors also showed that early brain computed tomography (CT) scan was an useful tool to assess the prognosis of comatose CA survivors; in particular, a loss of distinction between gray and white matter, indicating cerebral edema, was associated with a high risk of poor neurological outcome in this setting [96,97]. Importantly, the number of cerebral areas and the different indices for calculating the severity of edema (such as the ratio between the density on CT between the gray and white matter, GWR) need to be standardized, as the data from different studies cannot be easily compared.

How is prognosis assessed in the following days?

When sedation is discontinued, a recovery of the motor response to pain is a sign of favorable prognosis [98]; most of these patients would also have a continuous and reactive EEG pattern, and no further diagnostic tests are necessary if the patient's condition continues to improve in the following days. For patients who remain comatose, clinical examination remains the cornerstone for prognosis assessment. Absent motor response or posturing on days 2–3 after CA is associated with poor outcome; however, the FPR is unacceptably high (>20%) [99]. Similarly, myoclonus, especially if subtle

and not generalized, was observed in 10% of patients who eventually present a full neurological recovery, which should not be considered as a sign of irreversible brain damage [100]. Thus, neurological examination should always be completed by assessing the brain-stem reflexes; absent pupillary and corneal reflexes in combination with absent motor response or posturing reduced the FPR predicting poor outcome to <4% [101]. As the reactivity of constricted pupils or to corneal stimulation could be altered by drugs or preexisting diseases (e.g., diabetes and glaucoma), additional tests remain mandatory to provide useful information on the prognosis of patients. EEG monitoring is still indicated for detecting persistent "malignant" background and unreactive EEG patterns. Furthermore, seizures occurring in the rewarming phase, particularly in association with a continuous EEG background, could still be controlled with aggressive antiepileptic therapy, which sometimes results in good neurological outcome [102].

At that point in time (e.g., 48–72 h after CA), short-latency cortical responses (N20) to somatosensory evoked potentials (SSEPs) have been shown to be strong predictors of poor outcome. This cortical response can only be reliable when peripheral responses are present and are not influenced by moderate sedation or metabolic disturbances. When cortical responses are absent bilaterally in a technically well-performed test, the prediction of poor outcome had an FPR of 0.5% [103]. Unfortunately, only a small proportion of patients with a poor outcome after resuscitation have absent N20 bilaterally, which resulted in a low sensitivity of assessing the prognosis; in addition, preservation of the N20 response does not imply a favorable outcome, as almost half of patients with normal N20 will have poor outcomes [103].

The measurement of NSE levels on days 2–3 after CA was still associated with poor outcome, but with an FPR close to 20% [99] and no optimal cutoff value identified yet [103]. In a recent study, NSE values above 48 ng/ml on day 2 after arrest had an FPR of only 2%; further, 48 and 72 h after arrest, NSE predicted neurological outcomes with areas under the receiver-operating curve of 0.85 and 0.86, respectively [91]. In all patients with "uncertain" prognosis (e.g., still comatose in the absence of all possible predictors of poor outcome), cerebral magnetic resonance imaging (MRI) may be a better means of identifying brain damage using apparent diffusion coefficient (ADC) maps [104]. In particular, bilateral hippocampal hyperintense signals on diffusion-weighted imaging (DWI) and fluid-attenuated

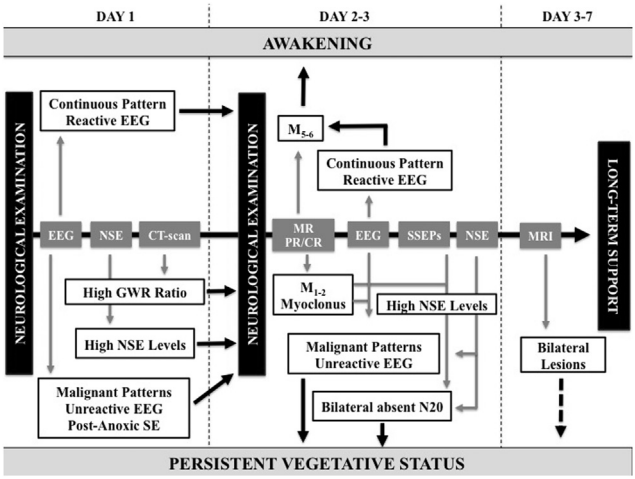

Fig. 3. Multimodal prognostication of coma after cardiac arrest and targeted temperature management (TTM). The figure summarizes the timing for using all available tools to predict poor outcome or neurological recovery from coma. EEG = electroencephalography; NSE = neuron-specific enolase; CT scan = computed tomography; GWR = ratio of the density of gray to white matter; SE = status epilepticus; MRI = magnetic resonance imaging; MR = motor response; CR = corneal reflexes; PR = pupillary reflexes; M1-2 = absent motor response or posturing; M5-6 = localize pain or execute orders; N20 = cortical responses to somatosensory evoked potentials.

inversion recovery (FLAIR) sequences were reported as a specific imaging indicator of poor prognosis in patients who suffer global hypoxic–ischemic injury [105].

Multimodal approach

The combination of several prognostic tools with clinical examination should be used to improve the accuracy of outcome prediction after postanoxic injury (Fig. 3). Although several proposals have already been published [106,107] and still need to be validated in large prospective trials, previous studies have already shown that a multimodal approach can increase the predictive value for neurological recovery after CA. As an example, the addition of NSE values to clinical examination and SSEPs can increase the predictability of poor neurological function from 64% to 76% [108]. In one study, all available tools were combined to assess the prognosis in 111 patients resuscitated from CA [109]; 15 of 34 patients who were comatose on day 3 had clinical generalized myoclonus and all died. Of the remaining 19 patients, seven had a "continuous EEG" and six regained normal consciousness. All patients with status epilepticus and burst suppression or flat EEG also died. One patient, however, awakened and presented continuous EEG background, normal MRI and low NSE levels, preserved brain-stem reflexes, and bilateral presence of N20 on SSEPs. Finally, in a recent study ($n = 134$), the combination of clinical examination, EEG reactivity, and NSE values yielded the best predictive performance (receiving operator characteristic areas under the curve of 0.89 for mortality and 0.88 for poor neurological outcome) [110].

Summary

Postanoxic brain injury remains a significant source of morbidity and mortality in patients who survive CA. Establishing therapeutic options after ROSC to decrease the burden of brain damage are warranted. Several therapeutic interventions, including noble gases, nitric oxide, EPO, statins, or glucocorticoids, are still under evaluation and clinical data are still scarce or inconclusive.

Accurate prognostication of comatose patients suffering from postanoxic injury, especially if treated with TTM, can only occur 72–96 h after CA, requiring a multimodal approach. Neurological examination remains the first step; the addition of EEG and NSE in a very early phase could better identify patients with a greater extent of brain injury. In particular, the presence of an early unreactive EEG background or burst-suppressed EEG pattern is associated with poor outcome. After sedative discontinuation (e.g., from days 2–3 after arrest), the bilateral absence of N20 h is invariably associated with a poor prognosis, thus confirming irreversible coma. Serum biomarkers of brain damage (NSE and S-100β) may be useful in assessing the severity of acute brain damage, which when combined with MRI findings can help identify patients with extended brain damage who remain comatose thereafter.

Practice points

- Neuroprotection strategies after CA are limited. Some promising drugs are currently under evaluation, and they may potentially be considered for future large clinical trials.
- Assessment of neurological prognosis after CA is a clinical challenge; neurological examination alone presents several pitfalls, and a multimodal approach should be implemented in these comatose patients.
- The presence of absent motor response or posturing in combination with absent pupillary and/or corneal reflexes and a "malignant" or unreactive EEG pattern or bilateral absence of cortical responses to SSEPs will predict poor outcome.
- A reactive EEG background and very low levels of NSE may be found in patients eventually presenting an intact neurological recovery.

Research agenda

- Limited clinical data are available on the effects of statins, antioxidants, minocycline, and adenosine in the treatment of HIE.
- Large prospective studies should validate models that combine neurological examination with additional tools (e.g., EEG, SSEPs, NSE, and MRI) and demonstrate their high accuracy of predicting outcome in comatose survivors after CA.

Conflict of interest

The authors declare no conflict of interest.

References

[1] Nichol G, Soar J. Regional cardiac resuscitation systems of care. Curr Opin Crit Care 2010;16:223–30.
[2] Atwood C, Eisenberg MS, Herlitz J, et al. Incidence of EMS-treated out-of-hospital cardiac arrest in Europe. Resuscitation 2005;67:75–80.
[3] Adielsson A, Hollenberg J, Karlsson T, et al. Increase in survival and bystander CPR in out-of-hospital shockable arrhythmia: bystander CPR and female gender are predictors of improved outcome. Experiences from Sweden in an 18-year perspective. Heart 2011;97:1391–6.
[4] Bobrow BJ, Spaite DW, Berg RA, et al. Chest compression-only CPR by lay rescuers and survival from out-of-hospital cardiac arrest. JAMA 2010;304:1447–54.
[5] Nichol G, Aufderheide TP, Eigel B, et al. Regional systems of care for out-of-hospital cardiac arrest: a policy statement from the American Heart Association. Circulation 2010;121(5):709–29.
[6] Herlitz J, Engdahl J, Svensson L, et al. Factors associated with an increased chance of survival among patients suffering from an out-of-hospital cardiac arrest in a national perspective in Sweden. Am Heart J 2005;149:61–6.
[7] Hallstrom AP, Ornato JP, Weisfeldt M, et al. Public-access defibrillation and survival after out-of-hospital cardiac arrest. N Engl J Med 2004;351:637–46.
[8] Dragancea I, Rundgren M, Englund E, et al. The influence of induced hypothermia and delayed prognostication on the mode of death after cardiac arrest. Resuscitation 2013;84(3):337–42.
[9] Adrie C, Laurent I, Monchi M, et al. Postresuscitation disease after cardiac arrest: a sepsis-like syndrome? Curr Opin Crit Care 2004;10:208–12.
[10] Deakin CD, Nolan JP, Soar J, et al. European resuscitation council guidelines for resuscitation 2010 section 4. Adult advanced life support. Resuscitation 2010;81:1305–52.
[11] Ma D, Wilhelm S, Maze M, et al. Neuroprotective and neurotoxic properties of the inert gas, xenon. B J Anaesth 2002; 89:739–46.
[12] Jawad N, Rizvi M, Gu J, et al. Neuroprotection (and lack of neuroprotection) afforded by a series of noble gases in an in vitro model of neuronal injury. Neurosci Lett 2009;460:232–6.
[13] Schmidt M, Marx T, Gloggl E, et al. Xenon attenuates cerebral damage after ischemia in pigs. Anesthesiology 2005;102: 929–36.
[14] Fries M, Brucken A, Cizen A, et al. Combining xenon and mild therapeutic hypothermia preserves neurological function after prolonged cardiac arrest in pigs. Crit Care Med 2012;40:1297–303.
*[15] Arola OJ, Laitio RM, Roine RO, et al. Feasibility and cardiac safety of inhaled xenon in combination with therapeutic hypothermia following out-of-hospital cardiac arrest. Crit Care Med 2013;41:2116–24.
[16] Brucken A, Cizen A, Fera C, et al. Argon reduces neurohistopathological damage and preserves functional recovery after cardiac arrest in rats. Br J Anaesth 2013;110(Suppl. 1):i106–12.
[17] Ristagno G, Fumagalli F, Russo I, et al. Post-resuscitation treatment with argon improves early neurological recovery in a porcine model of cardiac arrest. Shock 2014;41(1):72–8.
[18] Brücken A, Kurnaz P, Bleilevens C, et al. Delayed argon administration provides robust protection against cardiac arrest-induced neurological damage. Neurocrit Care 2015;22(1):112–20.
[19] Kohr MJ, Sun J, Aponte A, et al. Simultaneous measurement of protein oxidation and S-nitrosylation during preconditioning and ischemia/reperfusion injury with resin-assisted capture. Circ Res 2011;108:418–26.
[20] Nishida T, Yu JD, Minamishima S, et al. Protective effects of nitric oxide synthase 3 and soluble guanylate cyclase on the outcome of cardiac arrest and cardiopulmonary resuscitation in mice. Crit Care Med 2009;37:256–62.
[21] Dezfulian C, Shiva S, Alekseyenko A, et al. Nitrite therapy after cardiac arrest reduces reactive oxygen species generation, improves cardiac and neurological function, and enhances survival via reversible inhibition of mitochondrial complex I. Circulation 2009;120:897–905.
[22] Minamishima S, Kida K, Tokuda K, et al. Inhaled nitric oxide improves outcomes after successful cardiopulmonary resuscitation in mice. Circulation 2011;124:1645–53.
[23] Zoerner F, Wiklund L, Miclescu A, et al. Therapeutic hypothermia activates the endothelin and nitric oxide systems after cardiac arrest in a pig model of cardiopulmonary resuscitation. PloS One 2013;8:e64792.
[24] Roberts BW, Mitchell J, Kilgannon JH, et al. Nitric oxide donor agents for the treatment of ischemia/reperfusion injury in human subjects: a systematic review. Shock 2013;39:229–39.

*[25] Dezfulian C, Alekseyenko A, Dave KR, et al. Nitrite therapy is neuroprotective and safe in cardiac arrest survivors. Nitric Oxide 2012;26:241–50.
[26] Ruscher K, Freyer D, Karsch M, et al. Erythropoietin is a paracrine mediator of ischemic tolerance in the brain: evidence from an in vitro model. J Neurosci 2002;22:10291–301.
[27] Borovnik-Lesjak V, Whitehouse K, Baetiong A, et al. High-dose erythropoietin during cardiac resuscitation lessens postresuscitation myocardial stunning in swine. Transl Res 2013;162:110–21.
[28] Unden J, Sjolund C, Lansberg JK, et al. Post-ischemic continuous infusion of erythropoeitin enhances recovery of lost memory function after global cerebral ischemia in the rat. BMC Neurosci 2013;14:27.
[29] Incagnoli P, Ramond A, Joyeux-Faure M, et al. Erythropoietin improved initial resuscitation and increased survival after cardiac arrest in rats. Resuscitation 2009;80:696–700.
[30] Grmec S, Strnad M, Kupnik D, et al. Erythropoietin facilitates the return of spontaneous circulation and survival in victims of out-of-hospital cardiac arrest. Resuscitation 2009;80:631–7.
[31] Cariou A, Claessens YE, Pene F, et al. Early high-dose erythropoietin therapy and hypothermia after out-of-hospital cardiac arrest: a matched control study. Resuscitation 2008;76:397–404.
[32] De Loecker I, Preiser JC. Statins in the critically ill. Ann Intensive Care 2012;2:19.
[33] Sillberg VA, Wells GA, Perry JJ. Do statins improve outcomes and reduce the incidence of vasospasm after aneurismal subarachnoid hemorrhage: a meta-analysis. Stroke 2008;39:2622–6.
[34] Vrtovec B, Okrajsek R, Golicnik A, et al. Atorvastatin therapy may reduce the incidence of sudden cardiac death in patients with advanced chronic heart failure. J Card Fail 2008;14(2):140–4.
[35] Chang JJ, Mack WJ, Saver JL, et al. Magnesium: potential roles in neurovascular disease. Front Neurol 2014;5:52.
[36] Cannon LA, Heiselman DE, Dougherty JM, et al. Magnesium levels in cardiac arrest victims: relationship between magnesium levels and successful resuscitation. Ann Emerg Med 1987;16(11):1195–9.
[37] Mazer-Amirshahi M, Perman SM, Grossestreuer AV, et al. Magnesium depletion in patients treated with therapeutic hypothermia after cardiac arrest. Ther Hypothermia Temp Manag 2014;4(4):188–92.
*[38] Longstreth WT Jr, Fahrenbruch CE, Olsufka M, et al. Randomized clinical trial of magnesium, diazepam, or both after out-of-hospital cardiac arrest. Neurology 2002;59(4):506–14.
[39] Thel MC, Armstrong AL, McNulty SE, et al. Randomised trial of magnesium in in-hospital cardiac arrest. Duke Internal Medicine Housestaff. Lancet 1997;350(9087):1272–6.
[40] Wiard RP, Dickerson MC, Beek O, et al. Neuroprotective properties of the novel antiepileptic lamotrigine in a gerbil model of global cerebral ischemia. Stroke 1995;26:466–72.
[41] Crumrine RC, Bergstrand K, Cooper AT, et al. Lamotrigine protects hippocampal CA1 neurons from ischemic damage after cardiac arrest. Stroke 1997;28:2230–6.
[42] Feigin VL, Rinkel GJ, Algra A, et al. Calcium antagonists in patients with aneurysmal subarachnoid hemorrhage: a systematic review. Neurology 1998;50(4):876–83.
[43] Iwatsuki N, Ono K, Koga Y, et al. Prevention of postischemic hypoperfusion after canine cardiac arrest by nicardipine. Crit Care Med 1987;15(4):313–7.
[44] Vaagenes P, Cantadore R, Safar P, et al. Amelioration of brain damage by lidoflazine after prolonged ventricular fibrillation cardiac arrest in dogs. Crit Care Med 1984;12(10):846–55.
*[45] Brain Resuscitation Clinical Trial II Study Group. A randomized clinical study of a calcium-entry blocker (lidoflazine) in the treatment of comatose survivors of cardiac arrest. N Engl J Med 1991;324(18):1225–31.
[46] Schindler I, Steltzer H, Weindlmayr-Goettel M, et al. Nimodipine after circulatory arrest: effects on oxygen delivery and consumption. J Crit Care 1994;9(1):18–24.
[47] Cervantes M, Chávez-Carrillo I, Antonio-Ocampo A. Effects of nimodipine on multiunit activity of several brain structures following acute global cerebral ischemia-anoxia in cats. Bol Estud Med Biol 1992;40(1–4):21–30.
*[48] Gueugniaud PY, Gaussorgues P, Garcia-Darennes F, et al. Early effects of nimodipine on intracranial and cerebral perfusion pressures in cerebral anoxia after out-of-hospital cardiac arrest. Resuscitation 1990;20(3):203–12.
*[49] Roine RO, Kaste M, Kinnunen A, et al. Nimodipine after resuscitation from out-of-hospital ventricular fibrillation. A placebo-controlled, double-blind, randomized trial. JAMA 1990;264(24):3171–7.
[50] Stolp HB, Ek CJ, Johansson PA, et al. Effect of minocycline on inflammation-induced damage to the blood-brain barrier and white matter during development. Eur J Neurosci 2007;26(12):3465–74.
[51] Tang M, Alexander H, Clark RS, et al. Minocycline reduces neuronal death and attenuates microglial response after pediatric asphyxial cardiac arrest. J Cereb Blood Flow Metab 2010;30(1):119–29.
[52] Drabek T, Janata A, Wilson CD, et al. Minocycline attenuates brain tissue levels of TNF-α produced by neurons after prolonged hypothermic cardiac arrest in rats. Resuscitation 2014;85(2):284–91.
[53] Veech RL, Valeri CR, VanItallie TB. The mitochondrial permeability transition pore provides a key to the diagnosis and treatment of traumatic brain injury. IUBMB Life 2012;64(2):203–7.
[54] Hagl C, Tatton NA, Weisz DJ, et al. Cyclosporine A as a potential neuroprotective agent: a study of prolonged hypothermic circulatory arrest in a chronic porcine model. Eur J Cardiothorac Surg 2001;19(6):756–64.
[55] Cour M, Loufouat J, Paillard M, et al. Inhibition of mitochondrial permeability transition to prevent the post-cardiac arrest syndrome: a pre-clinical study. Eur Heart J 2011;32(2):226–35.
[56] Huang CH, Tsai MS, Hsu CY, et al. Post-cardiac arrest myocardial dysfunction is improved with cyclosporine treatment at onset of resuscitation but not in the reperfusion phase. Resuscitation 2011;82(Suppl. 2):S41–7.
[57] Knapp J, Roewer J, Bruckner T, et al. Evaluation of cyclosporine a as a cardio- and neuroprotective agent after cardiopulmonary resuscitation in a rat model. Shock 2015;43(6):576–81.
[58] Miclescu A, Basu S, Wiklund L. Methylene blue added to a hypertonic-hyperoncotic solution increases short-term survival in experimental cardiac arrest. Crit Care Med 2006;34:2806–13.
[59] Sharma HS, Miclescu A, Wiklund L. Cardiac arrest-induced regional blood–brain barrier breakdown, edema formation and brain pathology: a light and electron microscopic study on a new model for neurodegeneration and neuroprotection in porcine brain. J Neural Transm 2011;118:87–114.

[60] Wiklund L, Zoerner F, Semenas E, et al. Improved neuroprotective effect of methylene blue with hypothermia after porcine cardiac arrest. Acta Anaesthesiol Scand 2013;57(8):1073–82.
[61] Davreux CJ, Soric I, Nathens AB, et al. N-acetyl cysteine attenuates acute lung injury in the rat. Shock 1997;8:432–8.
[62] Silbergleit R, Haywood Y, Fiskum G, et al. Lack of a neuroprotective effect from n-acetylcysteine after cardiac arrest and resuscitation in a canine model. Resuscitation 1999;40:181–6.
[63] Schultz CH, Rivers EP, Feldkamp CS, et al. A characterization of hypothalamic-pituitary-adrenal axis function during and after human cardiac arrest. Crit Care Med 1993;21:1339–47.
[64] Pene F, Hyvernat H, Mallet V, et al. Prognostic value of relative adrenal insufficiency after out-of-hospital cardiac arrest. Intensive Care Med 2005;31:627–33.
*[65] Mentzelopoulos SD, Malachias S, Chamos C, et al. Vasopressin, steroids, and epinephrine and neurologically favorable survival after in-hospital cardiac arrest. JAMA 2013;310:270–9.
[66] Lai M, Horsburgh K, Bae SE, et al. Forebrain mineralocorticoid receptor overexpression enhances memory, reduces anxiety and attenuates neuronal loss in cerebral ischaemia. Eur J Neurosci 2007;25:1832–42.
[67] Jastremski M, Sutton-Tyrrell K, Vaagenes P, et al. Brain resuscitation clinical trial I study group. Glucocorticoid treatment does not improve neurological recovery following cardiac arrest. JAMA 1989;262:3427–30.
[68] Grafton ST, Longstreth Jr WT. Steroids after cardiac arrest: a retrospective study with concurrent, nonrandomized controls. Neurology 1988;38:1315–6.
[69] Varvarousi G, Stefaniotou A, Varvaroussis D, et al. Glucocorticoids as an emerging pharmacologic agent for cardiopulmonary resuscitation. Cardiovasc Drugs Ther 2014;28(5):477–88.
[70] McCullough LD, Hurn PD. Estrogen and ischemic neuroprotection: an integrated view. Trends Endocrinol Metab 2003;14:228–35.
[71] Lebesgue D, Chevaleyre V, Zukin RS, et al. Estradiol rescues neurons from global ischemia-induced cell death: multiple cellular pathways of neuroprotection. Steroids 2009;74(7):555–61.
[72] Noppens RR, Kofler J, Hurn PD, et al. Dose-dependent neuroprotection by 17beta-estradiol after cardiac arrest and cardiopulmonary resuscitation. Crit Care Med 2005;33:1595–602.
[73] Noppens RR, Kofler J, Grafe MR, et al. Estradiol after cardiac arrest and cardiopulmonary resuscitation is neuroprotective and mediated through estrogen receptor-beta. J Cereb Blood Flow Metab 2009;29:277–86.
[74] von Lubitz DK. Adenosine and cerebral ischemia: therapeutic future or death of a brave concept? Eur J Pharmacol 1999;371:85–102.
[75] Xu K, Puchowicz MA, Lust WD, et al. Adenosine treatment delays postischemic hippocampal CA1 loss after cardiac arrest and resuscitation in rats. Brain Res 2006;1071:208–17.
[76] Sachdeva S, Gupta M. Adenosine and its receptors as therapeutic targets: an overview. Saudi Pharm J 2013;21:245–53.
[77] Adrie C, Cariou A, Mourvillier B, et al. Predicting survival with good neurological recovery at hospital admission after successful resuscitation of out-of-hospital cardiac arrest: the OHCA score. Eur Heart J 2006;27:2840–5.
[78] Grossestreuer AV, Abella BS, Leary M, et al. Time to awakening and neurologic outcome in therapeutic hypothermia-treated cardiac arrest patients. Resuscitation 2013;84(12):1741–6.
*[79] Wijdicks EF, Hijdra A, Young GB, et al. 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):203–10.
*[80] 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):1310–23.
*[81] Mulder M, Gibbs HG, Smith SW, et al. Awakening and withdrawal of life-sustaining treatment in cardiac arrest survivors treated with therapeutic hypothermia. Crit Care Med 2014;42(12):2493–9.
[82] Arnaout M, Mongardon N, Deye N, et al. Out-of-hospital cardiac arrest from brain cause: epidemiology, clinical features, and outcome in a multicenter cohort. Crit Care Med 2015;43(2):453–60.
[83] Rossetti AO, Urbano LA, Delodder F, et al. Prognostic value of continuous EEG monitoring during therapeutic hypothermia after cardiac arrest. Crit Care 2010;14(5):R173.
[84] Rossetti AO, Logroscino G, Liaudet L, et al. Status epilepticus: an independent outcome predictor after cerebral anoxia. Neurology 2007;69(3):255–60.
*[85] Amorim E, Rittenberger JC, Baldwin ME, et al. Malignant EEG patterns in cardiac arrest patients treated with targeted temperature management who survive to hospital discharge. Resuscitation 2015;90:127–32.
[86] Rothstein TL, Thomas EM, Sumi SM. Predicting outcome in hypoxic-ischemic coma. A prospective clinical and electrophysiologic study. Electroencephalogr Clin Neurophysiol 1991;79(2):101–7.
*[87] Thenayan EAL, Savard M, Sharpe MD, et al. Electroencephalogram for prognosis after cardiac arrest. J Crit Care 2010;25:300–4.
[88] Rundgren M, Westhall E, Cronberg T, et al. Continuous amplitude-integrated electroencephalogram predicts outcome in hypothermia-treated cardiac arrest patients. Crit Care Med 2010;38(9):1838–44.
[89] Rundgren M, Cronberg T, Friberg H, et al. Serum neuron specific enolase – impact of storage and measuring method. BMC Res Notes 2014;7:726.
[90] Rundgren M, Karlsson T, Nielsen N, et al. Neuron specific enolase and S-100B as predictors of outcome after cardiac arrest and induced hypothermia. Resuscitation 2009;80(7):784–9.
*[91] Stammet P, Collignon O, Hassager C, et al. Neuron-specific enolase as a predictor of death or poor neurological outcome after out-of-hospital cardiac arrest and targeted temperature management at 33°C and 36°C. J Am Coll Cardiol 2015;65(19):2104–14.
[92] Rosen H, Rosengarten L, Herlitz J, et al. Increased serum levels of S-100 protein are associated with hypoxic brain damage after cardiac arrest. Stroke 1998;29(2):796–802.
[93] Pfeifer R, Borner A, Krack A, et al. Outcome after cardiac arrest: predictive values and limitations of the neuroproteins neuron-specific enolase and protein S-100 and the Glasgow Coma Scale. Resuscitation 2005;65(1):49–55.

[94] Tiainen M, Roine RO, Pettila V, et al. Serum neuron-specific enolase and S-100B protein in cardiac arrest patients treated with hypothermia. Stroke 2003;34:2881–6.
[95] Martens P, Raabe A, Johnsson P. Serum S-100 and neuron-specific enolase for prediction of regaining consciousness after global cerebral ischemia. Stroke 1998;29(11):2363–6.
[96] Sugimori H, Kanna T, Yamashita K, et al. Early findings on brain computed tomography and the prognosis of post-cardiac arrest syndrome: application of the score for stroke patients. Resuscitation 2012;83:848–54.
[97] Metter RB, Rittenberger JC, Guyette FX, et al. Association between a quantitative CT scan measure of brain edema and outcome after cardiac arrest. Resuscitation 2011;82:1180–5.
[98] Schefold JC, Storm C, Kruger A, et al. The Glasgow Coma Score is a predictor of good outcome in cardiac arrest patients treated with therapeutic hypothermia. Resuscitation 2009;80:658–61.
*[99] Bouwes A, Binnekade JM, Kuiper MA, et al. Prognosis of coma after therapeutic hypothermia: a prospective cohort study. Ann Neurol 2012;71(2):206–12.
*[100] Seder DB, Sunde K, Rubertsson S, et al. Neurologic outcomes and postresuscitation care of patients with myoclonus following cardiac arrest. Crit Care Med 2015;43(5):965–72.
[101] Rossetti AO, Oddo M, Logroscino G, et al. Prognostication after cardiac arrest and hypothermia: a prospective study. Ann Neurol 2010;67(3):301–7.
*[102] Rossetti AO, Oddo M, Liaudet L, et al. Predictors of awakening from postanoxic status epilepticus after therapeutic hypothermia. Neurology 2009;72(8):744–9.
*[103] 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 2: patients treated with therapeutic hypothermia. Resuscitation 2013;84(10):1324–38.
[104] 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.
[105] 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):412–20.
*[106] Sandroni C, Cariou A, Cavallaro F, et al. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine. Resuscitation 2014;85(12):1779–89.
*[107] Taccone F, Cronberg T, Friberg H, et al. How to assess prognosis after cardiac arrest and therapeutic hypothermia. Crit Care 2014;18(1):202.
[108] Meynaar IA, Oudemans-van Straaten HM, van der Wetering J, et al. Serum neuron-specific enolase predicts outcome in post-anoxic coma: a prospective cohort study. Intensive Care Med 2003;29:189–95.
[109] Cronberg T, Rundgren M, Westhall E, et al. Neuron-specific enolase correlates with other prognostic markers after cardiac arrest. Neurology 2011;77(7):623–30.
[110] Oddo M, Rossetti AO. Early multimodal outcome prediction after cardiac arrest in patients treated with hypothermia. Crit Care Med 2014;42(6):1340–7.