Neuroprognostication postcardiac arrest: translating probabilities to individuals

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Purpose of review
Predicting neurological recovery in patients who are comatose after cardiac arrest is an important activity during postarrest care, and this prediction can affect survival. As no early test or clinical finding perfectly predicts potential for recovery, guidelines recommend using data from multiple examinations or tests to estimate patient prognosis.

Recent findings
Studies reported accuracy of initial clinical examination, progression of clinical examination, early (<24 h) brain imaging, electroencephalography (EEG), evoked potentials, later (>24 h) brain imaging, blood markers of brain injury, and cerebral oximetry for predicting good or poor outcome. In multiple cohorts, patients with status myoclonus with particular clinical or EEG features have potential for good outcome. When multiple tests were compared, each test provided independent information.

Summary
Absence of cortical functional recovery over time is detected using multiple testing modalities and remains strongly associated with poor outcome. Early recovery of cortical function increases the probability of good outcome. Concordant assessments from multiple tests increase confidence in prognostication.

Keywords
cardiac arrest, coma, myoclonus, prognostication, resuscitation

INTRODUCTION

Determining the likelihood of a good or poor outcome in patients who are comatose after cardiac arrest is one of the most important activities in postarrest care. Clinicians and families who believe there is high probability of a poor prognosis may limit or withdraw life-sustaining therapies (WLST) in many countries [1▪]. In the majority of patients, brain injury is the primary driver of in-hospital mortality. Even in settings where WLST does not occur, early determination of prognosis can help teams anticipate long-term dispositions and expectations for the individual patient.

No single clinical exam finding, test or protocol that is perfect for determining neurological prognosis in all patients after cardiac arrest is available, perhaps because of the variability in patients and in the patterns of brain injury. International guidelines and scientific statements have summarized and refined the approach for estimating prognosis after cardiac arrest [2–4].

The basic tools for estimating potential for neurological recovery have changed little over time. Specific tests include clinical exam findings, electroencephalography (EEG), somatosensory evoked potentials (SSEP), computed tomography (CT) scans, MRI, and blood levels of various peptides released from brain tissue. This review examines the most recent research studies about neurological prognosis after cardiac arrest.

CURRENT STANDARDS FOR PROGNOSTICATION

Current guidelines caution against premature conclusion of a poor prognosis, because some patients who have good recovery require many days to emerge from coma. Changing patient directives to 'do not resuscitate' 12 h or before, after an in-hospital cardiac arrest

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KEY POINTS

- No single clinical examination finding or neurological test perfectly predicts good or poor outcome after cardiac arrest.
- Clinical, neurophysiological, imaging and blood marker tests provide independent information about neurological recovery.
- Combinations of multiple tests are more accurate for estimating prognosis than any individual test alone.
- Some patients with status myoclonus may have good outcome, and these patients can be identified with detailed clinical and neurophysiological testing.

was associated with lower survival and worse outcome in 24 899 patients at 236 hospitals [5]. In one clinical trial of out-of-hospital cardiac arrest, many patients died from nonneurological causes or showed clear improvement during the first 3 days of hospitalization, but 33% of 939 comatose patients required formal estimation of coma prognosis after 4 days [6▪]. In a Canadian clinical trial, an educational initiative reduced variability in use of prognostic testing and reduced but did not eliminate premature WLST [7].

As there is always uncertainty about the future outcome of a patient, prognosis is best expressed as a risk for a good or poor outcome. Tests and findings can refine estimated risk using a likelihood ratio. Any test with a likelihood ratio that differs from unity offers some incremental information about prognosis. As WLST is the most perilous and irreversible action based on poor prognosis, many studies of prognostic tests report the chance of incorrectly predicting a poor outcome as the false positive rate (FPR) [2]. Ideally, the literature would provide a strategy, test, or combination of tests with FPR close to zero with narrow confidence intervals. In recent articles, few combinations of findings and tests approach this high specificity.

INITIAL LIKELIHOOD OF SURVIVAL

Although guidelines recommend waiting for 3–5 days to render a prognosis, it is more accurate to state that clinicians should wait several days before taking action on the prognosis. Studies confirm caution interpreting neurological examination very early after cardiac arrest. In 49 patients examined in the emergency department, complete absence of neurological response had 21% FPR for in-hospital mortality [8]. Nevertheless, collection of data and development of a predicted risk begins immediately upon meeting a patient.

Patient status on arrival at the hospital or ICU provides pretest probability of survival and recovery. A clinical risk score for out-of-hospital cardiac arrest developed in 819 patients stratifies patients into low (39%), medium (81%) or high (100%) risk for unfavorable outcome [9]. This score is not primarily neurological and is based on age, nonshockable rhythm, time from collapse to basic life support, time from basic life support to return of spontaneous circulation, location of cardiac arrest, epinephrine dose and arterial pH. Investigators derived a similar score for survival after pediatric in-hospital arrest in 3893 patients, and confirmed its performance in 1297 patients [10]. This tool also used nonneurological variables: age, illness category, pre-event characteristics, arrest location, day of the week, nonshockable pulseless rhythm, duration of chest compressions and interventions in place at time of arrest.

The Pittsburgh Cardiac Arrest Category (PCAC) uses initial neurological examination and initial cardiopulmonary failure during the first 6 h to sort patients into four groups with different expected survivals: rapidly awakening (80% survival), coma without cardiopulmonary failure (60% survival), coma with cardiopulmonary failure (30% survival) and deep coma with loss of brainstem reflexes (10% survival). PCAC was validated in a prospective cohort of 393 patients at the same hospital where it was derived and in 214 patients at another hospital [11]. Over the next 3 days in the ICU, lack of improvement in clinical neurological examination predicts poor outcome with 96% specificity (4% FPR) [12].

INITIAL COMPUTED TOMOGRAPHY SCAN OR MRI

Early cerebral edema is a sign of severe postcardiac arrest brain injury. Decreased gray–white ratio (GWR) on CT scan is one radiographic sign of brain edema, though restricted diffusion of water on MRI, measured as a low apparent diffusion coefficient (ADC), is a more sensitive sign. Recent literature confirmed the association of lower GWR with poor outcome in cohorts where WLST never occurred, including 164 patients [13] and 119 patients [14]. Likewise, in 110 patients with MRI at 12 h after arrest, low ADC had high sensitivity for poor outcome [15]. Decreasing GWR was associated with restricted diffusion on MRI in 39 patients examined with both modalities [16], although the combination of decreased GWR and restricted diffusion was superior for predicting poor outcome than either alone.

Cerebral edema increases over time. Edema on CT scan was observed in 9.6% of 218 patients on day

of arrest and in 45.5% of 143 patients between days 1 and 7 [17]. Generalized edema was associated with higher blood levels of neuron-specific enolase (NSE) and predicted poor outcome with 1.6% FPR. Generalized edema combined with NSE greater than 38 μg/l predicted poor outcome with 0% FPR.

Cerebral edema may increase intracranial pressure, which can cause an increase in optic nerve sheath diameter (ONSD). ONSD is an attractive finding because it is easily quantified on imaging with CT, MRI or ultrasound. One study in 119 patients reported that increased ONSD on initial CT scan improved detection of patients with poor outcome compared with GWR alone [14], but this association of ONSD with outcome was not replicated in a separate cohort of 72 patients [18].

ELECTROENCEPHALOGRAPHY

Recent data support the utility of EEG monitoring for estimating prognosis. Among 331 comatose patients, malignant patterns on continuous EEG during the first 48 h in the ICU provided additional information relative to the clinical neurological examination alone [19]. Clips of EEG during the first 72 h after cardiac arrest in 100 patients also identified patterns, particularly suppression of cortical activity beyond 24 h, that are associated with unfavorable outcome [20].

EEG background is a strong predictor of recovery. In a series of 200 patients, return of continuous background within 12 h of cardiac arrest predicted good outcome with 0% FPR, whereas isoelectric EEG or persistent suppression at 48–72 h after cardiac arrest predicted poor outcome with 0% FPR [21]. Results were similar in a separate cohort of 430 patients [22], and in a cohort of 357 patients [23].

Recovery of EEG reactivity predicts awakening. This association was confirmed with auditory stimuli in 60 patients with temperature management at 36 °C [24,25]. Standardized methods for testing EEG reactivity are lacking, and a study in 60 patients found moderate agreement between multiple modalities [26]. Nipple pressure was the most sensitive stimulus.

One barrier to wide scale utilization of EEG for prognostication after cardiac arrest is the necessity of expert interpretation of a high volume of complex data. Among experts, agreement of interpretation is moderate to substantial for malignant patterns after cardiac arrest, but only fair for findings like reactivity [27]. One study of the National Inpatient Sample prior to 2012 estimated only 2% of patients hospitalized after cardiac arrest in the United State have EEG testing [28], though 8.2% of children with cardiac arrest had EEG in the Kids' Inpatient Database [29].

Simpler monitoring strategies reduce the burden of EEG data interpretation. In 28 postarrest patients, sensitivities were good of a limited montage (four channels) EEG for detecting background continuity (88%), epileptiform activity (92%) and sporadic discharges (91%), suggesting that reduced electrode EEG might be a less resource-intensive alternative for brain monitoring [30].

Quantitative EEG measures are another strategy to reduce need for expert interpretation. In 77 patients, poor outcome was associated with bispectral index (BIS) values of 0 anytime in the first 48 h after arrest (specificity 84%) and BIS values of 0 lasting over 30 min (specificity 100%) [31]. Increasing variability in BIS values were associated with seizures in 31 of 103 patients [32]. In 83 patients, quantitative assessment of spectral EEG variability (decreased variability in temporal leads) was associated with poor outcome (15% FPR) [33]. Quantitative measures of EEG synchronization or connectivity between different brain regions during the first 24 h after arrest also predict favorable outcome with 100% specificity in 94 patients [34].

A machine learning-derived index, the Cerebral Recovery Index, based on multiple quantitative descriptors of EEG was developed in 283 comatose cardiac arrest patients [35]. This measure predicts good and poor outcome after 12–24 h with FPR less than 6%.

Sedation may confound interpretation of quantitative EEG in postarrest patients. In 78 postarrest patients, sedation decreased integrated EEG amplitude and increased the proportion of time with EEG suppression [36]. Greater suppression of EEG in response to the sedatives predicted poor outcome. In an experimental study in 10 patients, induction of slow waves in response to propofol was associated with better outcome [37]. Thus, the pattern of response to sedative drugs may provide prognostic information.

STATUS MYOCLONUS

A major development in postarrest prognostication is the recognition that there are different categories of postcardiac arrest myoclonus, and that some patients with status myoclonus have good outcome. Myoclonic seizures occurred in 29% of 939 comatose patients during the first 7 days after cardiac arrest in one clinical trial, but these seizures were not perfectly predictive of poor outcome (FPR 4.3%) [38]. Video-EEG in 43 patients delineated three clinical appearances of myoclonus, only one of which portended no awakening [39]. Thus, careful description of the pattern of myoclonus is important.

The benign forms of myoclonus may be early Lance–Adams syndrome. In a cohort of 458 patients,

this syndrome occurred in 1.5% of cases [40]. These patients awakened 3–23 days after cardiac arrest. In a series of 401 comatose patients, 16% had early myoclonus [41▪▪]. In that series, EEG patterns could distinguish malignant status myoclonus from the early Lance Adams variety, which represented 12% of the patients with myoclonus. These patients awaken 50% of the time. Brief neuromuscular blockade may be necessary to accurately determine the EEG pattern in patients with myoclonus [42].

Taken together, these data suggest clinicians should carefully phenotype status myoclonus as part of the prognostic evaluation, probably reporting the specific EEG pattern. This will prevent inappropriate pessimism or even WLST for patients with early Lance–Adams syndrome who have a 50% chance of survival.

EVOKED POTENTIALS

Absence or low amplitude of SSEP is associated with poor outcome [43]. In 68 patients, brainstem auditory-evoked potentials were often abnormal but were not well correlated with outcome [44]. In 200 patients studied 12, 24 and 48–72 h after arrest, malignant EEG patterns and absent cortical responses on SSEP occurred independently [45]. Whenever both unfavorable results occur together, poor outcome is predicted with 0% FPR. These data indicate that these two tests provide complementary information and are imperfect whenever used alone.

NEAR INFRARED SPECTROSCOPY

Regional cerebral oxygen saturation measured using near infrared spectroscopy (NIRS) is a noninvasive measure that would be attractive as a prognostic tool. In 107 patients, increasing cerebral oxygenation was weakly associated with better outcome [46]. Measured values with NIRS have high interindividual variation, providing no reliable threshold as a prognostic indicator.

MRI

Data on MRI after cardiac arrest has been limited by the size of studies and the variability in what MRI parameter is tested. In 69 patients with MRI during the first 7 days after arrest, restricted diffusion (ADC $<650\times10^{-6}\,m^2/s$) in more than 2.8% of the voxels of the entire brain predicted not awakening with 0% FPR [47]. In 46 comatose patients studied with resting state functional MRI for less than 4 weeks after arrest, functional connectivity between regions in the default-mode network (prefrontal, parietal and temporal cortex) predicted favorable outcome [48]. These illustrate the great potential for exploring quantitative MRI parameters.

BLOOD MARKERS

The use of blood markers of brain injury for prognostication is variable, and there are few prior data on how treatments change these markers. Data from 115 patients found no difference in the temporal evolution of NSE and S-100B or relation of higher NSE and S-100B to poor outcome when hypothermia (33 °C) was applied for 24 versus 48 h [49]. Likewise, higher S-100B and NSE are associated with worse outcome during hypothermia at 36 or 33 °C in 687 patients [50,51]. S-100B has the strongest association with outcome at 24 h whereas measuring NSE at 48 h or serial NSE measurements are the best. One multicenter study in Europe in 1053 participants determined a threshold for serum NSE (>90 μg/l) measured 3 days after in-hospital cardiac arrest with 0.5% FPR [52]

Poor outcome is associated with elevations in other blood markers include serum tau ($n=689$ patients) [53] and glial fibrillary acidic protein ($n=100$ patients) [54].

Perhaps more specific than circulating peptides, levels of micro-RNA in blood may detect brain injury, cardiac injury or other organ changes that predict survival [55,56]. In 579 patients, higher blood levels of a brain related micro-RNA, miR-123-3p, at 48 h were independently associated with poor outcome [57].

QUANTITATIVE PUPILLOMETRY

Quantitative pupillometry uses a handheld infrared camera to examine pupil size and velocity of light reflex. In 103 patients, quantitative pupillary response at 48 h that is less than a set threshold predicted poor outcome with 0% FPR [58]. Quantitative pupillometry is repeatable and correlates with NSE and neurophysiological findings.

COMBINATIONS OF TESTS AND FINDINGS

Guidelines recommend that multimodal testing of a patient is preferred over reliance solely on physical examination. Combinations of clinical findings, neurophysiological testing, imaging and biomarker are more specific for detecting patients who will have a poor outcome, and can improve accuracy.

Combinations of EEG with SSEP ($n=200$ patients) [45] or EEG with clinical exam ($n=331$ patients) are superior to single tests [19]. In 240 comatose patients, combining initial clinical

Table 1. Recent literature on prognostic evaluation after cardiac arrest

Modality	Time of evaluation	Test or finding (reference)
Initial clinical exam	<24 h	*Useful*: Risk Score [9] Pediatric Risk Score [10] PCAC [11] *Probably not useful:* *Absent neurological exam in ED [8]
Progress of clinical exam	1–3 days	*Useful:* Pupillometry [58] Improving Exam [12]
Myoclonus	0–3 days	*Useful:* Lance–Adams subtype [40,41▪▪] Different clinical phenotypes [38,39]
Early imaging	<24 h	*Useful:* CT edema loss of GWR [14–17] MRI restricted diffusion [15,16] *Probably not useful:* Optic nerve sheath diameter [14,18]
EEG	12 h to 3 days	*Useful:* Continuous Background [21–23] Malignant patterns [19,20] Reactivity [24–26] Myoclonus subtypes [41▪▪,42] Cerebral Recovery Index [35] BIS [31,32] Other quantitative EEG [33,34]
Evoked potentials	1–3 days	*Useful:* SSEP [43,45] *Probably not useful:* Brainstem Auditory Evoked Potential [44]
Delayed imaging	1-7 days	*Useful:* Restricted diffusion MRI [47] Resting state functional MRI [48]
Blood markers	1-4 days	*Useful:* NSE, S-100B [49–51] Tau [53] GFAP [54] Micro-RNA [55–57]
Cerebral oxygenation	0–2 days	*Useful:* Increasing NIRS values [46]
Multimodal testing	0–3 days	*Useful:* Exam with CT scan with EEG [59▪▪] Exam and EEG [19] EEG and SSEP [45] CT scan and NSE [17]

CT, computed tomography; EEG, electroencephalography; GWR, gray–white ratio; NSE, neuron-specific enolase; PCAC, Pittsburgh Cardiac Arrest Category; SSEP, somatosensory-evoked potentials (SSEP).

examinations (either PCAC or FOUR score), GWR on initial CT scan, and malignant patterns on continuous EEG provides more accurate prediction of poor outcome than using any of these findings in isolation ($n = 240$ patients) [59▪▪].

CONCLUSION

The recent studies provide more data on optimal timing of tests and nuances of test interpretation in cohorts of patients receiving modern intensive care and in diverse healthcare settings (Table 1). Studies quantified the effects of sedation on EEG. Multiple series illustrated the importance of using EEG or other signs to identify patients with status myoclonus who may have a benign prognosis. A few studies examine how neurological tests work in combination, which can inform clinicians about how many tests are required for an individual patient and can guide the order in which data are obtained. Overall, data still support the need for multimodal testing to accurately estimate a prognosis during postarrest care.

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Conflicts of interest

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- ▪ of special interest
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This article illustrates assessment of the incremental information of a new test over and above the results of previous test. Studies like this will guide whether clinicians should or should not perform additional testing in a given situation.