Neurological prognostication of outcome in patients in coma after cardiac arrest

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Management of coma after cardiac arrest has improved during the past decade, allowing an increasing proportion of patients to survive, thus prognostication has become an integral part of post-resuscitation care. Neurologists are increasingly confronted with raised expectations of next of kin and the necessity to provide early predictions of long-term prognosis. During the past decade, as technology and clinical evidence have evolved, post-cardiac arrest prognostication has moved towards a multimodal paradigm combining clinical examination with additional methods, consisting of electrophysiology, blood biomarkers, and brain imaging, to optimise prognostic accuracy. Prognostication should never be based on a single indicator; although some variables have very low false positive rates for poor outcome, multimodal assessment provides resassurance about the reliability of a prognostic estimate by offering concordant evidence.

Lancet Neurol 2016; 15: 597–609

Published Online
March 23, 2016
http://dx.doi.org/10.1016/S1474-4422(16)00015-6

This online publication has been corrected. The corrected version first appeared at thelancet.com/neurology on April 13, 2016

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Introduction

Cardiac arrest is a major health problem,[1] with a yearly incidence of about 50–110 per 100 000 people worldwide.[2] A number of factors have contributed to an overall increase in cardiac arrest survival and frequency of discharge with good neurological recovery and quality of life over the past decade. These factors include progress in advanced life support, access to emergent coronary angiography, implementation of targeted temperature management (TTM; induced mild hypothermia to 32°C or strict normothermia at 36°C for 24 h),[3] optimum support of cerebral and organ perfusion, and prevention of extracerebral systemic insults (eg, hyperglycaemia and infections).[4–9] In line with this improvement, cardiac arrest has become a leading cause of coma and a frequent cause of admission to the intensive care unit. Clinicians involved in the care of adults in a coma after cardiac arrest are confronted with the increasingly optimistic expectations of next of kin and, in the early phase of intensive care management, neurologists are regularly requested to provide predictions of long-term outcome.

Brain dysfunction after cardiac arrest, predominantly resulting from global ischaemia-reperfusion injury, is the main determinant of prognosis. However, additional factors can further alter brain function—for example, sedatives used during TTM and post-cardiac arrest organ dysfunction; these aspects might substantially delay recovery of cerebral function for up to 6 days,[10] leaving caregivers and families with an unacceptably long period of uncertainty. In this scenario, despite neurological examination being the first and most important step in the assessment of patients,[11] a growing body of clinical evidence shows that the integration of additional methods, consisting of electrophysiological investigations, blood biomarkers of cerebral injury, and brain imaging, improves the accuracy of early (24–72 h) coma prognostication.

Neurological consultation and multimodal prognostic assessment has, nowadays, become an integral part of post-resuscitation patient management. In practice, a complete battery of tests is either not always necessary according to the clinical situation, or not available in every facility; although university medical centres might have optimal resources at their disposal, smaller or peripheral hospitals typically have to rely on fewer resources. In this Review, we critically appraise the scientific literature in this developing field and evaluate each prognostic method, emphasising false-positive rates (FPRs) and positive predictive values of poor and favourable prognosis. Experts in coma prognositication defined outcome by cerebral performance categories (CPCs; CPC 1 back to baseline, CPC 2 moderate impairment, CPC 3 severe impairment, CPC 4 vegetative or comatose, CPC 5: dead).[12] Here, for the general neurology audience, we refer to good (CPC 1 or 2) or poor (CPC 3-5) outcome. Of note, however, is that CPC 3 is heterogeneous; depending on the time of assessment and the possible improvement of the patient, it may be related to a favourable outcome. We acknowledge the scarce evidence supporting the use of each prognosticator and the inevitable limitation imposed by the possibility of confirmatory bias, or the so-called self-fulfilling prophecy (ie, if a variable is, a priori, believed to be indicative of poor prognosis and leads to withdrawal of life-sustaining treatment, it will ultimately determine the outcome).[13,14]

Our purpose is to provide a general neurology audience with an updated, critical review of available methods for coma prognostication after cardiac arrest in adults, summarise their respective value and potential clinical use, and suggest a stepwise multimodal paradigm, paying specific attention to appropriate timings and combination of prognosticators. Finally, an outlook on promising emerging methods will be offered.

Clinical examination

Neurological examination is an essential component of prognostication because it directly evaluates brain function. Assessment of brainstem reflexes, motor responses to pain, and myoclonus during the first 72 h after arrest represented the standard test before the advent of TTM[15] and retains its prognostic value in

patients given TTM (at target temperatures of 32–36°C).[16] However, these features can be altered by TTM and residual sedation, therefore repeated assessments are often necessary. Clinical improvement can be heralded by the appearance of eye tracking or movements to command. The predictive performance of clinical examination might be limited by the fact that it has been systematically used for clinical decisions in cohort studies, raising concerns about some degree of confirmatory bias.

Pupillary light and corneal reflexes

Bilateral absence of pupillary light reflexes at 72 h after cardiac arrest is a robust indicator of poor prognosis, whether the patient undergoes TTM or not (FPR 0·5% [95% CI 0–2] *vs* 0·5% [0–8]).[13,15–19] Although absence of pupillary reflexes during the first 24 h after arrest is not incompatible with good recovery, particularly in hypothermic patients (8% [1–25]),[18] the presence of pupillary reflexes at 72 h is not a strong indicator of good prognosis (predictive value 61% [95% CI 50–71]).[16] Absence of corneal reflexes at 72 h correlates with poor prognosis (FPR 5% [0–25]), although with lower certainty than pupillary reflexes, especially in patients who have received sedatives or neuromuscular blockade.[13,18] Similarly to pupillary reflexes, the presence of corneal reflexes is an unreliable predictor of good outcome (predictive value 62% [95% CI 51–72]).[16]

Motor response

Absent or extensor response to pain 72 h after cardiac arrest was deemed a reliable indicator of poor outcome before broad use of TTM.[15] However, this response is the physical sign most affected by sedatives, opiates, and neuromuscular blockade; consequently, motor responses are less reliable in patients undergoing TTM (FPRs up to 24% [95% CI 6–48]) than in those not receiving TTM.[13,15,20] Assessment of motor responses needs the application of a strong stimulus and exclusion of the residual effects of pharmacological sedation, which can be extended by TTM or reduced metabolic clearance (eg, hypothermia, or renal or liver dysfunction), or both.[10] Timing and proficiency of the examination can greatly affect the elicited response and therefore its prognostic accuracy. When motor responses are assessed, it should be remembered that although an extensor or absent response does not necessarily signify a poor prognosis, a flexor or even a localised movement does not always imply that the patient will recover (positive predictive value 81% [95% CI 66–91]).[14]

Myoclonus has long been known to predict poor outcome after cardiac arrest,[15,21] but there have been reports of patients who have recovered well despite having early post-anoxic myoclonus[22–25] and this evidence has raised questions about its prognostic accuracy. Indeed, up to 9% of patients with myoclonus survive.[23,26] The precise definition of what constitutes myoclonus is crucial. Not all so-called twitches have the same prognostic implication, rather their usefulness in predicting prognosis depends on semiology, duration, and associated EEG findings. Generalised status myoclonus (multifocal spontaneous twitches lasting for more than 30 min, occurring even under TTM and sedation) is commonly accompanied by malignant, unreactive EEG patterns (see next section) and is consistently associated with poor outcome (FPR 0% [95% CI 0–3]).[16] Conversely, brief myoclonic jerks mostly restricted to the face or trunk, controllable with sedatives, and accompanied with a more benign (ie, continuous and reactive) EEG, do not suggest an invariably poor outcome (up to 11% [3–26]).[18,20] These considerations could explain the markedly different FPRs across studies and emphasise the importance of careful clinical assessments and interpretation in the context of other prognosticators, especially EEG.

Electroencephalography

An electroencephalographical signal is generated by cortical post-synaptic potentials. Electroencephalography is widely available, non-invasive, and inexpensive, and provides real-time investigation of electrical brain activity. It has been used routinely for decades in coma prognostication;[27] however, there is increasing interest in the use of EEG in the intensive care unit, which parallels progress in post-cardiac arrest care. In the context of prognostication, EEG is very informative because several EEG features correlate with degree of neuronal injury.[28] The increasing availability of CT-compatible and MRI-compatible electrodes has facilitated the use of continuous EEG in the intensive care setting;[29] use aided by the development of automated EEG screening, which expedites EEG interpretation, although it does not negate the need for technical expertise.[30,31] The American Clinical Neurophysiology Society has published standardised guidelines for EEG interpretation,[32] which have been validated in the setting of coma prognostication.[33] EEG findings can be classified into three main aspects, discussed in the following three sections.

Mild hypothermia does not have a major effect on EEG measurements of brain activity,[34] whereas sedative drugs used during TTM can have substantial effects (especially background and reactivity), depending on the drug and dose used. Findings from several studies suggest, however, that despite sedative infusions in the range of 0·1–0·2 mg/kg per h (midazolam) or 2–3 mg/kg per h (propofol), prognostic accuracy of EEG is better during the first 24 h, with or without TTM, than after 2–3 days.[35–37] If, however, sedative doses are much higher than those stated above, EEG findings should be interpreted with caution. Of note, studies focusing on EEG reactivity or quantitative analysis are less challenged by confirmatory bias than are studies of EEG background and epileptiform features.

Background activity

Background activity is the first variable that needs to be assessed because it is representative of global cerebral functioning. Ischaemia-induced neuronal damage is associated with decreased amplitude and slowing of background activity. Several studies have assessed the association of several background activity parameters with poor prognosis: appearance of low-voltage (<20 μV) or isoelectric (suppressed) background at 24 h (FPR 0% [95% CI 0–17]);[37,38] burst suppression at any time (0% [0–11]);[37] burst suppression with identical bursts (0% [0–17]);[9] and spontaneously discontinuous background during TTM (7% [0–24])[28] are predictive of poor outcome. Conversely, continuous background activity as soon as 12 h after cardiac arrest has been correlated with a high likelihood of awakening (positive predictive value 92% [80–98]);[35] a normal voltage background at 24 h is similarly associated with a good outcome (positive predictive value 72% [53–86]).[37] An exception to the good prognosis related to background activity is an EEG profile indicative of α coma; this refers to an anterior prominent rhythm without reactivity (figure 1), and is associated with poor prognosis in up to 100% of patients.[40]

Figure 1: **α coma, a frontally predominant α rhythm in a 70-year-old woman in a coma, who was non-reactive to painful stimulation 3 days after cardiac arrest**
The patient did not show any brainstem reflexes and subsequently died. Bipolar longitudinal montage 30 mm/s, 10 μV/mm, high-frequency filter 70 Hz, low-frequency filter 1·0 Hz. Painstim=painful stimulation.

Background reactivity

Reactivity is an EEG response elicited by auditory or noxious stimuli and is characterised by either a transient attenuation or increase in electrical activity (figure 2). Absence of reactivity has been shown to correlate with poor outcome if assessed after TTM (FPR 7% [95% CI 1–15]);[14,41] this correlation is stronger if an absence of reactivity is seen during TTM (2% [0–9]).[36,42] Conversely, reproducible reactivity is associated with subsequent awakening when recorded during TTM (positive predictive value 86% [77–92])[43] and thereafter (78% [64–88]).[14] Stimulus-induced rhythmic, periodic, or ictal discharges, not representing physiological reactivity, occur in about 15% of patients and herald poor prognosis (FPR 2% [0–11]), particularly if recorded during TTM or sedation.[44] An important limitation of EEG reactivity is that it can be heavily subjective both in its administration—ie, strength of stimuli used, and assessment of EEG recordings (ie, variable inter-rater reliability);[33,45] therefore, a standardised stimulation protocol might improve the utility of EEG reactivity as a prognostic indicator.[46]

Figure 2: **Background reactivity (transitory diffuse amplitude attenuation) to auditory stimuli (claps) in a 57-year-old man in a coma during therapeutic hypothermia, 20 h after cardiac arrest**
On return to normothermia, the patient had preserved brainstem reflexes and somatosensory evoked potentials, and subsequently awoke. Reduced bipolar longitudinal montage 20 mm/s; 10 μV/mm; high-frequency filter 70 Hz; low-frequency filter 0·5 Hz.

Epileptiform features

Sharp waves, spikes, poly-spikes, and waves, collectively referred to as epileptiform features, are rarely recorded in isolation, as they typically occur in repetitive (periodic or rhythmic) patterns. Occurrence of these features after TTM is associated with poor outcome (FPR 9% [95% CI 2–21]);[14] the association is stronger when epileptiform discharges are recorded during TTM, when the patient is sedated with a drug with antiepileptic properties (0% [0–30]).[28,47] Nevertheless, a subset of patients with electrographic status epilepticus (epileptiform features) appearing after TTM and sedation weaning, especially those who have preserved brainstem reflexes, background reactivity, and somatosensory evoked potentials, might have reasonable functional recovery.[48] Quantitative analysis of EEG recordings suggests that patients with epileptiform features who achieve good functional recovery show higher background continuity and discharge frequency, but lower discharge periodicity, than do patients with poor clinical outcome.[49] In our experience, patients with epileptiform transients and concomitant features suggesting a potentially good prognosis on their

clinical and neurophysiological assessment (as illustrated above) should be treated aggressively with anticonvulsants and, if needed, pharmacologically induced coma. The optimum duration for such treatment in this context is not known, but it should not be extended beyond 2 weeks if the patient does not awake; to continue indefinitely beyond this timeline does not seem to modify the prognosis in our experience.

Standard versus continuous EEG

Some clinicians advocate the use of continuous EEG for up to 48 h;[35,37] however, it has been reported that two standard EEG recordings of 20–30 min duration, including stimulations for reactivity, completed within 48 h of cardiac arrest, are as informative as continuous EEG,[50] while being less demanding on resources.[51] With the exception of EEG monitoring of post-anoxic status epilepticus, for which continuous recording is recommended, intermittent EEG represents a valid alternative for centres with few resources. Because electrical activity can change with time,[38,52–54] repeated assessments are advisable, in particular, during the first 72 h after cardiac arrest. Reduced montages, with as few as two channels, allow for amplitude-integrated analysis and assessment of bispectral index.[52–55] Both non-continuous and reduced montage EEG recordings are viable alternatives to continuous EEG for assessment of background and reactivity; however, they are less sensitive than continuous EEG for detection of epileptiform transients and epileptic seizures. Recordings done too early after cardiac arrest could overestimate the degree of brain injury. Consequently, and considering that most epileptiform alterations appear after 12–24 h,[56] EEG assessments should be started 12 h after cardiac arrest.[50]

Somatosensory evoked potentials

Examination of somatosensory evoked potentials is a valuable complement to EEG, but less widely available.

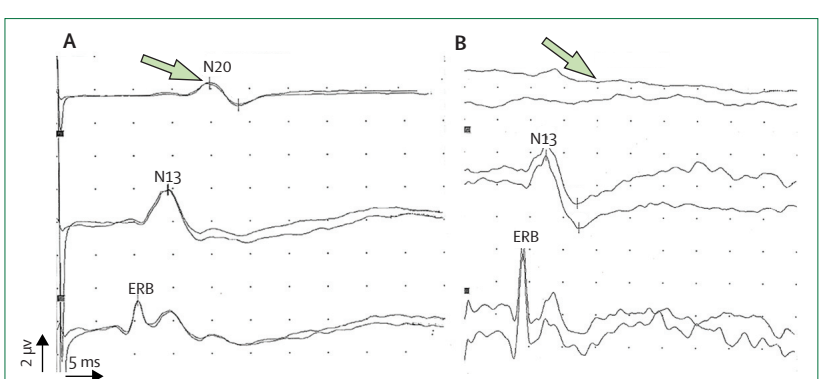

Figure 3: **Early-latency somatosensory evoked potentials (upper limb)**
(A) Example of a normal recording showing, from bottom to top, a plexus (Erb), cervical (N13), and cortical (N20, arrow) response in a 33-year-old man in coma who later awoke. (B) Example of absence of the N20 (arrow) despite presence of a plexus and cervical response in a 16-year-old girl in coma who did not survive.

Early-latency evoked potentials have been consistently studied in the setting of post-cardiac arrest coma prognostication, whereas middle-latency responses have received little attention.

Early-latency evoked potentials

Early-latency evoked potentials result from the averaging of cortical electrographic responses generated after repetitive electrical stimulations of the median nerve, transmitted to the contralateral post-central gyrus, and are represented by a negative deflection on the recording, about 20 ms after the stimulation (thus also called N20; figure 3). Bilateral absence of the N20 response is strongly correlated with a poor outcome, both during (FPR 0% [95% CI 0–2])[18,57] and after (0·5% [0–2])[10,13,35,36,57] TTM. Although the accuracy of evoked potentials is extremely high for prediction of poor prognosis (notwithstanding a degree of confirmatory bias), their accuracy in predicting a favourable outcome is disappointing; reports of the positive predictive values of bilaterally present N20 range from 40% (29–50)[35] to 58% (49–68),[36] substantially lower than that of a continuous reactive EEG (approximately 80%).[43] Furthermore, evoked potentials have a lower sensitivity than the absence of reactivity on EEG to predict a poor outcome (43% [31–57] and 74% [62–84] respectively);[36] notably, the study reporting these values did not include EEG reactivity in the decision to withdraw supporting care. In line with this finding, early-latency evoked potentials do not provide additional information when EEG, clinical assessment, and biomarkers are available.[35,36] Although electroencephalographic waves are generated by corticocortical interplays, early-latency evoked potentials only represent averaged signals of an afferent pathway.[58] Quantitative assessment of N20 amplitude has been suggested to offer additional prognostic information,[59] but this observation needs to be replicated in other patient cohorts.

Middle-latency evoked potentials

Middle-latency evoked potentials are elicited by intracortical associative interactions and can be recorded up to 100 ms after stimulation; similarly to early-latency evoked potentials, they are generated by averaging the response to several stimuli to cancel out the background EEG noise. Although middle-latency evoked potentials should better show the presence of functional connectivity than early-latency evoked potentials, and thus allow prognostication of awakening, they are used far less commonly than early-latency evoked potentials because they are difficult to record. The prognostic value of auditory middle-latency evoked potentials was predominantly investigated before the introduction of TTM. Although the presence of middle-latency responses has been reported to have a positive predictive value for awakening as high as 97%,[60] this finding has been challenged by subsequent reports of a positive predictive value of only 28%.[61] However, it has been suggested that

the presence of pain-induced middle-latency evoked potentials might be strongly predictive of consciousness recovery (positive predictive value 100% [95% CI 87–100]) even before EEG reactivity is observed.[62]

Biochemical markers

There is currently great interest in assessing the prognostic value of biomarkers of neuronal injury; however, because of the heterogeneity of patient cohorts , the collection and processing of biological fluids, and the detection methods of markers, the generalisability of much of the available evidence is limited.[63] Although a wide range of proteins have been identified as markers of cellular injury, only neuron-specific enolase (NSE; a marker of neuronal damage) and S-100 β (a marker of astrocyte damage) have been extensively studied by independent groups; this section thus concentrates on these two proteins, whereas other biomarkers are presented in the section on promising new prognostic methods section below. Studies of biomarkers are not immune to confirmatory bias.

Neuron-specific enolase

NSE is released by dying neurons and, so far, has been the most studied biomarker for post-cardiac arrest coma prognostication. NSE concentrations positively correlate with the extent of neuronal injury and malignant EEG changes.[28] Investigators of a prospective study, before the advent of TTM, noted that a serum NSE concentration of more than 33 μg/L between 24 h and 72 h after cardiac arrest was strongly associated with poor outcome (FPR 0% [95% CI 0–3]).[64] However, results were more variable in subsequent studies without TTM (9% [1–29] for the cutoff of 33 μg/L;[16] maximal concentrations in patients with good outcome ranging from 48 μg/L at 24 h to 80 μg/L at 72 h).[18,65]

The reliability of NSE as a prognostic indicator has been further questioned by studies done in patients who had received TTM at 33°C, in which unacceptably high FPRs (up to 29% [95% CI 16–36]) have been repeatedly reported when a serum NSE concentration threshold of 33 μg/L was used.[10,13,16,28,66,67] Whether a threshold exists beyond which good recovery is no longer possible is a matter of debate. However, existing data suggest that it is uncommon for a patient to experience functional recovery with a serum NSE concentration in excess of 80 μg/L within the first 72 h after cardiac arrest.[68,69] In a large multicentre study,[66] thresholds as high as 120 μg/L at 48 h and 50 μg/L at 72 h were necessary to keep FPRs below 1%. Exceptional cases have been reported, however, in patients with functional recovery despite serum NSE concentrations of up to 151 μg/L within the first 72 h after cardiac arrest.[67,70] Furthermore, concentrations of less than 33 μg/L are inconsistently related to good outcome (positive predictive value 63% [52–73]);[36] consequently, it is now not recommended to apply a single threshold for prediction of good or poor recovery.[18,26] The trend of serum NSE concentration from serial measurements taken over the first 72 h could be more accurate in prediciting outcome than a single value,[66] but the best way to interpret the results remains to be elucidated.

An important caveat to the use of biomarkers is sample handling and the skills of the laboratory staff. Variability in serum concentrations have been noted between laboratories and when different quantification methods are used,[71] and spurious results can be obtained when samples are haemolysed (eg, during hypothermia).[72] Biomarker concentrations could also theoretically increase because of haemolysis in patients who are treated with extracorporeal membrane oxygenation; the extent of this event deserves further investigation, so caution is advisable in this setting. It is also important to note that NSE is present in neuroectodermal cells and high concentrations can be seen in patients with small-cell lung carcinoma.

Serum S-100 β protein

Serum S-100 β protein is released by glial cells after brain insult and can also be released from extracerebral sources, such as adipose tissue and muscle. Concentrations of this biomarker are measured far less commonly than NSE, likely because of test availability (NSE also serves as a tumour biomarker), and because thresholds for uniform identification of poor outcome have been very variable across studies, irrespective of whether TTM was used.[18] In view of its short biological half-life, serum S-100 β concentration increases quickly after hypoxia-induced injury, and high concentrations (>0·5 μg/L) could signal poor prognosis, even within the first 24 h of cardiac arrest.[73,74] However, because early prognostication with a single variable is discouraged, the practical value of the difference in kinetics between NSE and S-100 β is questionable.

Neuroimaging

Brain imaging can help reveal structural alterations and quantify the extent of post-anoxic damage; its application for coma prognostication is quite new, and consequently it is used less frequently than other methods of prognostication. Most studies of the use of imaging in coma prognostication are retrospective and assess the value of imaging as a single method. In several studies, clinicians were not masked to imaging findings, which might have introduced some degree of confirmatory bias. However, when clinicians were blinded, a good correlation between extensive cortical injury seen with MRI and poor outcome was noted.[75,76]

Brain CT

CT provides valuable information if the cause of cardiac arrest is uncertain and an intracranial haemorrhage needs to be ruled out. However, intracerebral causes of cardiac arrest are very infrequent (particularly after ventricular

fibrillation), and the benefit of a routine brain CT on admission should be balanced with the potential delay in starting TTM and post-resuscitation care.[77] CT indications of brain hypoxia include loss of or reduced grey–white matter discrimination and sulcal oedema or effacement. Loss of grey–white matter discrimination within 2 h of cardiac arrest seems a reliable predictor of poor outcome (FPR 0% [95% CI 0–12]); inter-observer concordance is good, but identification of survivors is poor (positive predictive value 37% [9–75]).[78] Investigators of a multicentre study[79] of patients undergoing hypothermic TTM after cardiac arrest noted that, although reduced grey–white matter ratios could predict poor outcome with an FPR of 0%, sensitivity was extremely low (3·5–6·0%); furthermore, inclusion of CT findings in a multivariable model with other prognosticators did not improve the accuracy of outcome prediction. These results were in accordance with a previous study, which reported an FPR of 0% (0–4), sensitivity of 14–20%, and moderate-to-good inter-rater agreement.[75]

Brain MRI

MRI has higher resolution than CT, so allows for easier identification of structural abnormalities in the neocortex, deep grey nuclei, and hippocampi. Although the superiority of MRI to CT for outcome prediction has not been shown in a clinical trial, many investigations have focused on the use of MRI (particularly diffusion-weighted MRI) in this setting. In patients with a poor outcome, occipital and mid-temporal cortex and the putamen can show restricted diffusion, suggestive of cytotoxic oedema.[76] Findings from quantitative assessments of the association of poor outcome and analysis of diffusion-weighted MRI (figure 4) across different brain areas have shown an FPR of 0% (95% CI 0–22) for predicting poor outcome with MRI, with excellent inter-rater agreement.[80,81] Investigators of a retrospective multicentre study in the USA, assessing the association of apparent diffusion coefficient on MRI with poor outcome, reported a slightly poorer performance, however, noting an FPR of 9% (2–25)].[82] This finding is similar to the results from a large retrospective multicentre study from Korea,[83] where an FPR for poor outcome of 7% (2–18) was reported. However, diffusion-weighted MRI did not do as well in another study,[84] in which a very high FPR (54% [26–80]) was reported. Furthermore, absence of diffusion changes does not consistently predict a good outcome (positive predictive values 73% [45–92][80] or 75% [63–85][83]). It is recommended that MRI be done between 24–48 h and 7 days after cardiac arrest.[85]

In view of the low level of evidence,[86] diffuse structural signs of post-anoxic injury observed with either brain CT or MRI seem less robust predictors of outcome than brainstem reflexes and electrophysiological findings.[18] Difficulties inherent to transportation to the scanner of patients who are critically ill, and the still unclear prognostic value of imaging techniques (especially when assessed only qualitatively), explain why imaging remains optional in most prognostication algorithms.[18,87–89] In practice, we recommend brain CT for investigation of a cerebral cause of cardiac arrest if the cause is otherwise unknown. Brain MRI can be considered in centres with appropriate resources and expertise to complement multimodal assessments in patients who, despite lacking prognostic signs of poor outcome with clinical, electrophysiological, and blood tests, are in persistent coma after several days.

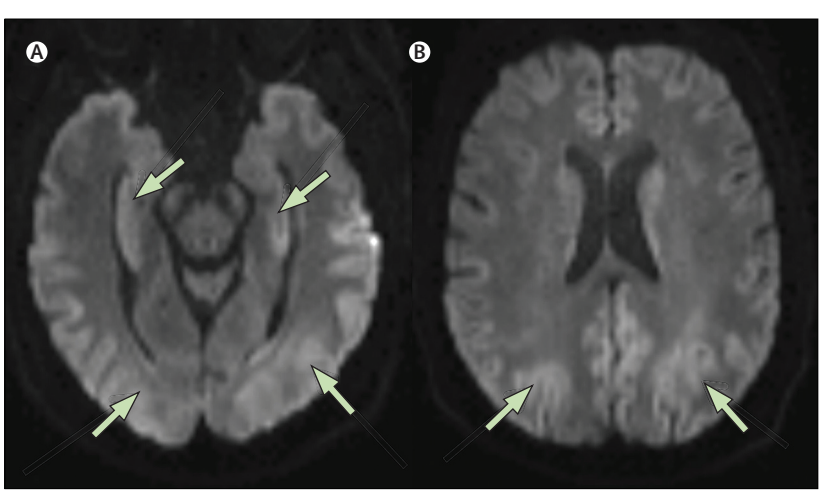

Figure 4: **Diffusion-weighted MRI of a 70-year-old female patient in a coma 7 days after a cardiac arrest of respiratory origin**
(A) Transversal view of mesencephalon and temporal-occipital regions. (B) Transversal view of fronto-parieto-occipital regions. Hyperintensities showing reduced water diffusion are mostly seen in posterior cortical regions and hippocampi (green arrows).

Prognostication in practice

The optimum prognostic method

Clinical examination is mandatory in every patient, and electrophysiology is strongly recommended. Even if pupillary light reflexes are absent at 72 h, we believe that either EEG or sensory evoked potential recording are necessary to substantiate prognostication of poor recovery. Evidence suggests that EEG might be superior to sensory evoked potential recording for predicting poor outcome because of its higher sensitivity.[36] EEG also allows for more accurate forecast of good recovery and higher accuracy regarding poor prognosis than sensory evoked potentials, and is able to identify seizure-associated activity. Additional investigative methods might be useful to corroborate clinical and electrophysiological assessments according to local practices and available resources. Available prognostic methods are summarised in tables 1 and 2; most are better able to accurately predict poor prognosis than good prognosis.

The optimum timing

Although EEG done 12–24 h after cardiac arrest can be informative, multimodal assessment, including clinical examination and electrophysiological studies (EEG, evoked potentials, or both), should be carried out after

	Feature related to good outcome	PPV (95% CI)	Feature related to poor outcome	FPR (95% CI)
Clinical examination				
Pupillary light reflex	Bilaterally present at >72 h	61% (50–71)	Bilaterally absent at >72 h	0·5% (0–2)
Corneal reflex	Bilaterally present at >72 h	62% (51–72)	Bilaterally absent at >72 h	5% (0–25)
Early myoclonus	NA	NA	Present at <48 h with epileptiform EEG (status myoclonus)	0% (0–3)
Early myoclonus	NA	NA	Present at <48 h with continuous reactive EEG	5–11% (3–26)
Motor reaction to pain	Flexion or better at >72 h	81% (66–91)	Absent or extension posturing at >72 h	10–24% (6–48)
EEG				
Background	Continuous at 12–24 h	92% (80–98)	Diffuse suppression or low voltage at 24 h	0% (0–17)
	Normal voltage at 24 h	72% (53–86)	Burst suppression at 24 h	0% (0–11)
Reactivity to stimuli	Present during hypothermia	86% (76–92)	Absent during hypothermia	2% (0–9)
	Present after return of normothermia	78% (64–88)	Absent after return of normothermia	7% (1–15)
SIRPIDs	NA	NA	Present at any time	2% (0–11)
Repetitive epileptiform transients	NA	NA	Present during hypothermia	0% (0–30)
			Present after return of normothermia	9% (2–21)
SSEP				
SSEP recording	Bilaterally present	58% (49–68)	Bilaterally absent after return of normothermia	0·5% (0–2)
NSE				
Serum NSE concentration	<33 µg/L at 48 h	63% (52–83)	>120 µg/L at 48 h	0% (0–1)
	..	..	>68 µg/L at 48 h	1% (1–3)
Imaging				
Brain CT	Normal grey–white matter at 2–48 h	37% (9–75)	Reduced grey–white matter ratio at 2–48 h	0% (0–12)
Brain MRI	Absence of reduced diffusion at 24 h to 7 days	73% (45–92)	Reduced diffusion at 24 h Reduced diffusion at 7 days	0% (0–22) 54% (26–80)

FPR= false postive rate. PPV= positive predictive value. NA=not applicable. SIRPID=stimulus-induced rhythmic, periodic, or ictal discharge. SSEP=somatosensory evoked potential. NSE=neuron-specific enolase.

Table 1: **Overview of prognosticators in adult patients given targeted temperature management**

	Strengths	Weaknesses
Clinical examination	Very low FPR for poor prognosis (especially pupillary light reflex); can identify early signs of awareness	Motor response might have high FPR (up to 25%) for poor prognosis; reliability might be reduced by residual sedation, organ failure, and hypothermia; myoclonus not invariably correlating with poor prognosis (needs to be integrated into EEG)
Electroencephalography	Low FPR for poor prognosis (especially absence of continuous background and reactivity); good accuracy in predicting favourable prognosis (especially presence of background and reactivity); allows detection and management of seizures	Absence of standardisation for stimulus application (reactivity); needs expert interpretation
Early somatosensory evoked potentials	Very low FPR for poor prognosis	Low accuracy in predicting favourable prognosis; has lower sensitivity than EEG for predicting poor prognosis; needs expert interpretation; not available everywhere
Biomarkers	Additional method to substantiate poor prognosis	Cannot reliably identify favourable prognosis; needs experienced laboratory staff and expert interpretation
Brain imaging	Additional method to substantiate poor prognosis	Cannot reliably identify favourable prognosis; needs high-volume centres and expert interpretation

FPR=false-positive rate.

Table 2: **Strengths and weaknesses of main prognostic methods**

return to normothermia and a sufficient time after discontinuation of sedation. The earliest time at which prognostication should occur is 48 h after cardiac arrest; nevertheless, repetition of clinical examination at 72 h is mandatory in those who do not show clear signs of awakening.[18,87] These early tests orient prognostication in most patients; those already starting to awaken or, conversely, who have convergent signs of irreversible brain injury (absent pupillary and corneal reflexes, EEG with suppressed or burst suppression background and no reactivity, and absent early somatosensory evoked potentials) do not need additional tests. Biochemical markers or imaging are confirmatory tests for poor prognosis, but not mandatory.

How to deal with uncertainty

Multimodal assessment is supported by a growing body of evidence and is strongly advocated whenever doubt persists because each single method when used alone carries risks of false prediction.[18,87,35,36] Research has focused on the optimum combination of prognostic variables; EEG background reactivity or continuity, clinical assessment (particularly myoclonus and brainstem reflexes), and serum NSE concentrations seem to have the best predictive value to identify patients with a poor outcome.[35–37] Unfortunately, so far, no combination of tests heralding good prognosis can be supported by sufficient high-quality evidence.

We propose a stepwise approach, summarised in figure 5. If, after the aforementioned investigations, the patient still remains comatose despite an absence of poor outcome predictors, intensive care should be continued while the two core prognostic methods (clinical examination and EEG) are periodically reassessed during subsequent days. At that point, the results of blood biomarker analysis should be available, but repeated assessment of biomarkers and sensory evoked potentials beyond 72 h after cardiac arrest does not seem to provide any additional useful information. Brain MRI can prove useful because it can reveal alterations suggestive of cerebral damage, the significance of which needs to be interpreted within the clinical context. Panel 1 presents an illustrative example in which all aforementioned prognostic methods were used. Despite MRI alterations potentially portending to poor prognosis, no other robust sign of poor outcome was noted. In particular, the presence of repeated, continuous, reactive EEG supported the continuation of intensive care, and the patient awoke shortly thereafter; 3 months after cardiac arrest, the patient showed moderate cognitive impairment.

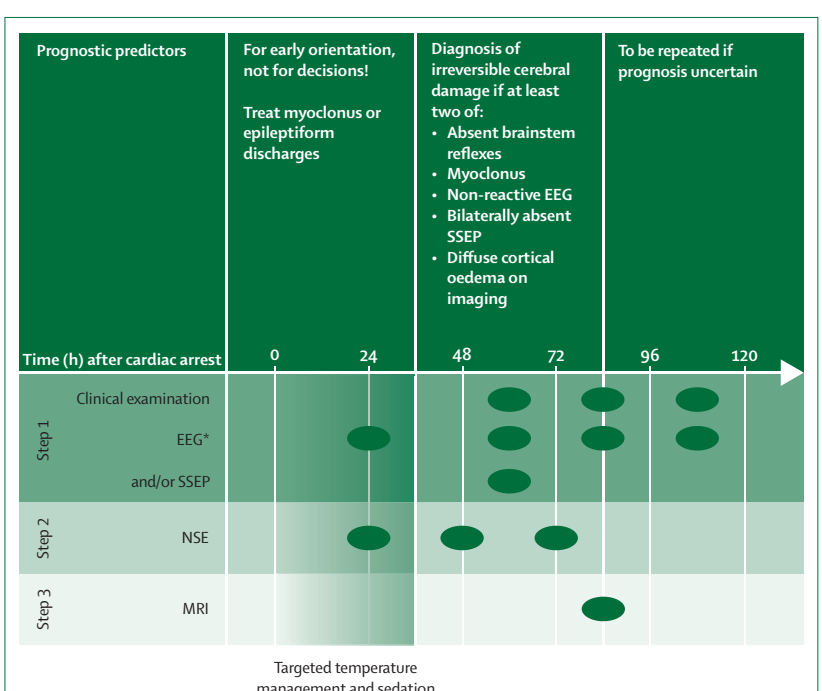

Figure 5: **Stepwise multimodal algorithm for outcome prognostication in adults in a coma after cardiac arrest**
Step 1 includes mandatory investigations, whereas steps 2 and 3 include confirmatory, optional tests. EEG=electroencephalogram. NSE=neuron-specific enolase. SSEP=somatosensory evoked potential. *Can be intermittent or continuous. For details, please see text.

Intensive care withdrawal

To minimise the risks of false pessimistic predictions, interruption of life-sustaining measures should be considered only when poor outcome is predicted by at least two methods with very low FPR for poor outcome—ie, clinical examination plus electrophysiology—without any discordant information between tests. Although FPR estimates of the aforementioned methods can be less than 2%, confidence intervals for EEG are wide, which reinforces the need for a multimodal approach. Panel 2 illustrates how clinical examination and EEG 48 h after cardiac arrest orient towards a poor prognosis with high accuracy, even with preserved sensory evoked potentials. Indeed, in this case, intensive care was withdrawn and the patient died shortly thereafter.

Making a decision regarding withdrawal of life-sustaining measures is an essential and challenging part of care. This decision should be reached through interdisciplinary consensus, including an intensivist and a neurologist or neurophysiologist, and with close involvement of the patient's family, considering the patient's known or written directives, and the patient's biological and psychosocial backgrounds. The multimodal paradigm used should always be tailored to the individual situation. When supportive care is continued in patients without overt clinical interaction with the environment for several weeks or months, only a subset will show improved awareness beyond a year after cardiac arrest; virtually all of them will remain in a severe, dependent state and have poor quality of life.[90] In the few instances in which prognosis cannot be established, detailed discussion with the next of kin should take place during the first 2–3 weeks after cardiac arrest to clarify what would be the maximum acceptable

and tolerated degree of functional impairment and provide commensurate care on the basis of individual preferences and values to avoid futile treatment.

Promising new prognostic methods

The need for identification of additional prognosticators derives from two considerations: the potential usefulness of quantitative assessments and the need for robust methods not only for poor but also for good outcome. In view of their exploratory nature, studies of new variables, such as those discussed below, are less hampered by confirmatory bias because they are not yet used for prognostication in clinical practice. The most important barriers to wide applicability of these techniques are uncertain generalisability (ie, most methods have been assessed by only a few research groups or in limited settings) and low availability of the necessary resources.

Automated pupillometry

Automated devices to quantify pupillary responses to light stimuli are commercially available; findings from preliminary studies suggest that quantitative infrared automated pupillometry might be more accurate than standard qualitative examination.[91] Until this technique has been further validated, correlation with direct visual examination remains necessary.[92]

Long-latency evoked potentials

Long-latency evoked potentials are high-order cortical reactions occurring more than 100 ms after stimulation of the primary sensory areas. The response to deviant auditory stimuli in a sequence of standard stimuli, called mismatch negativity, has been described for prognostication several days or weeks after cardiac arrest in the absence of TTM, and its presence is highly predictive of awakening.[93] This approach has been refined by means of automated voltage topography analysis of recordings done in patients in acute coma; most patients showing improved auditory discrimination between two assessment periods within the first 48 h of coma onset had a good recovery.[94] This new paradigm could identify patients with favourable prognosis at an early timepoint.[95]

Other biomarkers

Several proteins have been proposed as prognostic biomarkers, such as plasma neurofilament heavy-chain protein,[96] serum glial fibrillary acidic protein,[97] brain-derived neurotrophic factor, and tau protein;[98] however, studies of their use are limited by small sample sizes; further and more detailed data are needed before these biomarkers can be routinely used. Increased concentrations of systemically expressed proteins, such as serum procalcitonin, are found in the first 48 h after global ischaemia-reperfusion injury and have been associated with increased mortality.[99]

***Panel 1:* A case of a woman in coma after ventricular fibrillation**

A 70-year-old woman was admitted to the intensive care unit in coma after cardiac arrest due to ventricular fibrillation. The estimated total time from cardiac arrest to return of spontaneous circulation was 18 min. A myocardial infarction was diagnosed, and primary angioplasty of the occluded proximal right coronary artery was successfully done. On admittance to the intensive care unit, sedation and analgesia was administered and targeted temperature management at 33°C was maintained for 24 h. EEG during hypothermia was reactive and nearly continuous. After sedation weaning, the patient showed a return of brainstem reflexes, no reaction to pain, and bilaterally preserved early-latency evoked potentials. A second EEG showed diffuse, continuous slowing, preserved reactivity, and no epileptiform components. Serum neuron-specific enolase concentration peaked at 40 µg/L. 7 days after admission, the patient was still in a coma. Brain-diffusion MRI showed hyperintensities predominant in posterior cortical regions and hippocampi (figure 4). The EEG was unchanged.

***Panel 2:* A case of a woman in coma after respiratory failure**

A 60-year-old woman in coma was admitted to the intensive care unit after cardiac arrest of respiratory cause. The first rhythm was asystole and the estimated total time from cardiac arrest to return of spontaneous circulation was 22 min. The patient underwent targeted temperature management at 36°C for 24 h. At day 2 after cardiac arrest, off sedation, clinical examination showed an absence of motor response and all brainstem reflexes. The EEG was characterised by monotonous α activity predominant in the anterior regions and a non-reactive background to painful stimulation (figure 1). Somatosensory evoked potentials (N20) were bilaterally preserved. At day 3, a second EEG showed a diffuse, slow, and non-reactive background. Clinical examination differed from the previous day only for recovery of spontaneous breathing and presence of a right corneal reflex.

Cerebral oxygenation

Low cerebral oxygenation, a marker of poor prognosis,[100] can be assessed invasively, but this method is not practical in patients who have had a cardiac arrest. It can also be estimated non-invasively by means of near-infrared spectroscopy and measurement of regional cerebral oxygen saturation.[101] Non-invasive measurement of cerebral oxygenation was used to predict likelihood of resuscitation after cardiac arrest in an out-of-hospital setting.[102] Authors of a meta-analysis[103] including nine studies and 315 patients noted that higher initial and average cerebral oxygenation are associated with greater chances of return of spontaneous circulation, but, so far, not

enough robust data are available to support the use of this method to predict in-hospital or long-term prognosis.

Conclusions

Prognostication after cardiac arrest, which can be seen as an attempt to shed some light into the dark, has become an integral part of post-resuscitation care. Neurological consultation is increasingly requested, and neurologists are confronted by caregivers and families with expectations of highly accurate predictions of outcome. During the past decade, post-cardiac arrest prognostication has progressed towards a multimodal paradigm relying on clinical examination and judicious integration of information provided by many tests. Prognostication should never be based on a single indicator; although some variables have a very low FPR for poor outcome, they do not occur in isolation—eg, bilateral absence of cortical responses to somatosensory evoked potentials would not be expected in patients with localising responses on physical examination or a reactive EEG background. Multimodality assessment provides reassurance about the reliability of a prognostic estimation by offering concordant evidence from different sources, which should all make sense together; this approach is supported by an abundant body of clinical evidence and is strongly recommended.[18,87–89,104]

Confounders, however, exist; for example, sedative drugs undergoing delayed clearance with hypothermia and renal or liver injury must always be formally excluded as the cause of ongoing coma. Confirmatory bias, or the self-fulfilling prophecy, is an important issue, intrinsic to virtually all studies on prognostication after cardiac arrest.[13,14] We acknowledge that no major prognosticator has been tested in a strictly masked manner and that the level of evidence for its role is low worldwide. Notwithstanding these limitations, reliance on a multimodal approach incorporating all relevant clinical information is, at present, the best way to maximise prognostic reliability. When the prognosis remains uncertain, additional time and use of the full set of prognostication methods is clearly recommended.

Although most available literature focuses mainly on indicators of poor prognosis, in this Review we have tried to emphasise early predictors of good recovery, especially EEG background and reactivity. Estimation of prognosis after cardiac arrest is not only about delivery of bad news, but also, and hopefully more frequently so in the future, about the identification of reliable signs of good prognosis that can be confidently shared with next of kin. The sharing of positive news can prove very rewarding and is an important task for neurologists involved in the care of patients who have had a cardiac arrest. An additional, stimulating challenge for the coming years will be to further refine understanding of which factors can predict cognitive recovery.

Search strategy and selection criteria

We searched PubMed from Jan 1, 2009, to Jan 5, 2016, with the search terms "cardiac arrest", "hypoxic-ischemic encephalopathy", "prognosis", "outcome", "prognostication", "clinical examination", "myoclonus", "status myoclonus", "brainstem reflexes", "pupillary", "pupillometry", "motor reaction", "pain", "EEG", "reactivity", "background", "epileptiform", "status epilepticus", "seizure", "SSEP", "N20", "N70", "MMN", "NSE", "S100-b", "brain CT", "Brain MRI", and "diffusion". We further searched bibliographies of relevant articles. We reviewed only clinical studies, randomised trials, and reviews published in English. We generated the final reference list on the basis of relevance to the scope of this Review.

Contributors

All authors contributed equally to this Review, searching the literature, analysing the data, and drafting the report and reviewing it for important intellectual content. The figures were prepared by AOR.

Declaration of interests

AOR received unrestricted research grants from UCB Pharma and Sage Pharmaceuticals (unrelated to this Review). AAR and MO declare no competing interests.

Acknowledgments

The Swiss National Science Foundation provides financial support to AOR (CR3213_143780) and MO (32003B_155957) for research into coma prognosis. Jessica Scheurer (Service d'appui multimédia, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland) helped prepare figure 5.

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