

# Coma due to cardiac arrest: prognosis and contemporary treatment

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## Abstract

Approximately 80% of patients who are successfully resuscitated from cardiac arrest do not regain consciousness immediately after return of spontaneous circulation, and may remain in a coma for hours or weeks, or even be in a persistent vegetative state. Recent investigations have focused on the identification of early clinical characteristics and biomarkers that can reliably predict emergence from coma in those who survive, and on therapies that might improve neurologic outcome from the ischemic brain injury that can be caused by cardiac arrest.

## Introduction and context

Cardiac arrest results in the cessation of spontaneous circulation, which causes hypoxic-ischemic encephalopathy, the severity of which is primarily related to the time from arrest to restoration of spontaneous circulation. Prolonged intervals without spontaneous circulation result in death, long-term or permanent coma, persistent vegetative state, seizures, and myoclonus [1]. Predicting the outcome following cardiac arrest for survivors who are comatose following resuscitation is the source of much consternation among emergency room and intensive care unit (ICU) physicians, as well as family members. As acute care resources have become increasingly scarce and costly, there has been increasing emphasis on identifying clinical, imaging, or molecular biomarkers that can reliably predict long-term outcome.

The Quality Standards Subcommittee of the American Academy of Neurology has published a 'Practice Parameter' regarding prediction of outcome in comatose survivors of cardiac arrest [2]. That evidence-based review found that pupillary light response, corneal reflexes, motor responses to pain, myoclonic status epilepticus, serum neuron-specific enolase (NSE), and somatosensory evoked potential (SSEP) studies can reliably assist in accurately predicting poor outcomes in comatose patients. NSE is an enzyme active in the glycolytic pathway and is released from peripheral and central

neurons when they are damaged. The strongest predictors of outcome are the absence of the pupillary light response, absence of corneal reflexes, and extensor or no motor response to pain for at least 3 days after the arrest. Questions remain, however, about the sensitivity and specificity of serum biomarkers, as well as the role of imaging and electrophysiologic biomarkers.

There also has been intense interest in identifying therapies that may limit secondary brain injury after cardiac arrest. During the 1990s several pre-clinical studies found that therapeutic resuscitative hypothermia was very effective in improving neurologic recovery after arrest for various lengths of time. In 2002 the results of two large multicenter clinical trials were reported and they showed that patients with out-of-hospital cardiac arrest (OHCA) and an initial rhythm of ventricular fibrillation had a significantly better neurologic outcome if they were cooled to 32-34°C for 12-24 hours after the arrest [3,4]. Based on the positive results of those trials, the advanced life support task force of the International Liaison Committee on Resuscitation recommended therapeutic moderate hypothermia for patients with OHCA and ventricular fibrillation as the initial rhythm [5]. Subsequent clinical studies have documented as much as a twofold increase in the rate of good outcomes for this subgroup of OHCA patients treated with therapeutic hypothermia [6]. Several questions remain,

however, about the long term efficacy of hypothermia, and its benefit for other subgroups of patients with cardiac arrest, such as those with post-arrest rhythms of asystole or electro-mechanical dissociation.

## Recent advances

### Prognosis

Clinical risk factors associated with poor outcome after cardiac arrest continue to be extensively studied in the search for one or a combination of features with high enough specificity and sensitivity to be clinically reliable. In one cohort of 149 patients with OHCA who had initiation of professional cardiopulmonary resuscitation and who survived long enough to be hospitalized, 25.5% survived for at least 3 years [7]. The strongest predictors for long-term survival were age under 70 years, ventricular fibrillation as the initial rhythm, cardiopulmonary resuscitation without atropine, and ST-segment elevation myocardial infarction. In fact, the subgroup with ST-segment elevation myocardial infarction had a 1-year survival of 57.7%. Other recent studies also show that clinical findings independently associated with death or severe disability are older age, the presence of chronic obstructive pulmonary disease, the absence of corneal and pupillary reflexes, myoclonus, and, to a lesser extent, extensor or absent motor responses to painful stimuli [8-10]. In addition, duration of cardiac arrest greater than 25 minutes, defined as time from collapse to return of spontaneous circulation, is strongly associated with such poor outcomes [11,12] (Table 1).

The early onset of generalized myoclonic status is an ominous sign, although there is at least one case report of a patient who regained consciousness after successful treatment of the status [13]. Seizures may contribute to mortality, morbidity, and to increased ICU length of stay. In addition, most agree that a neurologic assessment-based prognosis of patients should be considered unreliable for at least the first 72 hours after the arrest, and particularly for those patients receiving therapeutic hypothermia [14].

**Table 1. Clinical characteristics of poor outcomes for patients who remain comatose after cardiac arrest\***

Absent papillary light reflexes
Absent corneal reflexes
Extensor or no motor response to pain
Age greater than 70 years
Non-ventricular fibrillation as initial post-arrest rhythm
Duration of arrest greater than 25 minutes
Presence of chronic obstructive pulmonary disease
Myoclonic status
Serum neuron specific enolase levels >80 ng/ml
N-20 waves of somatosensory evoked potentials absent bilaterally

\* Most reliable when assessed 72 hours or more after the arrest.

Some have also raised concerns that subclinical or nonconvulsive status epilepticus may be an important cause of prolonged coma after cardiac arrest. But electroencephalograms (EEGs) obtained from 169 patients admitted alive but comatose after OHCA found only two patients with EEG evidence of generalized myoclonic status without clinical manifestations [15].

### Molecular biomarkers

Cardiac arrest and loss of spontaneous circulation causes global cerebral ischemia. Molecular markers of neuronal distress might be expected to be elevated in proportion to the severity of ischemia, and thereby reflect the likelihood of prolonged coma. NSE levels of 80 ng/ml or higher have been found to predict persistent coma after OHCA with a sensitivity of 63%, specificity of 100%, positive predictive value of 100%, and a negative predictive value of 84% [16,17]. Thus, a serum NSE concentration exceeding 80 ng/ml is a highly specific but only moderately sensitive marker for death or severe neurological disability after resuscitation. Amaraz *et al.* [16] did conclude that the specificity of serum NSE levels >80 ng/ml is sufficiently high that, when used with other clinical and electrophysiological data, it could be useful as a prognostic indicator of neurologic outcome after cardiac arrest [16]. And in a prospective study of 80 patients successfully resuscitated after cardiac arrest, Prohl and colleagues [18] used multivariate logistic-regression analysis to show that 85% of the variance in the dichotomized Cerebral Performance Category (CPC) scores at 1 and 6 months after arrest could be explained by NSE levels at day 4, clinical examination score at day 4, and age, with a sensitivity of 92% and a specificity of 93%. There is some preliminary evidence that NSE may be unreliable as a predictor of poor outcome when patients have been treated with hypothermia, however.

NSE serum levels obtained from 12 to 36 hours after the arrest also have been found to be predictive of 6-month outcomes for patients with in-hospital cardiac arrest [19]. Those who achieved a favorable outcome, defined as mild, moderate, or no disability, had a median NSE level of 25 ng/ml, while those with a GOS (Glasgow Outcome Scale) score of 1-3 (dead, vegetative, or severely disabled) had a median serum NSE level of 44 ng/ml.

S-100B is a relatively non-specific biomarker of neuronal distress, and serum levels are elevated in a variety of stress related conditions. In one study of the ability of S-100B to predict outcomes for comatose OHCA patients at hospital discharge, S-100B was found to have a sensitivity of 100%, but a specificity of only 38% [20]. Threshold levels of serum S-100B at 24-48 hours after OHCA have been identified that predict moderate to

severe memory impairment. In addition, threshold levels that predict in-hospital death with absolute specificity also have been defined, but sensitivity is less than 50%, so at present most conclude that serum S-100B is not a clinically useful biomarker for outcome prediction [21].

Others have focused on serum levels of the cardiac neurohormone B-type natriuretic peptide, and found that, in 109 patients with OHCA who survived to be evaluated in the emergency room, a level of 80 pg/ml or less was an independent predictor of favorable neurological outcome [22].

### **Imaging biomarkers**

The relationship between the clinical manifestations of hypoxic-ischemic encephalopathy following cardiac arrest, and anatomic brain injury, is not entirely clear. In some cases at least, prolonged coma or vegetative state may be more due to a disruption of cerebral physiology than to anatomic injury. In one post-mortem study of 41 patients who fulfilled standard clinical criteria for brain death prior to discontinuation of life-support measures, only mild histologic change was present in one-third of the patients, though it should be noted that only two of these patients had cardiac arrest as their primary diagnosis – the rest were traumatic brain injury [23]. No distinctive neuropathologic features of brain death could be identified. However, there also is evidence for pathognomonic ischemic histopathology. For example, diffuse axonal injury is more common after traumatic brain injury; cytotoxic edema is most common after ischemic stroke; and cortical laminar necrosis is most common after cardiac arrest. As a result, there is some rationale for using magnetic resonance imaging (MRI) to identify early ischemic injury and distinguish the cause [24].

In a study of 80 comatose patients with cardiac arrest who underwent diffusion-weighted MRI, a reduction of the whole-brain apparent diffusion coefficient (ADC) was a significant predictor of death or severe disability [25]. The differences in ADC between those with a good versus those with a poor outcome were most prominent in the occipital and parietal lobes. Others also have found that the largest number of diffusion changes indicative of acute ischemia are seen in patients who die, and such changes are most common in the parietal lobes [26]. Diffusion-weighted MRI-based ADC thresholds for recovery of function and survival were defined in a very recent paper by Christine *et al.* [27]. Timing of the MRI relative to seizures is very important because seizures can cause reversible changes in the ADC map that are not related to prognosis.

A recent study of functional MRI also found a correlation between the level of BOLD (blood oxygenation-level dependent) activation of the primary sensory cortex following stimulation of the palm of the hand, and survival at 3 months [28].

### **Electrophysiologic biomarkers**

SSEPs are most helpful for predicting which patients will die or remain in a persistent coma following OHCA. In particular, the bilateral absence of the N20 potential is a very good predictor of death or persistent vegetative state. The PROPAC study of 407 patients from the Netherlands found that bilaterally absent early cortical responses (N20) following stimulation of the median nerve is the most reliable predictor of poor outcome, and especially the likelihood that the patient will not regain consciousness [10].

However, SSEPs are not very useful for predicting good outcomes, such as who will regain normal or near normal neurologic and cognitive functioning. While some have found a weak correlation between retention of the N20 waveform and such good outcomes [28], a study of 319 patients with coma following cardiac arrest found that only 28% of those with normal N20 and N70 potentials had a good outcome [29].

The continuous analyses of the EEG with the bispectral index (BIS) monitor also has been used to predict outcomes. In one study of 14 patients with coma after cardiac arrest, all 11 patients who had BIS values of zero either died or had severe neurologic deficits at 6 months after the arrest [30]. Again, however, BIS monitoring was not useful for predicting who would have complete neurologic and functional recovery, and 11 out of 31 patients with BIS values higher than zero died, while 17 had no or minor neurologic deficits 6 months after cardiac arrest.

It is very important to remember that EEG is suppressed by anesthetic agents and by hypothermia, both of which may produce electro-cerebral silence and burst suppression [31]. SSEP is less susceptible to sedative and anesthetic agents, but hypothermia has been shown to prolong evoked potential latencies.

### **Treatment of comatose cardiac arrest patients**

Therapeutic hypothermia is now considered standard of care for patients with OHCA and ventricular fibrillation as the initial rhythm, though clinical trials continue to be conducted to better define the benefits of the therapy, treatment parameters, and duration of effect. However, contemporary clinical trials no longer randomize patients to a normothermia arm. One study of 52

patients treated with therapeutic hypothermia found a 33% shorter length of ICU stay compared to historical normothermic controls [32]. In another study of OHCA, 79 patients who received hypothermia and were alive at hospital discharge had significantly better CPC scores compared with 77 patients who did not receive hypothermia and were admitted to the same hospital during the 2 years prior to the hypothermia treated group [33]. However, at 6 months after the arrest there was no difference in the Mini Mental Status Examination or the SF-36, a self-rated quality of life assessment, between the hypothermia and normothermia groups.

The impact of the rate of cooling on outcome is controversial. A review of the Swedish Hypothermia Registry of 975 patients with OHCA revealed that half of the patients who survived had minimal or no neurological deficits at long-term follow-up, but neither the time to initiation of therapeutic hypothermia nor time to reach target temperature had any effect on outcomes [34]. A separate study of 22 patients treated with hypothermia in the pre-hospital setting by infusion with large volumes of cold intravenous saline also found that, compared with 77 consecutive patients treated with standard prehospital resuscitation, there was no difference in the rate of good outcome at 1 year after the arrest [35]. However, a study of the use of endovascular cooling technology in 49 consecutive patients resuscitated from cardiac arrest found that the time to reach 33°C was an independent predictor of recovery of normal neurologic ability, and that those patients who reached target temperature the soonest also had the lowest serum levels of NSE [36].

For comatose patients with ST-segment elevation associated with acute myocardial infarction, there also is evidence that primary percutaneous coronary intervention to restore coronary perfusion, and therapeutic hypothermia, can safely be combined to improve outcomes in this subgroup of OHCA patients [37,38].

Hypothermia still has not been found to improve outcomes for those with nonventricular fibrillation rhythms, such as asystole or pulseless electrical activity, when cardiopulmonary resuscitation is begun [6].

#### Implications for clinical practice

During the past 2-3 years several studies have better defined the clinical characteristics, and molecular and electrophysiologic biomarkers that can be reliably used to predict poor long-term outcomes for those who survive OHCA. Thus, patients who are comatose and have absent pupillary and corneal reflexes, no spontaneous circulation after arrest for more than 25 minutes,

are older than age 70, and have serum NSE levels greater than 80 ng/ml and bilaterally absent N20 waves on SSEPs 3 or more days after the arrest will have a poor long-term outcome. Unfortunately, however, there still has been little progress toward defining clinical or laboratory characteristics that will reliably predict good outcomes. No new therapies for OHCA have been identified, but recent trials have better defined the short- and long-term effects of therapeutic hypothermia.

#### Abbreviations

ADC, apparent diffusion coefficient; BIS, bispectral index; BOLD, blood oxygenation-level dependent; CPC, Cerebral Performance Category; EEG, electroencephalogram; GOS, Glasgow Outcome Scale; ICU, intensive care unit; MRI, magnetic resonance imaging; NSE, neuron specific enolase; OHCA, out-of-hospital cardiac arrest; SSEP, somatosensory evoked potentials.

#### Competing interests

The author declares that he has no competing interests.

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