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# Neurological Prognostication After Cardiac Arrest in the Era of Target Temperature Management

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## Abstract

**Purpose of Review** The purpose of this study is to provide an updated review on neurological prognostication in comatose patients after cardiac arrest in light of current targeted temperature management (TTM) strategies.

**Recent Findings** With improved pre-hospital and hospital care, death due to cardiac arrest is decreasing. Yet, most survivors have poor neurological outcomes. While TTM has demonstrated to improve neurological outcomes, it may cloud our prognostic accuracy. A multimodal approach is currently used to diminish prognostic uncertainty.

**Summary** The neurological examination remains the mainstay for prognosis after cardiac arrest. The combination electroencephalogram, somatosensory evoked potentials, and neuron-specific enolase improve prognostic accuracy, mostly in patients who underwent TTM. Quantitative analysis of pupillary reaction and EEG background variability, neuroimaging (CT perfusion and DWI-MRI), and middle/long-latency evoked potentials are promising methods that may further improve the precision of outcome prognostication.

**Keywords** Cardiac arrest · Target temperature management · Prognosis

## Introduction

One of every 7.4 people in the USA dies of sudden cardiac death [1]. Two thirds of cardiac arrest episodes occur out of the hospital (OOHCA). Advances in pre-hospital and hospital management (early cardiopulmonary resuscitation [CPR], availability of automated external defibrillators, advanced cardiac life support, access to emergent coronary angiography, implementation of targeted temperature management [TTM], support of organ perfusion, and prevention of systemic complications) have decreased the mortality of post-cardiac arrest patients [1]. Yet, prognosis is still poor: only 10% of cardiac arrest patients survive hospitalization [1], 5% experience full neurologic recovery [2], and many survivors are discharged with a poor functional status. Furthermore, the neurological status of patients discharged with a good outcome may deteriorate overtime [3••].

The post-cardiac arrest syndrome includes anoxic brain injury, cardiac dysfunction, whole body ischemia, and reperfusion injury. Prognostication of good neurological outcomes is critical since brain injury is the main determinant of morbidity and mortality in these patients [4].

In this article, we provide an updated review of the state of the art on neurological prognostication in post-cardiac arrest survivors.

## Importance of Early Prognostication of Neurological Recovery

Two main questions arise in patients who remain comatose after cardiac arrest. Will the patient wake up? and if so, in what neurologic state? As there is no single test to reliably answer these questions, a multimodal diagnostic approach is currently used to minimize prognostic uncertainty. Even with current workup, high rates of late awakening have been recently published in two large registries, [5••, 6••] emphasizing the need of improving our ability to

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differentiate delayed awakening and irreversible brain damage. This is particularly important since withdrawal of life sustaining treatments (WLST) is a leading cause of death in post-cardiac arrest patients.

Current knowledge on the prognosis of neurological outcomes after cardiac arrest comes from observational studies, raising concerns of confirmation bias, also known as self-fulfilling prophecy [7, 8]. Therefore, to minimize false positive results, the results of ancillary tests should be carefully interpreted in combination (multimodal prognostic assessment).

## Consequences of Cardiac Arrest in Brain Function

The brain is highly susceptible to hypoxia due to its high metabolic demand. The hippocampal region C1A, cerebellar Purkinje cells, and pyramidal neurons of the neocortex are particularly sensitive. Within a few minutes of anoxia (first hit), brain glucose and adenosine triphosphate stores are rapidly depleted. The consequent dysfunction of the pump Na/K ATPase disrupts the electrochemical transmembrane gradient. The pathological depolarization and distortion of the transmembrane gradient cause cellular swelling and release of glutamate [9••]. Glutamate excess perpetuates a pathologic circle of cellular depolarization increasing intracellular calcium levels which in turn activates destructing enzymes and creates free radicals. This mechanism is known as excitotoxicity [2]. Restoration of cerebral blood flow, although indispensable for brain survival, can contribute to brain damage by reperfusion injury (second hit). Production of superoxide, peroxynitrite, and release of free iron, among others, are the main culprit mechanisms [9••]. The hippocampi, thalami, cerebral cortex, striatum, and cerebellar vermis are mainly affected [10].

## Targeted Temperature Management

Despite promising results in animal models, several interventions have failed to improve outcomes of post-cardiac arrest patients except for TTM (target temperature at 32–36 °C). The complex cascade of events following brain ischemia is temperature-dependent. At least theoretically, hypothermia could protect the brain through varied mechanisms. The basal brain metabolism slows down as core temperature decreases. Immediately, there is more energy available for restoration of normal brain function. Cerebral blood flow, excitotoxicity, lipid peroxidation, production of free radicals, systemic inflammation, activation of the coagulation cascade, and brain swelling are also reduced [11].

The first reports suggesting the efficacy of TTM for cardiac arrest patients were published in the 1950s [12, 13]. Later on, in the 1990s, three small pilot studies reported the safety and feasibility of this treatment [14–16] and were the starting point for additional randomized clinical trials [17–19] and metanalysis [20•] that confirmed the benefit of TTM for post-cardiac arrest patients. More recently, a pilot trial that randomized 150 patients with OOHCA to TTM at 32, 33, and 34 °C showed that the three approaches would be equally effective to achieve good neurological outcomes [21•]. However, there was a trend towards lower WLST among patients randomized to lower temperatures, suggesting that further research with lower temperatures is needed. A randomized trial comparing TTM at 33 °C vs fever control is ongoing https://clinicaltrials.gov/ct2/show/NCT02908308. Pre-hospital TTM effectively decreases body temperature at the time of hospital arrival. However, a trial showed that it does not improve rates of survival with good neurological outcome or overall survival and is associated with increased rates of re-arrest [22].

## Targeted Temperature Management May Cloud Post-Cardiac Arrest Prognostication

Hypothermia induces several systemic effects including the delayed clearance of sedatives. While the clinical examination at day 3 after cardiac arrest remains an accurate predictor of outcome after therapeutic hypothermia [23], it may be less reliable in patients who receive sedation [24]. This is particularly important because significant amount of sedatives is needed for induction and maintenance of TTM [24], and sedation clearance may be further delayed in patients with post-cardiac arrest syndrome with kidney and liver damage.

## Neurological Examination

The neurological examination arouse as the backbone for outcome prediction after cardiac arrest since the publication of a study by Levy et al. that compared the early neurological examination (from days 0 to 14) of 210 patients with their functional outcome at 1–12 months [25]. Absent pupillary light reflexes and motor responses other than extensor posturing identified a group of patients with poor prognosis. In 2006, an evidence-based review by Wijdicks et al. showed that the presence of myoclonus status epilepticus within the first 24 h, absence of pupillary responses within days 1 to 3, absent corneal reflexes within days 1 to 3, and absent or extensor motor responses after 3 days predict poor outcome with a low false positive ratio (FPR) [26]. The examination of post-cardiac arrest patients follows a standardized procedure focused on three main points: brainstem reflexes (pupillary light reaction [PLR], oculocephalic and corneal reflexes), motor response to pain, and presence of abnormal movements (paying special attention to myoclonus and seizures).

Negative PLR at 72 h after cardiac arrest strongly correlates with a poor prognosis regardless of TTM [7, 8, 23, 26–28]. In a recently published study, 5 of 79 patients with an absent PLR on day 3 had a favorable outcome (FPR 6%) [29••]. Neurological assessment by non-neurologists is a potential explanation for these findings. Caution is advised when interpreting negative PLR within the first 24 h, particularly in hypothermic patients, since up to 8% of them can achieve a good neurological outcome [30].

Absence of corneal reflexes also imply poor prognosis, yet with lower certainty in patients who required significant amount of sedatives or neuromuscular blockers [8, 30].

The examination of pupillary function with automated quantitative pupillometry may improve outcome prediction [31, 32]. The neurological pupil index (NPi) is a scalar value based on pupillary size, percentage constriction, constriction/dilation velocity, and latency that is minimally influenced by medications and ambient light. NPi < 2 has recently shown to predict an unfavorable outcome from day 1 after cardiac arrest with higher specificity than standard manual pupillary examination [29••]. Furthermore, its combination with somatosensory evoked potential (SSEP) predicts poor outcome with 58% sensitivity and 100% specificity [29••].

The presence of PLRs and corneal reflexes has low specificity for identifying patients who will have good outcome. This is explained by the resilience of brainstem to ischemia: abnormal brainstem reflexes are a sign of bad prognosis, but significant cortical ischemia is possible with intact brainstem function.

Absent or extensor motor response to pain at 72 h is very strongly associated with bad prognosis in patients who do not undergo TTM [26]. TTM and polypharmacy (sedatives, opiates, and neuromuscular blockers) specially affect the motor response to pain, with one fourth of patients with a poor response at day 3 achieving good neurological outcomes [8, 26, 33]. Similarly, to what happens with brainstem reflexes, good motor responses do not always imply good prognosis [7].

For many years, post-cardiac arrest myoclonus was deemed universally predictive of poor outcome. However, with the publication of several cases of post-anoxic myoclonus achieving good neurological recovery, it is now clear that it should not be interpreted in isolation as a marker of ominous outcome. A careful analysis of the semiology of myoclonic jerks (areas involved, duration, triggers, etc.) and associated EEG findings (most often burst suppression with epileptiform bursts) is necessary to identify true generalized post-anoxic status myoclonus (Table 1). While the presence of generalized status myoclonus is a strong predictor of poor neurological outcome, around 10% of patients with non-specific myoclonic jerks may achieve good recovery. The clinical definition of status myoclonus has a great variation in the literature, maybe explaining its variable accuracy as prognostic factor: A recent study classified myoclonus status on three types based on its semiology [22]. The authors suggested that this classification may improve prognostication, though this remains to be proven.

**Table 1** Distinctive clinical features of generalized status myoclonus

| Generalized status myoclonus | Other myoclonic jerks |
|---|---|
| Multifocal, spontaneous | Segmental |
| Continuous for > 30 min | Brief, intermittent |
| Appears under TTM | Controlled by TTM and sedation |
| Not controlled by sedation | Reactive EEG patterns |
| Malignant EEG patterns (see Table 2) | |

## Multimodal Prognostic Assessment

The addition of ancillary tests to serial neurological examinations reduces prognostic uncertainty in post-cardiac arrest patients, particularly in those who underwent TTM. These tests include electrophysiological investigations, serum biomarkers, and brain imaging.

## Electroencephalogram

A comprehensive and updated review of the value of EEG after cardiac arrest has been recently published [34••]. EEG in post-cardiac arrest patients has a dual utility: prognostication of neurological outcome and diagnosis of non-convulsive seizures. EEG is very sensitive to detect brain injury, is widely available, non-invasive, and has a robust body of evidence supporting its utility for prognostic purposes. Altogether, these advantages explain why it is the most commonly used ancillary test for neurological prognosis after cardiac arrest [35]. The use of different classification systems and interrater variability are important limitations. A standardized interpretation based on accepted classification systems improves EEG prognostic accuracy [36•]. A cohort study including 357 patients who underwent TTM found that the presence or absence of background reactivity to external stimulation seems to be the best discriminator between good and poor outcomes [37••]. Confounding clinical factors, such as hypothermia and sedation, should be taken into account when analyzing the EEG tracing, particularly background activity and reactivity. Sedative drugs, especially at high doses (> 0.1–0.2 mg/kg per hour of midazolam or 2–3 mg/kg per hour of propofol), can substantially affect the EEG. Background activity, reactivity, and the presence of epileptiform discharges should be carefully analyzed in

**Table 2** Standardized EEG analysis for prognostic purposes: predictors of poor and good outcomes

| | |
|---|---|
| Predictors of poor outcomes | Generalized suppression (activity < 10 μV during the entirety recording) |
| | Low-voltage EEG (activity < 20 μV during most of the recording) |
| | Burst suppression (periods of suppression constitute > 50% of the recording) |
| | Burst suppression with generalized epileptiform discharges and with identical bursts (identical bursts have identical first 500 ms) |
| | Discontinuous background (periods of suppression constitute < 50% of the recording) |
| | Alpha/theta coma (non-reactive background with bifrontal alpha (8–12 Hz) and theta (4–7 Hz) activity) |
| | Spindle coma (spindles at 9–14 Hz with vertex sharp waves and K-complexes) |
| | Generalized periodic discharges |
| | Stimulus-induced rhythmic, periodic, or ictal discharges (periodic, rhythmic, or ictal discharges triggered by stimulation) |
| | Lack of reactivity and variability |
| Predictors of good outcomes | Continuous background |
| | Rhythmic delta activity |

order to identify malignant EEG patterns associated with poor prognosis (Table 2).

Continuous recording is recommended in patients with post-anoxic status epilepticus for monitoring and titration of antiepileptic drugs. In other circumstances, two 30-min EEG recordings including stimulation for reactivity may provide sufficient information and be more cost-effective [38, 39]. EEG recording may be started after the first 12 h given that most epileptiform discharges appear after 12–24 h [40]. Post-anoxic status epilepticus affects 20–30% of survivors after cardiac resuscitation, and it is usually refractory [41, 42••]. A recently published study shows that, on average, refractory status epilepticus (RSE) starts on day 3 after cardiac arrest and lasts for 5 days. In this study, with aggressive treatment, 54% of patients who developed RSE were alive at 6 months, and most of them (44%) had a good neurological outcome [42••]. On the other hand, no patients with generalized periodic discharged (GPDs) or malignant EEG patterns achieved such outcome [42••]. These data justify the aggressive treatment of post-cardiac arrest patients with RSE and otherwise favorable multimodal prognostic indicators.

The use of quantitative EEG analysis may detect subtle fluctuating background and background reactivity. This approach has the potential benefit of being independent of the human eye and especially useful when expertise on EEG interpretation is not available. Several quantitative methods have been reported with varied success rates [43, 44, 45•].

## Somatosensory Evoked Potentials

Somatosensory evoked potentials (SSEPs) measure the cortical response after an electrical stimulus is applied to the median nerve. The presence of a positive deflexion in the contralateral post-central gyrus 20 ms after stimulation (short latency SSEPs) implies integrity of the peripheral and, most importantly, central sensory pathways. SSEPs have been extensively investigated in comatose patients. While bilateral absence of N20 is invariably associated with a poor prognosis, their presence has a poor predictive value for recovery of consciousness. Importantly, the prognostic value of SSEPs is not influenced by TTM [46].

Assessing SSEPs as a dichotomous variable (present/absent) may limit their prognostic value. The quantitative assessment of N20 amplitude has been suggested to offer additional prognostic information, but this observation needs further confirmation in large cohorts.

Middle latency SSEPs assess brain connectivity and can be recorded between 70 and 100 ms after stimulation. Their main utility is to identify patients with a good potential for recovery, with positive predictive values as high as 97%. Yet, their use is limited by technical and practical issues. Promising initial observations were later challenged by other studies showing positive predictive values as low as 28%. SSEPs triggered by painful stimuli may identify patients who will regain consciousness with a PPV of 100%. These observations need to be replicated and validated in larger cohorts.

Brainstem auditory evoked potentials do not seem to add more information to SSEPs [46]. Long-latency evoked potentials can be recorded in sensory areas > 100 ms after auditory stimulation. The progression of auditory discrimination from hypothermia (at 33 and 36 °C) to normothermia has shown a high predictive value for early awakening, adding valuable data to continue life support [47••, 48•]. While promising, these findings warrant further research.

## Biochemical Markers

At first glance, serum biomarkers could objectively assess the degree of ischemic brain injury while being easily obtained and not affected by sedation. However, different

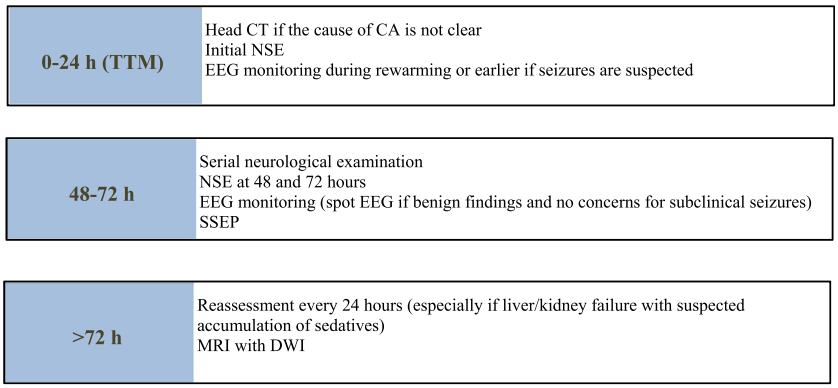


**Fig. 1** Diagnostic workup used at the authors' institution. CT computed tomography, CA cardiac arrest, NSE neuron-specific enolase, EEG electroencephalogram, MRI magnetic resonance imaging, DWI diffusion-weighted imaging

quantification methods, spurious results with hemolyzed samples (e.g., hypothermia, extracorporeal membrane oxygenation, handling issues), and ectopic production (e.g., small-cell lung carcinoma for neuron-specific enolase [NSE], adipose tissue, and muscle for S-100 β protein) are important limitations.

NSE (released after neuronal damage) is supported by the largest body of evidence and is currently recommended by international guidelines. Initial studies showed that a serum concentration > 33 μg/L between 24 and 72 h after cardiac arrest reliably identified patients with poor outcome [26, 49–51]. Conversely, concentrations of less than 33 μg/L were inconsistently related to good outcome. However, additional studies suggested that higher cutoff values should be used to predict poor outcomes in patients with and even without TTM [30, 52]. Furthermore, several confounders, including TTM, have been recognized [23, 50, 53]. More recently, a substudy of the TTM trial found that not only higher cutoff values (in the 40–60 μg/L range), but particularly the uptrend in serial measurements within the first 72 h have higher specificity for outcome prediction [54, 55•].

Serum S-100 β protein is released by injured glial cells. Concentrations > 0.5 μg/L within 24 h of cardiac arrest are associated with poor outcome [51, 56]. Nonetheless, S-100 β has a lower prognostic accuracy than NSE and has not shown to be an independent predictor of outcome in the TTM trial [57]. Also, based on its short half-life and the fact that prognostication with single measurements is discouraged, its value in clinical practice is questionable [58••].

MicroRNAs (miRNAs) are 20–22-nucleotide-long RNA molecules that actively regulate multiple biologic pathway functioning as paracrine factors. Circulating levels of miRNAs may reflect the physiologic status of a specific organ [59•]. miRNA-124-3p is brain specific, and it has been found elevated in post-cardiac arrest patients with poor prognosis [60, 61••]. Potential advantages of miRNA compared to classic biomarkers are their stability in the bloodstream and their ability to cross the blood-brain barrier [59•]. While promising in preliminary studies, the role of miRNA in clinical practice requires further research.

## Brain Imaging

Brain CT is usually recommended to investigate for possible cerebral causes of cardiac arrest (e.g., intracerebral or subarachnoid hemorrhages) when the cause is otherwise unknown or to assess consequences of head trauma that may occur as the patient collapses from the cardiac arrest. Yet, it may also offer some useful information for neurological prognostication. Most available data come from low evidence studies including patients from < 20 min to 20 days after return of spontaneous circulation [62]. Loss of differentiation between grey and white matter, diffuse cerebral edema, mass effect, cerebral atrophy (chronic), bicaudate ratio, low Hounsfield units in putamen and cortex, and low density in basal ganglia and thalamus have been found to predict poor outcomes [62]. A pilot study enrolled 10 comatose post-cardiac arrest patients who had a CT perfusion (CTP) within 6 h after TTM rewarming. CTP correctly identified the two patients with a mRS < 2 at discharge [63•].

Brain MRI is more sensitive than CT scan to detect ischemic injury, especially through the use of diffusion-weighted sequences. Quantitative assessments of ischemic changes with diffusion-weighted MRI have shown conflictive results in terms of outcome prediction across different studies [64–68]. Also, performing a brain MRI in unstable critically ill patients is time-consuming and requires complex logistics. Thus, brain MRI can be considered in centers with appropriate resources and expertise in patients with uncertain prognosis after 72 h despite complete multimodal assessment.

Diffusion tensor imaging, especially the calculation of fractional anisotropy (FA), allows to quantify white matter injury after global anoxia. Recently, a prospective, observational, multicenter cohort study analyzed the value of the normalized whole white matter FA (WWM-FA) to predict neurological outcome at 6 months after cardiac arrest [69••]. The prognostic accuracy was higher with normalized WWM-FA value compared to the standard criteria for unfavorable outcome or other MRI sequences. These results need to be replicated in larger studies with strict protocols that standardize the decision to proceed with withdrawal of life sustaining treatments [69••].

## Conclusions

Neurological prognostication after cardiac arrest is a complex task for which neurologists need constant training. To minimize prognostic uncertainty, a multimodal prognostic approach is recommended. TTM improves neurological outcomes. However, TTM by itself and the polypharmacy required for its implementation, as well as the consequences of systemic ischemia (liver and kidney failure), may confound the prognostic assessment. The selection and timing of ancillary tests should be tailored to individual clinical situations, and the capabilities and expertise available in each medical center (Fig. 1). While the current prognostic tests have a high positive predictive value to detect poor outcomes, their ability to detect patients with a good potential for recovery is still limited. The neurological examination is the mainstay of the multimodal prognostic approach. Serial examinations within the first 3–5 days are necessary to optimize prognostic accuracy. EEG and SSEPs are the ancillary tests with highest yield. EEG recording also allows diagnosis of non-convulsive seizures. Brain MRI may be useful for patients who remain in coma more than 3 days after cardiac arrest when other ancillary tests are inconclusive. In most cases, it is ill advised to provide a neurologic prognosis within the first 48 h after the cardiac arrest.

### Compliance with Ethical Standards

**Conflict of Interest** Maximiliano Hawkes and Alejandro Rabinstein each declare no potential conflicts of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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