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CONSENSUS PAPER AND GUIDELINE

Neuroprognostication after adult cardiac arrest treated with targeted temperature management: task force for Belgian recommendations

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Abstract The prognosis of patients who are admitted to the hospital after cardiac arrest often relies on neurological examination, which could be significantly influenced by the use of sedative drugs or the implementation of targeted temperature management. The need for early and accurate prognostication is crucial as up to 15–20% of patients could be considered as having a poor outcome and may undergo withdrawal of life-sustaining therapies while a complete neurological recovery is still possible. As current practice in Belgium is still based on a very early assessment of neurological function in these patients, the Belgian Society of Intensive Care Medicine created a multidisciplinary Task Force to provide an optimal approach for monitoring and refine prognosis of CA survivors. This Task Force underlined the importance to use a multimodal approach using several additional tools (e.g., electrophysiological tests, neuroimaging, biomarkers) and to refer cases with uncertain prognosis to specialized centers to better evaluate the extent of brain injury in these patients.

Keywords Cardiac arrest · Prognosis · Hypothermia · EEG · Evoked potentials · Biomarkers · Neurological examination

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The problem of post-anoxic encephalopathy

Sudden cardiac arrest (CA) is the most common cause of natural deaths in Western countries and, despite the initiation of resuscitation attempts, leads to a mortality rate greater than 90% [1]. The continuous improvement in the management of CA patients, including high-quality cardiopulmonary resuscitation (CPR) and early defibrillation, has allowed more patients to achieve a return of spontaneous circulation (ROSC) and to be admitted alive to the hospital [2, 3]; however, no more than one-third of them will be eventually discharged with a good neurological recovery [4].

In this setting, early mortality is often related to the initial myocardial stunning and cardiogenic shock, which result in tissue hypoperfusion and the development of multiple organ failure [5, 6]. Nevertheless, among those who survive the first days since hospital admission, prognosis is mostly related to the severity of brain injury [7]. The pathophysiology of this post-anoxic brain injury is extremely complex and is related not only to the initial ischemic event, but also to additional damages due to the restoration of blood flow (e.g., "reperfusion injury"), which exacerbate excito-toxicity, intra-cellular acidosis,

oxidative stress, mitochondrial dysfunction, neuro-inflammation and eventually induce cell death [8]. Among all potential therapeutic interventions, only the use of targeted temperature management (TTM) provided significant benefits in terms of neurological recovery among CA survivors [9–11], although the evidence supporting this approach is not the same according to the type and location of arrest. Nevertheless, the need of sedatives and analgesic drugs during TTM may delay the accuracy of neurological examination to assess prognosis of such patients [12]. International recommendations underline that a multimodal prognostication approach should be initiated in CA patients who remain comatose at ≥72 h from arrest [13]. However, a recent survey conducted in Belgium showed that one-third of intensive care unit (ICU) physicians ($n = 82$) assessed neurological function in these patients too early after the arrest (≤48 h), which may potentially lead to erroneous life-sustaining therapies withdrawal (LSTW) decisions in these patients [14]. Considering that the quality of evidence for almost all studies supporting recent guidelines was very low, the Belgian Society of Intensive Care Medicine (SIZ) has created a multidisciplinary Task Force to provide some practical issues on the optimal approach for monitoring and refine prognosis of CA survivors in our country. A structured review of the existing literature, including all studies reported in recent guidelines [13], was used while no specific attempt to grade the evidence of recommendations was undertaken.

When to start neuroprognostication?

Early CA characteristics, such as unwitnessed arrest, asystole as presenting rhythm, prolonged CPR, are strong predictors of mortality in this setting [15]. However, these findings should never be used to predict poor neurological outcome as they may result in a misclassification of 15–20% of cases: up to one out of 5–6 patients who is considered to have no chance to recover and in whom life-sustaining therapies may be discontinued will eventually awaken in the next days following arrest.

Moreover, neurological examination must not be used to prognosticate during the cooling phase of TTM and when patients are on sedative and/or analgesic treatment as clinical findings could lead to inappropriate prediction of poor outcome in almost one-third of patients [16, 17]. Finally, TTM reduces drug elimination, in particular by reducing the activity of cytochrome P450 (e.g., sedative and opiates effects are still present 24–72 h after therapy has been discontinued) and might lengthen the time of cerebral recovery [18], although this might not happen when some short-acting agents, such as propofol, remifentanil or inhaled anesthetics are used [19, 20].

All these issues explain why up to 30% of CA patients treated with TTM will regain consciousness after 72 h from arrest [12]. In one study ($n = 163$), mean time of awakening for these patients was 3.8 days and 21% of them regained neurological responsiveness after 5 days from arrest, in particular if cooled at lower target temperatures (32–33 °C) [21]. Moreover, renal insufficiency, older age and post-resuscitation shock were the most important determinants of delayed awakening in these patients [22]. Nevertheless, in the absence of confounders, the chance of neurological recovery remain unchanged after 7 days from arrest, with only 2% of comatose patients becoming responsive and being discharge with good neurological function after that time-point [23, 24].

Recommendations

1. Neuroprognostication based on clinical examination of comatose CA survivors should be initiated after discontinuation of TTM for at least 24 h and of all drugs that may potentially influence the neurological examination.
2. The absence of good neurological function within 48–72 h after arrest does not rule out recovery of consciousness.
3. The optimal time to perform a reliable neurological examination is between 3 and 7 days after arrest, with a wide variability between patients depending on the target temperature used during TTM, risk factors for residual sedation and the severity of co-morbid conditions.

Clinical examination (including myoclonus)

The cornerstone of neuroprognostication after CA is a reliable clinical neurological examination. Clinical examination of comatose CA patients should be as complete as possible. Nevertheless, as it is often performed by non-neurologists and biased by the presence of drugs that influence patients' responsiveness, the clinical findings that were extensively evaluated in this setting and have the highest prognostic significance are the assessment of motor response, brainstem reflexes and the presence of myoclonus. During the initial period after CA, in particular for the cooling period, the only reliable prognostic information is the presence of dilated, unreactive pupils and loss of all brain stem functions that may suggest in some patients large brain infarction and/or herniation [7], which should be confirmed with additional diagnostic tests. Motor response is a physical sign highly affected by sedatives, opiates and neuromuscular blockade and should not be

used for prognostication before 48–72 h after arrest. Recovery of at least a localizing motor response to pain (Glasgow Coma Score—Motor Response, GCS-M, ≥5) after discontinuation of sedation is a sign of a favorable prognosis and no additional tools are necessary as the patient will improve over the following days [25]. Moreover, in clinical practice, those patients who are restless, moving their arms and legs, and requiring high doses of sedation may also present good possibility to recover. For patients who remain unresponsive, a GCS-M of 3 or 4 will require complementary prognostic tests. Importantly, absent motor response or extensor posturing (GCS-M ≤2) to external stimuli even at 72 h after arrest was associated with a false positive rate (FPR) of 24% [26] to prognosticate poor outcome and may lead, if used alone, to a wrong decision of LSTW.

The association of a poor motor response with the bilateral absence of pupillary light reflex at 72 h after arrest is a strong predictor of poor prognosis with an FPR of 0–4% [26, 27]. However, the presence of pupillary reflexes at 72 h after arrest is not a strong indicator of good neurological recovery (positive predictive value, PPV of 60%) and its absence in the first 24 h after the arrest, in particular during the cooling phase, may still result in an FPR of 10% [27]. Bilateral absence of corneal reflexes at 72 h from CA has a slightly less specificity than pupillary reflexes to predict poor outcome, partly due to interference from residual effects of sedatives or neuromuscular blocking agents (FPR 5–7%). Similarly, presence of corneal reflexes at 72 h is not reliable for prediction of good outcome (predictive value of 62%) [13, 27].

Myoclonus is defined as brief, sudden and involuntary muscular twitching; status myoclonus as continuous multifocal twitches lasting for more than 30 min and involving several parts of the body. Status myoclonus starting within 48 h from CA is consistently associated with a poor outcome (FPR 0.5%) [26, 27]. However, the development of late myoclonus, the so-called Lance–Adams syndrome, has been observed in patients who regained consciousness and presented a good outcome [28]. In one study, post-hypoxic myoclonus was reported in 20% of patients; 9% of them showed a good neurological recovery outcome [29]. In another study, 18% of CA patients treated with TTM exhibited myoclonus [30]; favorable neurological outcome at hospital discharge was observed in 9% of these patients. One limitation of these studies is the analysis of both subtle and status myoclonus as one clinical variable, as these entities may not reflect the same severity of post-anoxic brain damage. Moreover, as in post-anoxic patients, myoclonus may be cortical or subcortical and be associated with specific electroencephalographic (EEG) correlates, it is important to assess EEG background activity. Indeed, patients with myoclonus and epileptiform activity or unreactive EEG (see paragraph below) had a lower likelihood of neurological recovery than others (FPR 0–2%) [29].

Recommendations

1. Patients showing a localizing motor response to pain at discontinuation of TTM/sedation will evolve towards a neurological recovery.
2. The combination of a poor motor response (e.g., absent or posturing) and the bilateral absence of pupillary and/or corneal reflexes at 72 h or more after CA is highly predictive of poor outcome, but false positive exist (FPR 0–4%).
3. Up to 10% of patients with myoclonus may present an intact long-term neurological function; additional prognostic tools (in particular EEG) should be used in these patients.

EEG (including status epilepticus)

The use of EEG after CA is advocated to respond to at least three main questions: (a) is there any seizure or status epilepticus (SE)? (b) What is the EEG background? (c) Is the EEG reactive to external stimuli? These issues should be explored both in the early and late phase after arrest, which means that EEG monitoring should be started as soon as possible after hospital admission, even during the cooling phase. It remains still unclear whether continuous EEG monitoring would provide a better predictive performance than standard intermittent and repeated EEG in these patients [31].

Seizures and status epilepticus

While standardized definitions of seizures and SE have been proposed, there is a surprising variability in the criteria used to define post-anoxic SE in clinical studies. Myoclonic, tonic, tonic–clonic and non-convulsive SE can all occur [32]. EEG correlates are variable and include rhythmic ictal activity ≥3 Hz, as well as periodic and rhythmic discharges <3 Hz. Some authors also consider suppression-burst with myoclonus as a subtype of myoclonic SE [33]. Recent changes in seizures and SE definition or terminology [34, 35] would lead to clinically relevant and statistically significant reduction of false positive diagnoses of SE and to minimal loss in sensitivity; this terminology should be mandatory is all future studies investigating EEG in CA patients.

The prognosis of patients with post-anoxic SE or seizures is poor overall [36]. However, it is important to recognize that a small minority of patients with post-anoxic

myoclonic or non-convulsive SE can have a good outcome [37]. In these patients, SE will develop after return to normothermic conditions (>40 h after ROSC) when compared to those with a poor outcome, who have an earlier onset. In addition, all survivors had preserved brainstem reflexes, continuous background and reactive EEG, low levels of biomarkers of brain injury, which triggered a consequent and aggressive therapy [38, 39].

EEG background

Studies have typically used variable definitions of EEG patterns and EEG recordings were performed at variable time-points, introducing potential sources of bias, as the significance of an EEG pattern depends on the time it is observed and how it is categorized. On the other hand, TTM and sedative administration seemed to exert minor effects on the EEG background and its prognostic value [40, 41]. Indeed, studies using continuous EEG monitoring and consensus definitions have shown that EEG had the best predictive value at 12 and 24 h after ROSC [40, 42, 43]. A normal voltage, continuous EEG devoid of periodic or epileptiform discharges (referred to as "benign" EEG) at 12 h or, to a lesser extent, at 24 h after ROSC is most often associated with good recovery [42] (Fig. 1a). On the contrary, a suppressed (<10 μV) or suppression-burst (including generalized periodic discharges on a suppressed background) background (referred to as "highly malignant" EEG) at 24 h is associated with lack of neurological recovery [42–44] (Fig. 1b–e). In particular, a form of suppression-burst pattern in which bursts exhibit a highly stereotyped shape (suppression-burst with identical bursts) is invariably associated with poor outcome [44]. A low-voltage (10–20 μV; thus not reaching complete suppression) or discontinuous (10–50% suppression; thus not reaching suppression-burst) background also carries a poor prognosis, but this is not always the case especially during the first 24 h [42, 45]. The significance of periodic, rhythmic and sporadic epileptiform discharges is less clear; they most often occur during or after rewarming and are not invariably associated with a poor outcome [46]. In some patients, they evolve from a highly malignant pattern, in which case the outcome is invariably poor [47]. The patterns of alpha coma, spindle coma and theta coma also carry a poor prognostic value but they are seldom encountered [32].

EEG reactivity

There is a strong but imperfect association between lack of EEG reactivity and poor outcome, with FPR ranging from 0 to 15% [43, 45]. One limitation with the assessment of reactivity is the variability in the stimulation. Several noxious and non-noxious stimuli with varying intensity can be applied and it is unclear which combination is optimal. Noxious stimuli in general increase the chance of producing a change of the EEG background [48]. Another limitation of EEG reactivity testing resides in its relatively low inter-observer agreement, as indicated by a κ coefficient ranging from 0.26 to 0.53 [42].

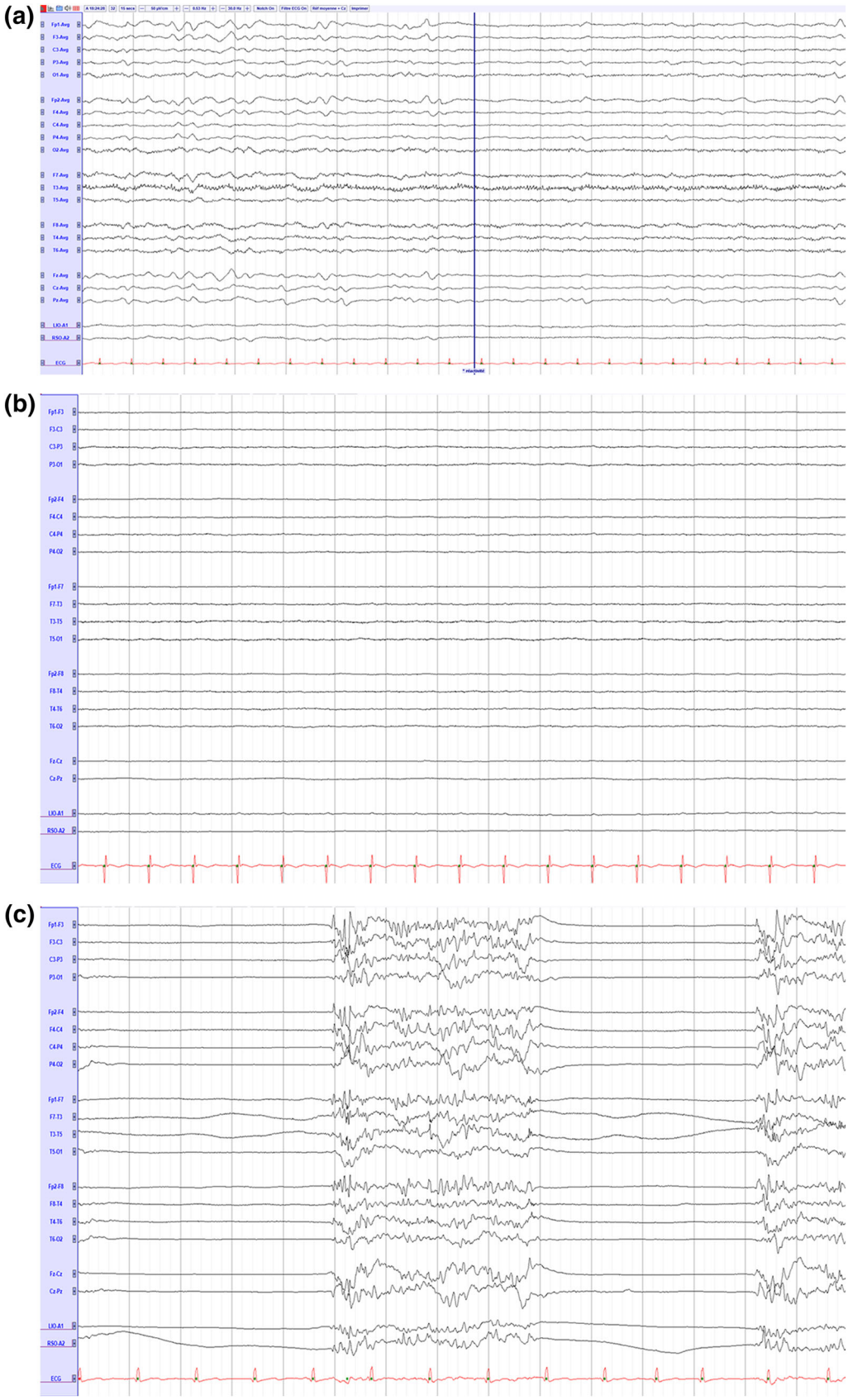
Fig. 1 **a** Continuous EEG pattern; **b** suppressed background; **c** suppression-burst background; **d** GPDs on a suppressed background; **e** continuous spike and waves ▶

Recommendations

1. EEG recording should be started as soon as possible after hospital admission, either with a continuous monitoring or with intermittent repeated tracings.
2. Post-anoxic SE appearing during TTM and sedation is almost invariably associated with poor outcome; in case of late onset of SE and if other favorable prognostic markers are observed, an aggressive treatment should be considered as a minority of patients may eventually awake.
3. Assessment of EEG background for prognostication purposes should be performed at least once between 12 and 24 h after ROSC. "Highly malignant" (burst-suppression, GPDs on a suppressed background and suppression) and "benign" (continuous, normal voltage) patterns are useful and can be used for prognostication. All other patterns of intermediate malignancy (low-voltage, discontinuous background and presence of periodic, rhythmic and epileptiform discharges on a normal voltage background) are less reliable and should be interpreted with more caution.
4. Assessment of EEG reactivity using a standardized stimulation protocol with multimodal stimulation including at least one noxious stimulus gives significant information on the extent of the post-anoxic cerebral injury. Nevertheless, apparent lack of EEG reactivity should also be interpreted cautiously, given its substantial FPR (0–15%) and low inter-observer agreement.

Somato-sensory evoked potentials

In CA patients, the somato-sensory evoked potentials (SSEP) are obtained using an electrical stimulus to the median nerves; cortical responses (N20, expected to appear 20 ms after nerve stimulation) are reliable only when peripheral (N9) and spinal (N13) responses are clearly identified [49]. After CA, the bilateral absence of N20 can predict poor neurological outcome with an FPR <1% [27, 50] when the test is performed at 48–72 h after arrest. The assessment of SSEPs during TTM may result in a lower voltage of the signal and in a delayed appearance of the cortical responses, which may lead to misclassification in 8%


(a)
(b)
(c)

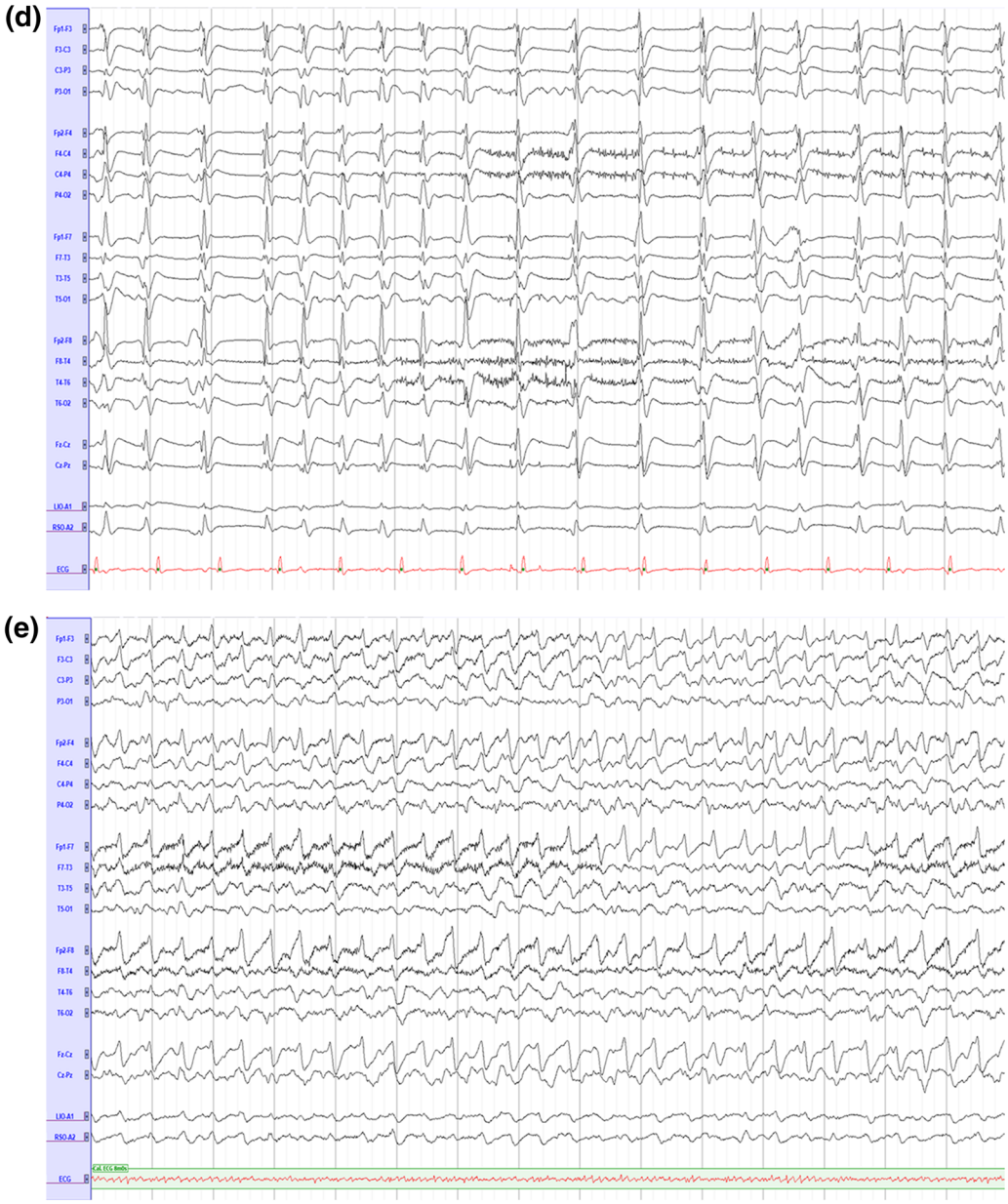


Fig. 1 continued

of patients [50]. If the absence of N20 is highly predictive of a poor prognosis, the presence of N20 has a poor sensitivity to predict good outcome [51]. More recently, Endisch et al. showed that an SSEP amplitude (e.g., the highest short-latency amplitude of 4 cortical recordings) <0.62 mV was found in all patients with poor neurological prognosis, suggesting an additional possibility to increase the accuracy of SSEPs to predict outcome in this setting [52].

A key point for SSEP interpretation is the quality recording for reducing the risk of FPR. So the reduction of background noise and interferences significantly increase the inter-observer agreement of SSEPs [53]. The recommended SSEP recording parameters are summarized in Table 1.

Recommendations

1. In case of good-quality recording, the bilateral absence of N20 cortical responses invariably predict poor neurological outcome in CA comatose patients.

Brain imaging (CT-scan and MRI)

In recent years, several studies have given further evidence of the potential prognostic value of brain computed tomography (CT) and magnetic resonance imaging (MRI)

Table 1 Median nerve somatosensory evoked potentials (SSEPs): suggested stimulus value (range) and recording variables (minimal requirement) adapted from [45, 49]

Stimulus duration	0.1–0.2 ms
Stimulus rate	<5 Hz
Stimulus intensity	above motor threshold, higher level than in conscious patient
Analysis sweep time	50 ms
Filter band pass	3–3000 Hz
Notch filter	should be turned off
Number of trials	500–1000 averaged responses
	Repeat twice for reproducible response
Artifact level	<0.25 μV
Electrical impedance	<500 kΩ
Measurements	Peak latency of N9 potential (Erb's point electrode)
	Peak latency of N13 potential (posterior spinal cervical electrode)
	Peak latency of N20 potential (parietal contralateral electrode
	Inter-peak interval of N20–N13
	N20 amplitude

findings in CA patients; although there are still not enough data to make specific recommendations on their use in this setting. In most comatose CA survivors, cerebral CT-scan is frequently used in the diagnostic workup to exclude non-cardiac causes of the arrest, such as intracranial bleeding. Nevertheless, non-specific signs of poor prognosis, such as brain swelling, may also be observed. The loss of differentiation between grey and white matter on early (<24–48 h) CT-scan has been associated with poor neurological outcome [54–56]. This can be quantified by calculating the ratio, in Houndsfield Units (HU), of grey over white matter (GWR), which is lower in those patients with poor neurological outcome. Although most of these studies have calculated this ratio at the level of the basal ganglia, there is no consensus on the region of interest where the optimal prognostic information should be obtained. In addition, differences in timing of the CT and GWR thresholds, ranging from <1.18 when the imaging is performed within 48 h from arrest [54] to <1.22 if within 24 h [55], make an exact recommendation difficult. Moreover, a low GWR was more effective to predict the neurologic outcome in a CA with hypoxic etiology rather than a nonhypoxic etiology [57]. In patients who were treated with TTM, an averaged GWR (taken at the basal ganglia and cortical levels) of <1.16 was predictive of poor outcome [58]. CT can also be combined with other predictors to improve the predictive performance. Median whole-brain HU combined with the day 3 Glasgow coma score (GCS), or with AAN practice parameters, resulted in an increased sensitivity and specificity over the clinical parameters alone [59]. When combining CT and the biomarker neuron-specific enolase (NSE), the predictive performance of both was improved [60].

MRI is considered to be an even more appropriate tool for prognostication and has been used in different studies to evaluate the extent of ischemic brain damage after CA. Diffusion-weighted imaging (DWI) is most suited for early ischemic changes, whereas the fluid-attenuated inversion recovery (FLAIR) sequences become positive in the early subacute period (24 h to 2 weeks). MRI with DWI is used to calculate apparent diffusion coefficient (ADC) values, a measure of the magnitude of diffusion of water molecules within tissue [61]. The data on MRI for neuroprognostication come from small studies, often performed in heterogeneous populations and should be interpreted with some caution because of the inherent bias of selection, either through not including those patients with clinical signs of recovery or through withdrawal of life-sustaining therapies in those with an estimated poor prognosis because of pathological MRI findings. In these studies, absence of ADC depression or DWI changes was associated with good neurological recovery [61, 62]. In two larger studies, lower whole-brain median ADC and the percentage of brain volume with an ADC value below the threshold of 650–700 $\times$ 10^{-6} mm^2/s were significant predictors of poor outcome [63, 64]. When using ADC depression as a prognosticator in patients who were cooled after CA, it is important to realize that hypothermia per se can cause ADC depression, as was demonstrated in a rat model and a patient study [65, 66]. Therefore, MRI has to be reserved for the rewarming phase, and is ideally performed few days after the arrest. In prolonged comatose patients with uncertain outcome, functional MRI (fMRI) and diffusion tensor imaging (DTI) could be useful to map disruptions in connectivity. In general, more extensive amounts of disruption could be associated with worse outcome [67]. More specifically, the patterns of disruption could be informative to predict the functional consequences with regards to recovery [68].

Recommendations

1. A low GWR at cerebral CT-scan could be assessed in the early phase after hospital admission (<48 h) to identify post-anoxic brain injury and could be integrated with other tools for prognostication to predict poor outcome.
2. Brain injury on MRI should be evaluated in CA patients who remain comatose for more than 5 days; DWI and ADC are the MRI parameters that could better identify ischemic alterations. MRI findings should always be integrated with other tools to predict poor outcome in these patients.

Biomarkers

The two biomarkers of brain injury that have been largely evaluated in comatose survivors from CA are neuron-specific enolase (NSE) and S-100β. Although non-survivors have significantly higher NSE values than survivors in several studies, a clear cut-off of this peptide to accurately assess prognosis in CA patients has not been identified yet. If the same cut-off of 33 μg/L than what proposed in CA patients not treated with TTM would be used [69], the FPR to predict poor outcome would range from 7 to 30% [50, 70], suggesting the need of much higher NSE cut-offs to identify patients with poor prognosis in this setting. Moreover, as TTM attenuates neuronal injury and may reduce serum NSE levels, repeated measurements are necessary [71]. In a recent study, Stammet et al. evaluated NSE levels 24, 48, and 72 h after ROSC in 686 patients admitted after out-of-hospital CA and randomized to TTM at either 33 or 36 °C [72]. At 48 and 72 h, NSE predicted neurological outcome with areas under the receiver-operating curve of 0.85 and 0.86, respectively. The NSE cut-off to have ≤2% of FPR at 24, 48 and 72 h were 66, 48 and 38 μg/L for patients treated at 33 °C and 68, 48 and 41 μg/L for those at 36 °C.

High concentrations of S-100β have also been found in CA patients with poor neurological outcome when compared to others, with different cut-offs (from 0.2 to 1.5 mg/l) to predict poor outcome [73, 74]. In a recent study, initial and 72-h S100B levels predicted mortality [75]. Although S-100β has a very short half-life and could be very effective to detect extensive brain damage in the early phase after CA, most of the existing data in the literature relate to NSE, which should be considered as the most reliable biomarker in this setting. Importantly, none of the biomarkers should be used alone to predict outcome as several pitfalls exist for NSE (e.g., hemolysis, cancers, handling of blood samples) or S100β (chondrocytes lysis, vascular diseases) that may increase their serum levels independently from brain damage [76].

Recommendations

1. High NSE and S100β levels may help to identify CA patients with poor neurological recovery.
2. As the optimal predictive cut-offs and the more specific time-point to measure these two biomarkers have not been clearly identified, NSE and S100β should be repeatedly assessed and then be integrated with other tools for prognostication to predict poor outcome.

Brain perfusion

After an anoxic injury, the brain is subjected to a sequence of pathophysiological changes, affecting cerebral perfusion/oxygenation balance. Indeed, immediately after ROSC a short-lasting cerebral hyperemia followed by an increase in cerebrovascular resistance finally resulting in a decrease in the cerebral blood flow has been described [77]. Experimental CA studies revealed that the severity of brain damage was mainly influenced by the mismatch in the oxygen extraction rate (CEO_2) to cerebral blood flow (CBF) during the reperfusion period [78, 79]. A better understanding of these cerebral hemodynamic disturbances may therefore have an impact on the post-CA management and may allow a better prognostication.

Lemiale et al. combined jugular bulb oximetry (SjO_2), as estimate of cerebral perfusion adequacy, and transcranial Doppler recordings (TCD) to assess cerebral hemodynamics in 18 post-CA patients [79]. Their observations concluded to a mismatch between CBF and CEO2 in the first 72 h post-CA, leading to a "luxurious perfusion", especially in non-survivors. Buunk et al. reported TCD results on 30 post-CA patients (21 non-survivors and 9 survivors); they observed limited changes in cerebral blood flow velocities during the first 24 h after CA while SjO_2 significantly increased only in non-survivors [80]. In another study, no differences in TCD measurements were found between the patients with favorable and unfavorable neurological outcome after CA [81].

Near-infrared spectroscopy (NIRS) provides information on brain oxygenation by monitoring the regional cerebral oxygen saturation (rSO_2) at the microvascular level of the frontal area [82]. In recent years, several studies investigated whether NIRS could be used during the post-CA stage to assist with neuroprognostication. Overall, significant higher rSO_2 values were observed at different time-points in the post-CA phase in patients with a favorable compared to those with unfavorable outcome. Meex

et al. measured rSO_2 in 28 post-CA patients during the cooling phase and observed a significant decrease in rSO_2 at induction of TTM, with significant lower rSO_2 values in non-survivors [83]. Ahn et al. measured rSO_2 for 48 h post-arrest in 21 patients; only during the first 24 h, median rSO_2 was significantly higher in survivors compared to non-survivors [84]. Storm et al. monitored rSO_2 in 60 CA patients and found significantly lower average rSO_2 within the first 40 h after ROSC in patients with a poor outcome, but with large overlap between groups [85]. Outcome prediction by area of rSO_2 below a critical threshold of 50% within the first 2 days after arrest yielded 70% specificity and 86% sensitivity to predict poor outcome.

Recommendations

1. From current observations we cannot recommend the use of any specific TCD value or NIRS threshold as prognostic indicator of CA patients.

Multimodal approach

Previous studies have suggested some benefits of a multimodal approach [40, 86–88]; the combination of at least three different prognostic tools can increase the predictability of outcome in up to 85% of CA patients [88]. Taking into account all the most important studies in this field, we recommend a combination of several prognostic tools to improve the accuracy of predicting outcome after CA when TTM is used (Fig. 2).

After hospital admission, continuous or repeated EEG monitoring should be initiated even during sedation and TTM. The presence of early SE, "highly malignant" EEG patterns or an unreactive EEG, especially if in combination, would suggest a poor neurological outcome. Importantly, none of these EEG finding should be used to LSTW and need to be correlated with neurological examination $\geq$3 days from arrest. Whenever available, NSE assessment (e.g., high levels) could be useful to confirm the severity of post-anoxic brain damage. Early brain CT-scan (GWR $<$1.2) might also be useful although it should not delay other important therapeutic interventions for the patients (e.g., TTM and coronary angiography). On the contrary, evidence of reactive EEG or continuous background activity indicates a high probability of good neurological recovery.

At TTM and sedation discontinuation, repeated neurological examination should search for signs of good (e.g., motor response $\geq$5) or poor (motor response $\leq$2 with absent brainstem reflexes and/or generalized myoclonus) outcome. In case of status myoclonus, EEG is necessary to find concomitant correlates of poor prognosis (SE, "highly malignant" EEG patterns or generalized discharges). In patients who remain comatose, SSEPs should be performed at 72 h from arrest and if bilateral absence of N20 potentials is found poor neurological outcome can be anticipated. Repeated daily NSE assessment would also be useful in these patients as an additional marker of extended brain injury. If all these "negative" findings are absent, prognostication becomes more difficult and should include MRI; considering its limitations, no final decisions on LSTW should be made before 7 days and a prolonged observation period (1–2 weeks) should be considered in case of uncertain prognosis.

Importantly, it remains actually unknown which would be the best approach to these patients when they are admitted into hospitals without facilities for electrophysiological tests or assessment of biomarkers. The absence of a complete protocol to prognosticate would expose almost 15% of patients with functionally favorable survival to a potentially avoidable decision of LSTW [89]. Thus, we recommend contacting experienced centers to discuss and eventually refer patients with uncertain prognosis and/or in case no additional tests for prognostication would be available. Another possibility would be to repeat neurological examination for at least 7 days and, if persistent poor motor response persists without any further improvement and presence of confounders, poor prognosis would be expected in more than 98% of cases.

Recommendations

1. A multimodal approach incorporating at least 2 or 3 additional tools, including at least EEG in all patients, in addition to clinical examination should be used in comatose CA survivors to predict outcome.
2. Referral to experienced centers would be necessary in case of patients with uncertain prognosis and/or absence of multimodal approach.

Conclusions

In this manuscript, we have summarized the current literature on prognostication of comatose CA patients and have underlined the need for a multimodal approach to avoid misclassification. Considering actual practices in Belgium, this kind of approach together with the help of specialized centers should be widely spread and become the common management of such patients. Future studies on new tools to improve the prediction of outcome in this patients' population (e.g., automated pupillometry, quantitative EEG monitoring, event-related cortical potentials, new

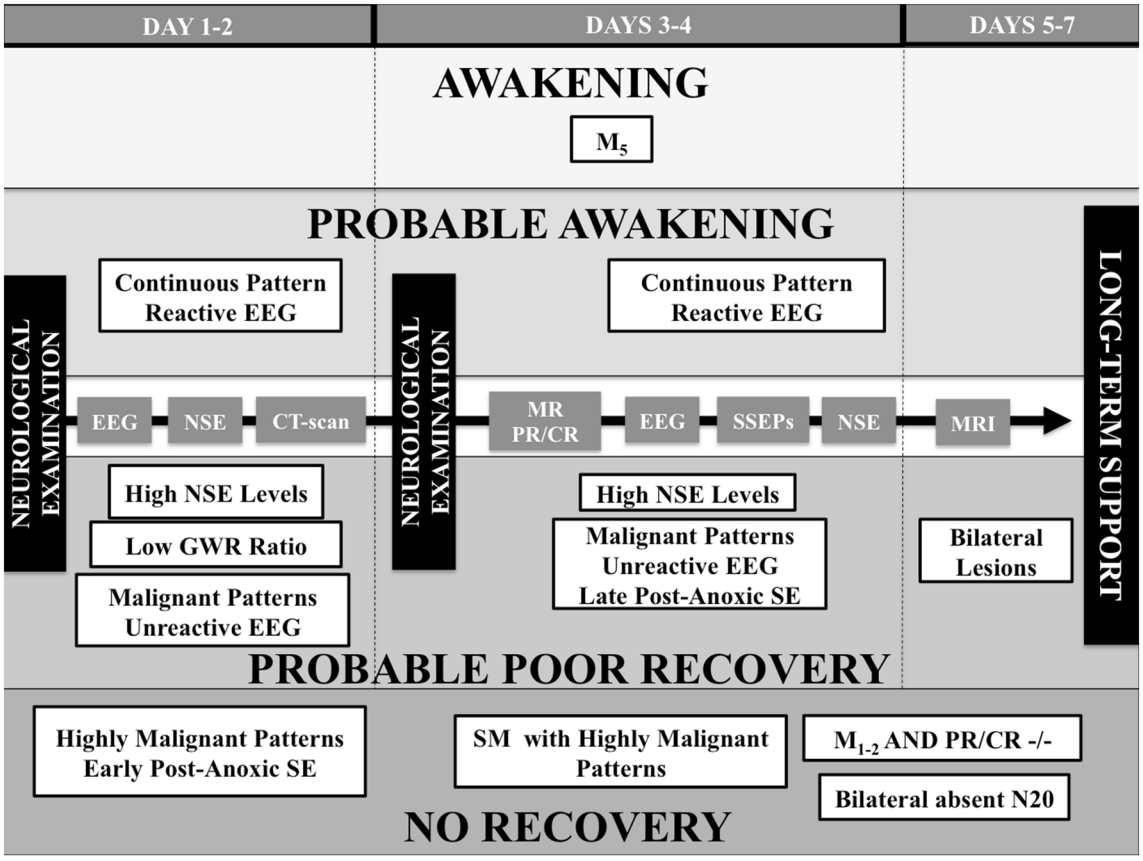


Fig. 2 Multimodal approach for prognostication of neurological outcome after cardiac arrest. *EEG* electroencephalogram, *NSE* neuron-specific enolase, *CT* computed tomography, *MR* motor response, *CR* corneal reflexes, *PR* pupillary reflexes, *GWR* grey- to white-matter ratio, *SSEPs* somato-sensory evoked potentials, *MRI* magnetic resonance imaging, *SE* status epilepticus, *SM* status myoclonus, *M1–2* absent or posturing motor response, *N20* cortical responses during SSEPs

biomarkers, assessment of optic nerve diameter) could potentially influence the approach to such patients and may give new insight to the investigation of post-anoxic brain injury.

Compliance with ethical standards

This article does not contain any studies with human participants or animals performed by any of the authors.

Conflicts of interest None to declare.

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