CLINICAL PRACTICE

# Neurologic Prognosis after Cardiac Arrest

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*This* Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

**A 55-year-old man collapses while jogging through the park. A bystander finds him unconscious and without a pulse and initiates cardiopulmonary resuscitation (CPR) while an ambulance is summoned. On arrival in the emergency room, the patient is in ventricular fibrillation; the partial pressure of oxygen in arterial blood is 200 mm Hg, the pH is 7.25, and the bicarbonate level is 18 mmol per liter. Spontaneous circulation is reestablished, but he remains comatose with absent pupillary reflexes. He is then treated with hypothermia, achieving a core temperature of 34°C in 4 hours, which is maintained for 24 hours, after which he remains unconscious. What would you advise regarding his neurologic prognosis?**

## THE CLINICAL PROBLEM

About 450,000 Americans have cardiac arrest annually.[1] About 80% of cardiac arrests occur at home, for which the rate of death is at least 90%.[1,2] More than half the survivors have permanent brain damage of varying degrees.[3,4] The use of an implantable cardioverter–defibrillator in appropriate patients[5] and the availability of public-access defibrillators have improved survival with an acceptable quality of life.[6-9] In-hospital arrests have slightly better outcomes than those that occur outside the hospital, with restoration of circulation in 44% of patients and survival to discharge in 17% of patients. Two randomized, controlled trials showed a positive effect of hypothermia on mortality and morbidity after cardiac arrest.[9-11]

When patients are comatose after resuscitation (a state commonly referred to as anoxic–ischemic encephalopathy), there is a spectrum of outcomes, ranging from brain death to good recovery (Table 1). Some progress has been made in the prediction of outcomes for initially comatose patients, mainly in the prediction of poor outcomes.

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## STRATEGIES AND EVIDENCE

### PREDICTORS OF OUTCOME

Most studies that have assessed predictors of outcome in patients with anoxic–ischemic encephalopathy have as their prime objective the reliable prediction of an outcome no better than a vegetative state or severe disability with total dependency at 3 to 6 months after arrest (a Glasgow Outcome Scale score of 3 or less) (Table 1).[12] The vegetative state consists of wakefulness but no evidence of conscious awareness.[13] The rationale for emphasizing poor outcomes is that most patients would choose not to continue living in such a disabled state; thus, a poor prognosis usually leads to the consideration of withdrawal of life support. To avoid withdrawal of support in patients who have a plausible chance at recovery, tests should have a near zero rate of false positives for determining a poor prognosis. The prediction of a

**Table 1. Glasgow Outcome Scale Scoring System.**

| Score | Definition |
|---|---|
| 1 | Dead |
| 2 | Vegetative state; awake but not aware; does not interact in any cognitive way with the environment; does not fixate or follow with eyes; vegetative functions preserved |
| 3 | Severe disability; able to follow commands but cannot live independently; requires support for activities of daily living |
| 4 | Moderate disability; able to participate in activities of daily living, but work and social life are compromised because of mental or physical disability |
| 5 | Good recovery; able to return to work or school |

graded outcome that is better than a vegetative state is more difficult and is not a realistic goal for current testing.

Studies involving patients after cardiac arrest need to be scrutinized to avoid cases of "self-fulfilling prophecy," in which support is withdrawn because of the test result that is being evaluated. The best evidence regarding prognostic testing comes from well-designed prospective studies with an adequate number of patients, in which the test result does not bias care and the patients are allowed to survive for at least 3 days. At that time, motor responses that are better than extensor posturing will have returned in the vast majority of patients if consciousness is to be regained, at least for patients who are not treated with hypothermia. A limitation of the available studies of prognosis after cardiac arrest is that most were performed before the use of hypothermia, which has an ameliorating effect on brain damage; further studies should address whether the use of hypothermia affects the validity of prognostic assessments.

## MEASURES OF PROGNOSIS

### *Clinical Signs*

The absence of a pupillary reaction to light suggests a poor prognosis but has unclear specificity when assessed early after a cardiac arrest. In prospective studies involving 491 patients, 152 of whom had an absent pupillary light reflex on hospital admission, false positive rates (i.e., outcome better than poor despite a positive test result) ranged from 0 to 31%.[14-19] However, all 108 patients whose pupillary reactions were absent at day 3 after cardiac arrest had poor outcomes (false positive rate, 0%; 95% confidence interval [CI], 0 to 3).[14-20]

The motor response to noxious stimuli also provides useful prognostic information. Several prospective studies, including one multicenter study involving more than 400 patients with cardiac arrest, showed that a motor response to noxious stimuli that was no better than extensor posturing (i.e., a decerebrate response or no response) at 72 hours was associated with no false positives for a poor outcome (95% CI, 0 to 9); this response occurred in 35% of the patients.[15,18,20] Although these studies did not include patients treated with hypothermia, a small study of 37 initially comatose patients who underwent hypothermia[21] showed recovery of awareness (on day 6) in 2 of 14 patients who had a motor response that was no better than extensor posturing on day 3. Thus, caution is warranted in relying on the motor response alone before day 6 (or possibly later, given the small number of patients in the series) for patients who have received hypothermia therapy.

The corneal reflex is tested by touching the cornea with a gauze or cotton swab and looking for contraction of the orbicularis oculi on either side. In two prospective studies, the absence of a corneal reflex at 72 hours was associated with no false positives for a poor outcome (95% CI, 0 to 14 in one study[18] and 0 to 41 in the other[20]); this response was observed in approximately 13% of the patients. The absence of eye movements in response to irrigation of the ear canals with ice water at 72 hours is another indicator of poor outcome. In one study, this response was absent in about 43% of patients, with no false positives for a poor outcome (95% CI, 0 to 41).[20] However, the caloric response can be blunted by many sedative drugs, including narcotics.[22] To avoid the confounding effects of cumulative or large doses of sedative, anesthetic, and analgesic drugs, it is best to put off testing until there is ample evidence that they have been cleared from the circulation.

Myoclonic status epilepticus (bilaterally synchronous twitches of limb, trunk, or facial muscles) is likewise a marker of a poor outcome.[20,23] In a prospective study involving 407 patients, myoclonic status epilepticus at 24 hours after arrest was associated with no false positives (95% CI, 0 to 14).[20] Myoclonic status epilepticus must be differentiated from generalized tonic–clonic seizures and from multifocal, asynchronous myoclonus, a nonspecific indicator of a metabolic encephalopathy without prognostic value. An autopsy

series of patients with myoclonic status epilepticus after cardiac arrest revealed widespread ischemic cell changes throughout the central nervous system, consistent with anoxic–ischemic damage.[24]

Other clinical variables have insufficient predictive value to be useful in practice. In two large prospective studies involving 774 patients, who had a 6-month rate of death of more than 80%,[25] variables that were not strongly correlated with a poor outcome included age, sex, cause of arrest, type of arrhythmia (e.g., ventricular fibrillation or asystole), total arrest time, and duration of CPR. The body temperature and initial Glasgow Outcome Scale score differed significantly between survivors without severe disability and nonsurvivors, but there was too much overlap for these measures to be clinically useful.[12]

Many patients who do not have the abovementioned unfavorable clinical features still have poor outcomes. The brain stem is more resistant to anoxic–ischemic damage than the cerebral cortex; thus, compromise of brain-stem reflexes suggests that the cortex must be severely damaged. However, preserved brain-stem reflexes do not imply intact cortical function.

Because there is no clinical method for assessing cerebral cortical damage in the unconscious patient, reliance on clinical criteria alone requires prolonged observation for evidence of recovery. In a prospective cohort study involving patients with nontraumatic coma (including but not limited to coma after cardiac arrest), 11% of patients recovered consciousness after 3 months; most but not all had severe disability.[13] Hence, there is a need for a more direct assessment of cortical integrity and function.

*Electrophysiological Signs*

The measurement of somatosensory evoked potentials (SSEPs), especially the N20 response from the primary somatosensory cortex (assessed 20 msec after electrical stimulation of the median nerve at the wrist), has emerged as the most accurate predictor of a poor outcome in patients with anoxic–ischemic encephalopathy (Fig. 1). In a meta-analysis of studies involving 801 patients, bilateral absence of the N20 response was associated with essentially no false positives (pooled 95% CI, 0 to 2).[26-28] In some patients, N20 responses are intact at 24 hours after arrest but are lost by 72 hours; once lost, they are not regained, and outcomes are poor.[29]

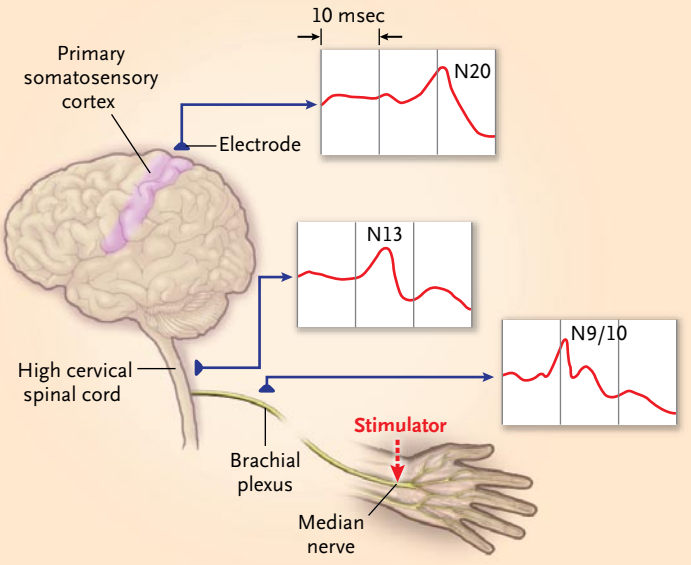


**Figure 1. Somatosensory Evoked Response with Median-Nerve Stimulation.**
The measurement of somatosensory evoked potentials is a predictor of a poor outcome in patients with anoxic–ischemic encephalopathy. The principal peak is the N20 response from the primary somatosensory cortex, which is assessed 20 msec after electrical stimulation of the median nerve at the wrist. The placement of an electrode over the posterior columns of the high cervical spinal cord results in the associated N13 peak, whereas the placement of an electrode over the brachial plexus (Erb's point) results in the associated N9/10 response. Vertical lines on the schematic graphs are 10 msec apart. The N20 is the response from the primary sensory area and is the signal of interest. When the N20 is absent, there is no upward deflection at 20±2 msec from the time of the stimulus. To ensure that the sensory pathway up to the brain is intact, responses from the brachial plexus (N9) and the cervical spinal cord (N13) are also recorded.

### BIOCHEMICAL SIGNS

Several chemicals are released from the brain into the blood and cerebrospinal fluid after cardiac arrest. Of these, the serum concentration of neuron-specific enolase (NSE) has appeared promising as a predictor of a poor outcome. In one prospective, multicenter study involving 231 patients, an NSE level of more than 33 $\mu$g per liter, sampled between 1 and 3 days after cardiac arrest, was strongly predictive of a poor outcome with no false positives (95% CI, 0 to 3).[12,20] However, this finding has not yet been confirmed in other large prospective cohorts, and the timing of testing and cutoff values for NSE have varied in other

studies of this marker.[30,31] Moreover, assays for biomarkers, including NSE, are not commonly available in North America. Elevated levels of S100 (glial protein), the BB fraction of creatine kinase in cerebrospinal fluid or serum, and neurofilament protein have not had high specificity for a poor outcome.[12] However, limited data suggest that measurements of both S100 and NSE on days 1 and 3 may improve the prediction of a poor prognosis.[32]

### NEUROIMAGING AND OTHER IMAGING

Computed tomographic (CT) images are usually normal immediately after a cardiac arrest, but by day 3 they often show brain swelling and inversion of the gray–white densities (with the use of quantitative measures) in patients with a poor outcome.[32] Further study is needed to assess the clinical use of these findings in establishing prognosis.

Magnetic resonance imaging (MRI) has also been proposed as a means of assessing prognosis after cardiac arrest, but limited data call its use into question. Among four case series, each with no more than 12 patients assessed with MRI at variable time points,[33-36] two studies showed that diffusely abnormal findings on diffusion-weighted imaging and fluid-attenuated inversion recovery correlated with a poor outcome.[34,35] A study involving 138 patients suggested that optimal specificity is achieved when diffusion-weighted imaging is performed 49 to 108 hours after cardiac arrest.[36] The use of apparent diffusion coefficient (ADC) mapping was reported to add greater precision in predicting a poor outcome.[37] (Diffusion-weighted imaging and ADC are measures of the diffusion of water molecules in tissue and vary over time after ischemic injury.) None of these studies monitored for seizures, which could have reversibly affected MRI findings.

MR spectroscopy (e.g., for pH and *N*-acetyl aspartate, a neuronal marker) has been reported to correlate with a poor outcome in small studies,[38-40] but more data are needed. Measures of cerebral metabolism with positron-emission tomography and determination of intracranial pressure, brain oxygen, or jugular venous oxygenation have not appeared sufficiently discriminatory for a poor outcome to be clinically useful, although studies are small.[12,34]

### ETHICAL CONSIDERATIONS

Brain death is equivalent to death in most countries, and its diagnosis means that life-support measures are appropriately discontinued. Caution is needed in predicting a poor prognosis in poorly responsive patients with anoxic–ischemic encephalopathy who do not meet brain-death criteria. In the United States, the Patient Self-Determination Act of 1991 recognizes the right of the patient to leave advance directives regarding CPR or limiting levels of care. However, in most cases, decision making is delegated to a substitute advocate or durable power of attorney. Members of the health care team should identify and meet with the person charged with decision making early in a patient's course to explain the process by which prognosis is assessed and then follow up to present results of assessments and discuss prognosis and recommendations, including withdrawal of care, where appropriate.

## AREAS OF UNCERTAINTY

The effect of hypothermia on the predictive value of various assessments remains uncertain. Limited data suggest that this therapy reduces the predictive value of motor response for a poor outcome early after cardiac arrest.[21]

It remains unclear whether electroencephalographic (EEG) findings have clinical use in predicting a poor outcome.[12,41] Seizure activity (especially nonconvulsive seizures or nonconvulsive status epilepticus) is common in patients with anoxic–ischemic encephalopathy and may contribute to brain damage and prolonged coma.[42,43] However, the presence of seizures does not preclude a favorable outcome. EEG studies have not specifically examined certain subcategories of findings, such as complete suppression of cortical activity, which may be highly predictive of a poor outcome.[41] Where feasible, continuous EEG monitoring is nonetheless recommended during treatment with hypothermia, so that seizures occurring in pharmacologically paralyzed patients can be recognized and appropriately treated.[42-46]

More attention is needed to improving the prediction of a positive outcome. Purposeful movements, eye contact, and obeying commands in the first few days after arrest are encouraging findings. Patients with EEG reactivity (changes in rhythms and amplitudes in response to stimuli) do better than those who do not have such a response.[41]

Evoked responses other than the N20 response and event-related responses (cerebral responses to stimuli that require discriminative functions of the

brain) may have value in predicting recovery of awareness[29] but have not been sufficiently studied. One such event-related response — "mismatch negativity" (a negative shift of brain potential in response to a novel stimulus) — was shown to predict a better outcome among comatose patients with traumatic brain injury.[47,48] In a preliminary study involving 19 patients who were initially comatose after cardiac arrest, the intensity of response in the primary somatosensory area with functional MRI directly correlated with various categories of outcome on the Glasgow Outcome Scale.[49] Although some progress has been made in predicting favorable outcomes, the measures that are used for prediction are unlikely to be sufficiently precise for the individual patient.

## GUIDELINES

In 2006, the American Academy of Neurology published an algorithm to facilitate prognostic determination in patients who are resuscitated within 24 hours after cardiac arrest (Fig. 2).[12] However, the algorithm may require modification as more information accrues on the effects of hypothermia and with validation of other tests for poor and favorable outcomes.

## CONCLUSIONS AND RECOMMENDATIONS

If a patient remains comatose for more than 24 hours after resuscitation from cardiac arrest or after therapeutic hypothermia, as in the case described in the vignette, the prognostic guidelines developed by the American Academy of Neurology should be used to assess whether the patient has a poor prognosis. Clinical features predicting a poor outcome are likely to be reliable regardless of whether hypothermia was used, but the motor response may be delayed until 6 days or more in hypothermia-treated patients. If SSEP responses are absent at day 1, they can be repeated at day 3 or beyond; if N20 responses are lost, the prognosis is poor. Measurement of serum NSE, if immediately available, may also be useful in the prediction of a poor outcome, although validation is needed.

In cases in which a definitive prognosis cannot be made in the days after cardiac arrest, reexamination is indicated over longer periods; only

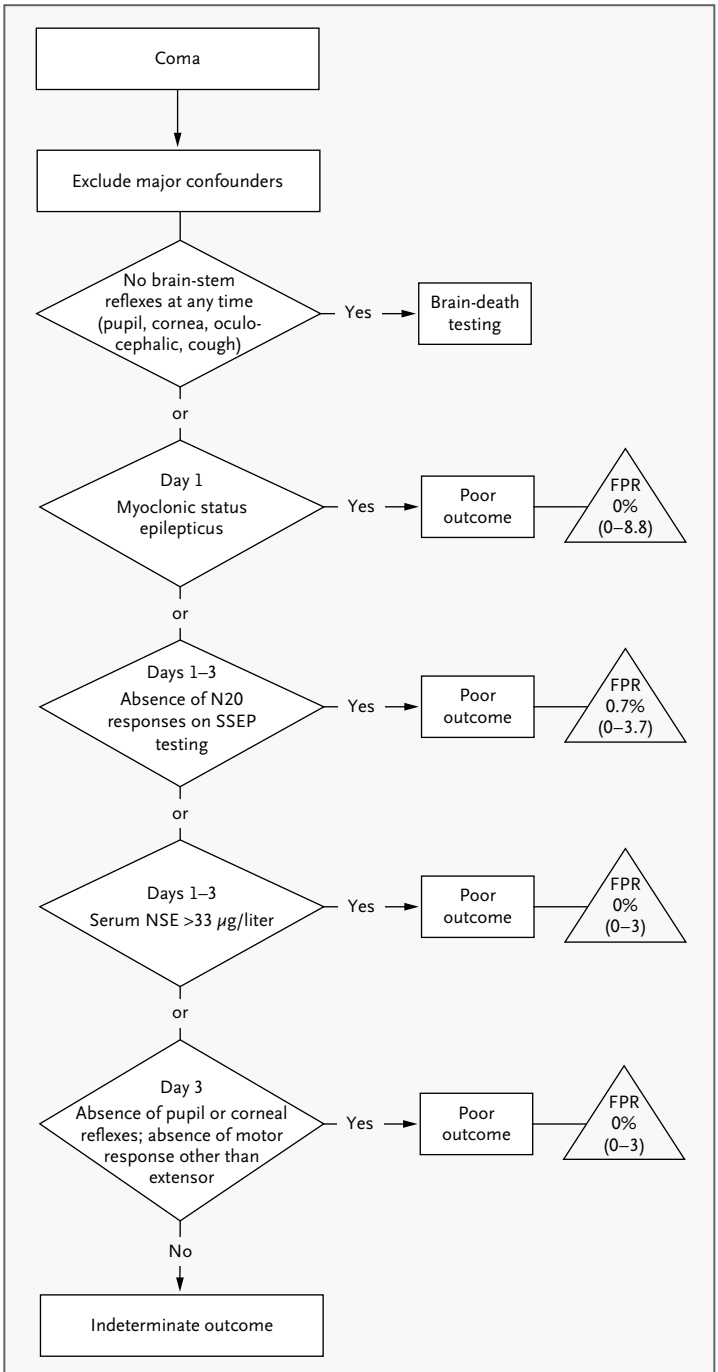


**Figure 2. Decision Algorithm for Use in Outcome Prediction for Comatose Survivors of Cardiac Arrest.**

Major confounders include the use of neuromuscular blocking agents, large doses of sedative drugs, the use of hypothermia, the presence of organ failure, and shock. FPR denotes false positive rate, NSE neuron-specific enolase, and SSEP somatosensory evoked potential. Numbers in parentheses are 95% confidence intervals. Data are from Wijdicks et al.[12]

when a poor prognosis is reasonably certain is it ethically justifiable to withdraw support. The presence of purposeful movements and EEG reactivity within the first 3 days after cardiac arrest suggest a more favorable prognosis, but these and other available markers cannot distinguish effectively between patients who are likely to have an excellent neurologic recovery and those who are likely to have persistent deficits.

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