The Neurohospitalist
2014, Vol. 4(3) 144-152

DOI: 10.1177/1941874413509632
nhos.sagepub.com
SAGE

An Update in Postcardiac Arrest Management and Prognosis in the Era of Therapeutic Hypothermia

Elizabeth A. Cahill, PhD[1], David L. Tirschwell, MD, MSc[1], and Sandeep Khot, PhD[1]

Abstract

Prognostication of patients who remain comatose following successful resuscitation after cardiac arrest has long posed a challenge for the consulting neurologist. With increasing rates of early defibrillation, out-of-hospital cardiopulmonary resuscitation, and expanding use of therapeutic hypothermia, prognostication in hypoxic–ischemic encephalopathy has become an increasingly common consult for neurologists. Much of the data we previously relied upon for prognostication were taken from patients who were not treated with therapeutic hypothermia. In this review, we examine useful prognostic tools and markers, including the physical examination, evaluation of myoclonus, electroencephalogram monitoring, somatosensory-evoked potentials, biochemical markers of neuronal injury, and neuroimaging. Neurologists must avoid overly pessimistic prognostic statements regarding survival, awakening from coma, or future quality of life, as such statements may unduly influence decisions regarding the continuation of life-sustaining treatment. Conversely, continuation of aggressive medical management in a patient without any hope of awakening should also be avoided. Thus, an understanding of the utility and the limitations of these prognostic tools in the era of therapeutic hypothermia is essential.

Keywords

hypoxia–ischemia, brain, cerebrovascular disorders, evoked potentials, techniques, neurohospitalist, clinical specialty, neurocritical care, clinical specialty, electroencephalography, techniques

Introduction

The annual estimated incidence of out-of-hospital cardiac arrest (CA) is greater than 300 000 persons in the United States, with an additional approximately 200 000 in-hospital CA.[1] Survivors of resuscitation have widely variable outcomes, ranging from minimal motor and cognitive deficits with a return to independent living to a persistent coma or death. Approximately 80% of the survivors of CA remain comatose for at least 1 hour[2] and hypoxic–ischemic encephalopathy has become one of the more common causes of persistent coma, along with traumatic brain injury and stroke. The neurologist is frequently called upon to predict the chances of awakening after CA and advise on the utility of continued aggressive medical support. In 2006, the American Academy of Neurology (AAN) published practice parameters for predicting outcome in comatose patients following resuscitation from CA based upon data collected between 1966 and 2006.[3] However, the majority of studies included in this practice parameter were completed before the era of therapeutic hypothermia (TH). This review will address prognostication in patients treated with TH after successful resuscitation from CA.

The neurologist's prognosis for survival, awakening from coma, or future quality of life can strongly influence decisions regarding the continuation of life-sustaining treatments. Regardless of the accuracy of the prognostic statement, patient's families are profoundly affected by these predictions. Accuracy in prognosis is thus nearly a moral imperative. Overly pessimistic prognostic statements have the potential to create a "self-fulfilling prophecy," where test results that portend a poor outcome influence treatment decision to the withdrawal or withholding of life support. Thus, a poor prognosis can lead to the withdrawal of life support in a patient who has the potential for meaningful recovery and an acceptable functional status.[4] Continuation of aggressive medical treatments in a patient without any hope of awakening, or survival in

[1] Department of Neurology, Harborview Medical Center, Seattle, WA, USA

Corresponding Author:
Elizabeth A. Cahill, Harborview Medical Center, 325 Ninth Avenuse, Seattle, WA 98104, USA.
Email: eacahill@uw.edu

an unwanted severely impaired state has attendant emotional and financial costs.

One goal of using standardized prognostic tests to improve decision making after CA is to remove, or at least ameliorate, physician bias that may overly influence the course of a patient's hospitalization and decisions to withdraw life support. Approximately 5% of patients have a good recovery following CA if they remain comatose by day 3 and the probability of motor and cognitive deficits increases with the time to awakening.[5] This time course may be unchanged in the setting of TH. In one small study, 91% of those who eventually awaken following CA and treatment with TH do so by day 3,[6] but prognostication among patients treated with TH necessitates extreme caution. Therapeutic hypothermia may alter the time course for the recovery of consciousness through a direct mechanism or, alternatively, may increase the use and decrease the therapeutic window of sedating medications in the setting of TH.[7,8] The prognostic factors and ancillary tests that are commonly used by neurologists include the neurological examination, with a focus on brain stem and motor responses, the presence or absence of myoclonus, biochemical laboratory studies, neuroimaging, and electrophysiological studies, especially somatosensory-evoked potentials (SSEPs) and electroencephalogram (EEG).

When interpreting the tests for prediction of outcome following successful resuscitation after CA, it is imperative to avoid falsely pessimistic predictions. The ancillary tests and examination findings used for prognostication need to have high positive predictive value with a low number of false positives; that is, patients who are predicted to have a poor outcome do, in fact, have a poor outcome. In practice, there are no studies with a 100% positive predictive value and no false positives. Thus, to avoid falsely pessimistic predictions, an approach that relies on multiple ancillary tests may minimize false-positive rate (FPR) and push specificity toward 100%. Although these ancillary tests may accurately predict who will not awaken, no test has been shown to reliably predict who is likely to awaken or the quality of life of those that awaken.

Theory

The use of TH to improve neurologic function was first introduced in the 1950s and more recently has been used in traumatic brain injury in the treatment of raised intracranial pressure.[9] The use of deep hypothermia (<30°C) following CA or traumatic brain injury is thought to improve outcome by decreasing the metabolism of the brain and suppressing inflammation. In the early years of TH, there were multiple complications with high morbidity and mortality. This was partly due to the lack of intensive care units, unreliable methods for both cooling and rewarming patients, and cardiac arrhythmias related to hypothermia.[8,10] Interest in hypothermia was revived after animal studies showed positive outcomes in rats treated with mild TH following reperfusion after CA.[11] More recent studies also revealed a more complicated mechanism, including the reduction in both early hyperemia and delayed hypoperfusion after CA.[8] The findings that mild hypothermia, rather than the previously employed deep or moderate hypothermia, could be utilized raised the possibility of an effective treatment with a better side effect profile.

In 2002, 2 seminal randomized controlled trials demonstrated an improvement in neurologic outcome among patients treated with mild hypothermia (32°C-34°C for 12-24 hours) following CA due to ventricular fibrillation or pulseless ventricular tachycardia compared to patients treated with normothermia.[12,13] In an Australian study, a favorable outcome, defined as survival with discharge to home or to a rehabilitation facility, was reported in 49% of the patients treated with TH compared to 26% of the patients in the normothermia group.[13] In a European multicenter trial, a favorable neurologic outcome after 6 months, defined as either good performance or moderate disability (cerebral performance category of 1 or 2), was reported in 75% of the patients treated with TH compared to 55% in the normothermia group.[12] The European multicenter study also showed a significant reduction in mortality after 6 months in patients treated with TH. The benefit of mild TH following resuscitation from CA appears to be restricted to patients with ventricular fibrillation or pulseless ventricular tachycardia without a clear benefit in patients with other initial cardiac arhythmias.[14] A recent study of prehospital TH, however, suggests a trend toward a favorable outcome among patients with pulseless electrical activity or asystole when the cause of the arrest is related to a cardiac etiology.[15] Contraindications for TH include patients with a premorbid coma or terminal illness, initial presentation of hypothermia, coagulopathy, or pregnancy.[2]

Although TH has become common in the early treatment of comatose patients after CA, there continues to be uncertainties surrounding technical aspects of treatment, including the optimal degree of hypothermia,[16] the speed and timing of induction,[15,17] the technique used to achieve TH,[18] sedation, and analgesia.[2,19] Elements of the neurologic examination can also be affected by TH due to changes in metabolism of drugs[20] and an increased use of sedative medications.[7]

Therapeutic hypothermia alters pharmacokinetic and pharmacodynamic parameters potentially resulting in smaller therapeutic windows and, therefore, potential for drug toxicity, failure, and compromise of prognostic tests such as the neurologic examination and electroencephalography.[7,8,20,21] Various mechanisms are at play in the alteration. TH decreases the clearance of drugs metabolized by the cytochrome P450 enzyme system, which is involved in both activation and detoxification of many drugs frequently used following CA including, but not limited to, midazolam, fentanyl, vecuronium, rocuronium, atracurium, propofol, phenobarbital, pentobarbital, phenytoin, propranolol, and various antimicrobials.[20] The effect of TH is thought to decrease the activity of these enzymes from 7% to 22% per degree below 37°C.[20] The result of the decreased enzyme activity can vary

and is unpredictable. In animal models, impaired enzyme activity during TH has been shown to increase the plasma concentrations and decrease the clearance of fentanyl.[22] In clinical studies, patients with traumatic brain injury treated with moderate hypothermia had significantly higher levels of plasma propofol concentrations (up to 30%) as well as prolonged action of neuromuscular blockade with atracurium.[23] The mechanisms for the changes in drug effects include impaired clearance, change in the volume of distribution (particularly in the setting of pH abnormalities commonly seen after CA), and change in enzyme-binding affinities and absorption.[20,21] The lingering effects of medications may be present as long as 72 hours following administration during TH. Higher drug levels and prolonged effects of sedating or paralytic drugs can confound the neurologic examination and potentially result in less effective treatments, making monitoring drug levels and avoidance of excess drug administration more important.[7]

Physical Examination

The physical examination is typically the first prognostic finding available to neurologists, and a number of examination findings at fixed time intervals have been shown to have high positive predictive value for poor outcome. [3,24] As TH is often initiated in the prehospital setting or early in the hospitalization, many of these time intervals likely need to be reassessed in patients treated with TH. The use of pharmacologic paralysis and increased levels of sedation in TH makes findings of the early physical examination either not interpretable or unreliable.[7]

The parts of the neurologic examination most utilized in the setting of hypoxic–ischemic encephalopathy are the brain stem examination, including corneal reflex, oculocephalic and pupillary response, and the motor response to painful stimulation. Similar to other prognostic tests, the findings of the examination have only been used to predict the chance of poor prognosis; there are no clinical signs that have been found to predict a good neurological outcome.

A meta-analysis of 11 studies and over 1900 patients assessed the accuracy of the findings of the neurologic examination among comatose survivors of CA prior to the widespread use of TH.[25] Patients without corneal and pupillary light reflexes at 24 hours and no motor response at 72 hours had the poorest prognosis.[25] In 2006, the Prognosis in Postanoxic Coma (PROPAC) study reported on 407 patients who remained comatose for at least 24 hours following resuscitation.[26] The study found that the predictive value of absent pupillary or corneal reflexes was 100% specific for a poor outcome only at 72 hours with a 0% FPR (sensitivity 13%), whereas absent motor responses at this point had an FPR of 5%.[26] The lower specificity at earlier time periods in PROPAC study patients after TH was in stark contrast to the earlier findings in the AAN practice parameter.[3] The AAN practice parameter reported a 0% FPR and narrow confidence intervals for poor outcome, defined as death or coma after 1 month or death, coma, or severe disability after 6 months, in patients with an absence of pupillary or corneal reflex within days 1 to 3 after resuscitation or with absent or extensor motor responses after day 3.[3]

Others have also found higher FPR for brain stem examination findings among patients treated with TH. In a prospective study of mortality at hospital discharge in 111 comatose survivors of CA treated with TH, incomplete brain stem reflexes assessed within 72 hours after resuscitation yielded an FPR of 8%—good functional outcome in 2 of 25 patients with at least 1 absent brain stem reflex.[27] The absence of motor response to pain was even more unreliable within the first 72 hours, with an FPR for mortality of 24%—survival in 11 of the 45 patients.[27] In another prospective study of 85 survivors of CA with poor outcome defined as death or vegetative state at 3 months, sedative medications were found to be important prognostication confounders. In this study, sedative medications were more frequently given in patients treated with TH than in normothermic patients.[7] The study reported that these physical examination variables were accurate with no false positives if patients in sedation within 12 hours of the 72-hour neurologic examination were excluded. In this population, absent pupillary response at 72 hours accurately predicted poor prognosis in both TH and normothermic patients with 0% FPR (sensitivity 43%).[7] Although absent pupillary response at 72 hours after CA is specific for poor prognosis, the sensitivity for this examination finding is low, limiting its importance. Finally, in a retrospective study of 37 survivors of CA treated with TH in which responsiveness at hospital discharge was assessed, extensor or absent motor response was seen in 2 of the 14 patients who subsequently regained awareness, 1 of whom was left with only minor disability.[28] As a group, these studies suggest that the recommendations from the AAN practice parameters regarding examination findings should be interpreted with caution when applied to patients treated with TH.

Myoclonus

Myoclonus, shock-like movements arising from the central nervous system, can be either positive with a brief contraction of muscles or negative with a loss of postural tone.[29] Myoclonus following CA is common and includes both posthypoxic myoclonus (PHM) and myoclonic status epilepticus (MSE) also known as generalized status myoclonicus.[30,31] Myoclonus can be spontaneous or stimulus provoked in either condition, rendering differentiating these drastically different syndromes difficult (see Table 1). PHM occurs mostly after a primary respiratory arrest and is thought to originate from the sensory cortex though can also be subcortical.[32] The EEG can show generalized epileptiform discharges. The prognosis in PHM is favorable with motor and cognitive

Table 1. Two forms of myoclonus after resuscitation from cardiac arrest (adapted from Longstreth, 2001)).

Postarrest Myoclonic Status	Posthypoxic Action Myoclonus
Symmetric jerking spontaneously and with stimulation	
Onset during coma	
Can occur with convulsions	
Difficult to control with most medications	
Effect of acute treatment unknown	
Usually after cardiac arrest	Usually after respiratory arrest
Gone within a few days	Persists
Evidence of severe brain damage on physical examination and ancillary tests	No evidence of severe brain damage on physical examination and ancillary tests
EEG often with burst suppression	EEG often with generalized epileptiform discharges
Usually fatal outcome	Good cognitive recovery, variable motor disability

Abbreviation: EEG, electroencephalogram.

recovery, though with the potential of a persistent movement disorder requiring antiepileptic therapy.[29]

MSE is thought to originate in the brain stem and is seen in the setting of severe brain injury, where the cerebral cortex is incapable of generating organized epileptiform discharges necessary for the development of seizures.[33] MSE is a clinical definition that is applied to comatose patients who develop 5 to 30 minutes of generalized and continuous myoclonus within 24 hours after CA.[34,35] MSE is considered an agonal brain pattern[36] with high morbidity and mortality. In a prospective study of 114 adult survivors of CA, myoclonus occurred in 35% of the patients, and MSE was diagnosed in 17% of these patients. Myoclonus alone did not portend a poor outcome, but none of the patients with MSE regained consciousness or survived to hospital discharge.[37] Likewise, the PROPAC study investigators[26] and others[36] have demonstrated similar dismal outcomes following MSE. The AAN practice parameter reports that MSE predicts a poor outcome with a 0% FPR following a primary cardiac arrest.[3]

In the setting of TH, however, survival among patients with MSE has been reported. In a study of 24 patients with electrographic and clinical evidence of status epilepticus who were treated with TH after CA, 23 patients had myoclonus and 1 patient returned to baseline with good functional recovery. Myoclonus without ictal EEG changes, considered reticular or brain stem myoclonus, occurred in 5 patients; all of these patients died.[38] In another case series of 3 patients treated with TH who exhibited ''massive myoclonus'' within 4 hours after resuscitation, 2 patients recovered to their prearrest baseline, whereas the third patient recovered with moderate disability.[35] The AAN practice parameter's recommendation to use myoclonus as a uniformly poor prognostic indicator is, therefore, of limited utility in the era of TH.

Seizures and EEG

Seizures and status epilepticus are common following CA,[32,34,37,39] though there remains no consensus on the optimal timing for diagnosis and therapeutic management. The EEG monitoring and evaluation is of unclear benefit in terms of both prognostication and outcome, though continuing to be an active area of research. Some inherent problems in EEG monitoring include differences in interpretation between readers,[40,41] lack of a unified classification system,[42,43] and the effect of medications and metabolic abnormalities on the EEG. Questions also remain about the usefulness, or even potential danger, in treating subclinical seizures and the optimal timing of EEG monitoring.

In a study of 39 survivors of either primary cardiac or respiratory arrest, a 5-level EEG grading system was created in which higher grades portend a worse neurologic outcome.[44] The classification scheme demonstrated a poor outcome in most patients with grade IV or grade V EEG, though with 1 false-positive patient with a grade IV EEG and subsequent recovery. Patients with grade I EEG were conscious at the time of EEG recording, whereas grade II or III EEG patterns had variable outcomes. The idea of a classification scheme has been revisited numerous times,[42,45,43] though prognostication and antiepileptic medication therapy based on EEG patterns remains of uncertain clinical value.

Certain EEG patterns, such as electrocerebral silence (<20 μV), burst suppression, or generalized periodic complexes on a flat background, have been associated with a poor prognosis, though not uniformly, with an FPR of 3% for a poor outcome (death or persistent vegetative state).[3] In a prospective case series of 34 comatose patients after CA or severe hypotension, the presence of malignant EEG patterns held a specificity of 71% for no recovery.[46] Status epilepticus has been associated with a high rate of poor outcome, while seizures alone do not have a similar prognostic value.[37] In patients treated with TH, continuous EEG monitoring is frequently used for evaluation of background activity or reactivity and for the detection of subclinical seizures or nonconvulsive status epilepticus and to distinguish seizures from myoclonic status epilepticus. In addition, continuous EEG monitoring is being increasingly used in patients undergoing TH to detect seizures during induced paralysis or severe shivering, partly due to the

higher risk of seizures during this period. A recent retrospective study of continuous EEG monitoring in 38 comatose patients after CA revealed electrographic seizures in 23% of the patients, with 78% of seizures meeting criteria for status epilepticus (defined as seizures lasting longer than 30 minutes).[34] In this study, the median onset of seizures was 19 hours following CA, a period when most patients treated with TH are typically under pharmacologic paralysis or heavy sedation.[34] In this study, a poor neurologic outcome was seen in 94% of the patients with any epileptiform activity and in 100% of the patients with electrographic seizures. Another retrospective study of 54 patients undergoing TH after CA also showed a poor outcome in patient with seizures or epileptiform discharges despite treatment.[43] In yet another study, however, of 28 survivors of CA with status epilepticus (defined as clinical and electrographic seizures lasting more than 5 minutes), 6 patients treated with TH improved beyond a vegetative state.[38] The authors report that certain patient characteristics, seen in 11% of the patients, could predict awakening after status epilepticus, including preserved brain stem reflexes, preserved cortical SSEP responses, and EEG background reactivity. Thus, although status epilepticus has been shown to confer an independent risk factor for mortality in patients treated with hypothermia,[47] exceptions in the literature should give pause to neurologists counseling families or decision makers regarding the presumed dire prognosis in patients with seizure activity after CA.

It also remains unclear whether seizures and status epilepticus represent devastating brain injury and an independent poor prognostic indicator or a marker of severe though modifiable neurologic injury. Given the inherent limitations of EEG monitoring, the use of this modality alone in prognostic decision making is currently not recommended. EEG monitoring is also not included in the AAN practice parameters.[3,48]

Somatosensory-Evoked Potentials

SSEP is used to evaluate an early cortical N20 response in comatose patients following CA. A strength of SSEPs in prognostication after CA is that the study is less affected by sedating drugs than EEG or the neurologic examination. Limitations include interrater reliability issues (both with technique and interpretation), the effects of focal abnormalities along the somatosensory pathway, and potential effects of TH on the distinction between bilateral absent or severely reduced N20 amplitudes.

A meta-analysis of over 1100 patients with SSEPs performed early during anoxic coma found that bilaterally absent N20 responses were predictive of not awakening with 100% specificity.[25] The sensitivity of SSEPs in this setting, however, was 42%. The PROPAC study also found that patients with bilateral absent N20 after 24 hours of coma had a poor outcome (death or persisting unconsciousness after one month) with a 0% FPR (sensitivity 45%). Absent N20 responses were found in 246 of the 407 patients at 48 hours, making this the most frequently found abnormal marker.[26] Other studies have also reported that the finding of bilaterally absent N20 was uniformly predictive of a poor outcome.[25,46] Taken together, these studies led to the recommendation in the 2006 AAN practice parameters that bilateral absence of cortical SSEP response with median nerve stimulation recorded on days 1 to 3 or later after resuscitation could accurately predict a poor outcome.[3] However, exceptions have been reported where bilaterally absent SSEPs did not carry such a dire prognosis. In one case, a 16-year-old boy who had a CA and was not treated with TH had a good outcome despite repeatedly absent cortical SSEP responses (at days 3 and 9).[49]

The use of TH has also been shown to have effects on the N20 response. In a prospective cohort study of 77 patients, all 13 (17%) patients who remained comatose after rewarming with bilaterally absent N20 responses had a poor outcome (0% FPR).[50] Of note, one of these patients had bilaterally absent N20 responses during hypothermia but intact responses after rewarming suggesting that the SSEP study should not be performed during TH.[50] Others have also shown a dismal prognosis in patients treated with TH with bilaterally absent N20 responses.[27,51] However, one clear exception emerged in a retrospective study of 185 patients treated with TH. Of the 36 patients found to have bilaterally absent N20 responses, 35 patients either died or remained in a persistent vegetative state but 1 patient regained consciousness and normal cognitive function with accompanying recovery of bilateral N20 responses at both 9 days and 18 months after resuscitation.[52]

Biochemical Markers

Three biochemical markers have been evaluated for predicting awakening: cerebrospinal fluid (CSF) creatine kinase BB isoenzyme (CKBB) activity, serum and CSF neuron-specific enolase (NSE), and serum S-100b. All of these biomarkers act as indicators of cerebral injury and avoid many of the issues of interpretation and interrater reliability inherent in other prognostic variables. The AAN practice parameters found strong evidence that NSE >33 μg/L at 1 to 3 days following resuscitation could accurately predict poor outcome but found insufficient evidence for utilization of CKBB or S100b.[3]

The brain is rich in CKBB, which leaks from the cytoplasm of neurons into the extracellular fluid after brain injury. The levels of CKBB peak at 48 to72 hours after CA. In one retrospective study of 351 comatose patients following CA, CSF CKBB sampled between 48 and 72 hours was strongly associated with neurologic prognosis, with a high specificity for never awakening or never achieving independence following awakening (using different cutoffs).[53]

Neuron-specific enolase, a glycolytic enzyme predominantly found in neurons, is produced in both the central and the peripheral nervous system. Serum NSE is the only

biochemical marker that has been extensively studied in the era of TH.[3] In the prospective PROPAC study where physicians were blinded to biochemical marker results, NSE was tested in 231 comatose patients at multiple time points following CA, and levels greater than 33 μg/L at any time were uniformly associated with a poor neurologic outcome (0% FPR, sensitivity 60%).[26] In another prospective study of 111 comatose survivors of CA treated with TH, all 17 patients with NSE levels greater than 33 μg/L at 48 hours failed to recover consciousness, and this cutoff was associated with other markers of brain injury, including abnormalities on brain magnetic resonance imaging (MRI) and absent responses on SSEPs. Other studies, however, assessing the NSE cutoff value in the setting of TH have noted exceptions. In a prospective study of patients with CA treated with TH in which 12 of the 31 patients survived to hospital discharge, NSE levels > 33 μg/L measured between days 1 to 3 were associated with a poor outcome but with an FPR of 29.3%.[51] Similarly, in a prospective study of CA survivors, serum NSE levels >33 μg/L obtained less than 72 hours after the arrest were found to accurately predict poor outcome in those not treated with TH but found to have an unacceptably high FPR of 22% among patients treated with TH. The highest reported NSE in a patient with good outcome in this study was 85 μg/L. One study of patients treated with TH following cardiopulmonary arrest reported a cutoff of 43 μg/L to obtain a 0% FPR,[54] whereas another reported an NSE cutoff level of 78.9 μg/L to achieve an FPR of 0%.[55] Therefore, the AAN practice parameter's NSE cutoff level of 33 μg/L 1 to 3 days after resuscitation appears to be of limited utility in the setting of TH.

S100b, an astroglial and Schwann cell protein, is elevated in brain injury, and tests for the protein are commercially available. The PROPAC study found that the levels of S100b >0.7 μg/L were associated with a 0% FPR (sensitivity 35%) at 72 hours but a higher FPR at 24 and 48 hours, making this test more time dependent than NSE.[26] In a prospective study of patients treated with TH, levels of S100b were elevated among those that remained unconscious compared to those who regained consciousness and a cutoff level of ≥0.5 μg/L was necessary to have a 0% FPR on day 3 (sensitivity 75%).[54]

Neuroimaging

The use of neuroimaging in CA prognostication remains an area of active and promising research, though currently it has not yet been validated as a reliable tool for accurate predictions of neurologic outcome. Most patients who remain comatose after resuscitation from CA undergo a head computed tomography (CT) and sometimes a brain MRI. Certain imaging findings, such as diffuse cerebral edema or loss of gray–white differentiation, are presumed to portend a worse neurologic outcome. An evaluation of CT scans obtained within 72 hours of CA found that a decrease in whole brain or putamen Hounsfield units correlated with worse outcome.[56] The authors reported that the combination of a decrease in whole brain Hounsfield units with the clinical data of day 3 Glasgow coma scale was 100% specific for a poor outcome (modified Rankin scale of <4) with 73% sensitivity.[56] In a study of 25 comatose patients following CA for whom a CT scan was obtained within 48 hours, a difference in the gray matter to white matter ratio of <1.18 Hounsfield units at the level of the basal ganglia was predictive of death (0% FPR in 12 patients but with a wide confidence interval of 0%-22%).[57] Also, similar studies have had a low interrater reliability.[58]

Brain MRI is frequently unremarkable despite other abnormal prognostic variables. One study has suggested that widespread early and persistent MRI changes are predictive of a poor outcome.[59] A small study found that no patient with extensive cortical abnormalities obtained a neurologic outcome better than vegetative state.[60] In this study, the most frequently affected areas were the occipital, parietal, and frontal lobes though many different patterns of injury were observed.[60] One study of the quantitative diffusion-weighted imaging (DWI) analysis found that the ideal time window for obtaining brain MRI for prognostication following CA was between 49 and 108 hours, the period when DWI abnormalities were most prominent.[61] Another group similarly reported that early MRI had fewer apparent diffusion coefficient (ADC) changes than those imaging done between 24 and 96 hours.[62] In this study, 61% of the patients were treated with TH, but all brain MRI studies were completed when patients were normothermic. Patients who had more than 10% of brain volume with an ADC value less than the threshold value of 650×10^{-6} to 700×10^{-6} mm^2/s had a poor outcome with 81% sensitivity and 0% FPR.[61] There were, however, wide confidence intervals in the FPR, suggesting that more studies are needed for brain MRI to be considered a reliable prognostic tool.

In a study where independent, blinded investigators evaluated brain MRI studies of patients with CA, differences in DWI data of individual brain structures were noted between good and poor outcome patients. Specifically, investigators found that good outcome patients more often demonstrated increased DWI involving the temporal and occipital lobes, corona radiata, and hippocampus, whereas poor outcome patients more often demonstrated DWI restriction in cortical structures, the occipital and temporal lobes, and the putamen.[63] Another small study of 80 consecutive patients with CA, however, found a 100% specificity for poor prognosis (modified Rankin Scale greater than 4) among the 18 patients with bilateral hippocampal hyperintensities on DWI imaging.[64]

Diffusion and perfusion MRI has also been examined in a small study of 20 comatose CA survivors. Similar to the other previously discussed studies, this study found that most patients with larger amounts of diffusion changes on MRI did not survive (16 of 20).[65] Of the 8 patients that underwent perfusion imaging, all 4 of the patients who died showed

markedly increased perfusion. The hyperperfusion may represent reactive hyperemia that has been associated with diffusion restriction or, alternatively, may be an independent measurement that could be used for prognostication.[65] Further research is needed before any conclusions can be drawn from the study, and the role of diffusion and perfusion MRI in the setting of TH remains unclear.

Multimodal Approach

One of the roles of the neurohospitalist may be to eschew uninformed prognostication while also helping families with substituted decision making. Some have argued that at least 2 predictors of poor neurologic outcome are needed before concluding that the prognosis is poor for recovery of conscious awareness.[38,66] In a Swiss study with a prospective arm of 74 patients, the 3 patients with status epilepticus who regained consciousness all had preserved brain stem responses, reactive background EEG, and preserved cortical SSEPs. The authors concluded that the combination of these 3 findings, which occurred in a minority of patients with postanoxic status epilepticus, were strongly associated with neurologic recovery. However, one potential limitation of the study was the concern for a self-fulfilling prophecy, as a decision to withdraw supportive care was made by the research team in patients with bilaterally absent cortical SSEPs and brain stem reflexes or persistent status epilepticus for more than 1 day despite antiepileptic treatment.

In another study by the same group, comatose survivors of CA were evaluated while off sedation immediately after TH by neurologic examination, EEG, and SSEPs. With neurologic recovery assessed at 3 and 6 months, the authors found an FPR of 4% in patients with incomplete brain stem response though an FPR of 0% when the examination finding was in combination with 1 of 3 other negative predictors (early myoclonus, unreactive EEG, or absent cortical SSEPs).[27] The confounding effects of sedative medications on the findings of neurologic examination, especially the evaluation of brain stem reflexes and motor response, have also been reported.[7] Others have found improved sensitivity of poor outcome by combining the use of NSE and S100B levels.[54]

Discussion

With the increasing rates of early defibrillation, out-of-hospital CPR, and expanding use of TH, prognosis after CA has become an increasingly common consult for neurologists. Oftentimes, the discussion about what the patient might consider an acceptable quality of life is uncertain even to the patient's representative, as such conversations have not occurred prior to the CA. The ancillary prognostic tests are limited with high specificity for not only awakening but also providing information about quality of life or recovery of independent function. Further complicating this picture in the era of TH is the increasing number of false positives reported among the findings of prognostic tests and neurologic examination. In our opinion, prognostication and decision making after CA should be delayed until multiple ancillary tests, including brain MRI, SSEPs, EEG, or any biochemical markers, can be obtained and when the neurologic examination can be performed with patients off from all sedative medications for a reasonable amount of time. Given the limitations of each prognostic test, a multimodal approach is needed to avoid any falsely negative predictions. For this reason, at our institution, we typically recommend continued life-sustaining treatment for a minimum of 3 days in order to best ensure accurate predictions. In patients treated with TH, we recommend a longer time period, typically 2 to 3 days after achieving normothermia and after cessation of all sedative medications, before presenting family or legal decision makers with the results of all prognostic testing. Further, providers should avoid overly pessimistic prognostication in the absence of multiple negative prognostic factors and should advise patient representatives of the limitations in prognostic tests. In cases where the multiple prognostic tests do not uniformly suggest a poor outcome and there remains uncertainty regarding outcome, we consider employing an approach described with severe stroke in which the provider uses ''time-limited trials,'' where a period of time is recommended to achieve consensus about goals of care and allow families to cope with difficult decision making.[67] We feel that such a balanced approach may avoid the pitfalls of a self-fulfilling prophecy, where 1 test is used to establish the basis of withdrawal of life support. Above all, the neurologist should make all efforts to provide an insightful and honest prognosis to patient representatives who are facing difficult decisions about continuation of life-sustaining treatments.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

References

1. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics–2013 update: a report from the American heart association. *Circulation*. 2013;127(1):e6-e245.
2. Holzer M. Targeted temperature management for comatose survivors of cardiac arrest. *N Engl J Med*. 2010;363(13):1256-1264.
3. Wijdicks EFM, Hijdra A, Young GB, Bassetti CL, Wiebe S. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the quality standards subcommittee of the American academy of neurology. *Neurology*. 2006;67(2):203-210.

4. Becker KJ, Baxter AB, Cohen WA, et al. Withdrawal of support in intracerebral hemorrhage may lead to self-fulfilling prophecies. *Neurology*. 2001;56(6):766-772.
5. Longstreth WT, Inui TS, Cobb LA, Copass MK. Neurologic recovery after out-of-hospital cardiac arrest. *Ann Intern Med*. 1983;98(1):588-592.
6. Fugate JE, Wijdicks EFM, White RD, Rabinstein AA. Does therapeutic hypothermia affect time to awakening in cardiac arrest survivors? *Neurology*. 2011;77(14):1346-1350.
7. Samaniego EA, Mlynash M, Caulfield AF, Eyngorn I, Wijman AC. Sedation confounds outcome prediction in cardiac arrest survivors treated with hypothermia. *Neurocrit Care*. 2011; 15(1):113-119.
8. Polderman KH. Mechanisms of action, physiological effects, and complications of hypothermia. *Crit Care Med*. 2009;37(7 suppl):S186-S202.
9. Varon J, Acosta P. Therapeutic hypothermia: past, present, and future. *Chest*. 2008;133(5):1267-1274.
10. Polderman KH. Induced hypothermia for neuroprotection: understanding the underlying mechanisms. In: Vincent J-L, ed. *Yearbook of Intensive Care and Emergency Medicine*. Berlin Heidelberg: Springer ; 2006:328-346.
11. Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurological injuries. *Lancet*. 2008; 371(9628):1955-1969.
12. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. 2002;346(8):549-556.
13. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002;346(8):557-563.
14. Don CW, Longstreth WT, Maynard C, et al. Active surface cooling protocol to induce mild therapeutic hypothermia after out-of-hospital cardiac arrest: a retrospective before-and-after comparison in a single hospital. *Crit Care Med*. 2009;37(12):3062-3069.
15. Bernard SA, Smith K, Cameron P, et al. Induction of prehospital therapeutic hypothermia after resuscitation from nonventricular fibrillation cardiac arrest. *Crit Care Med*. 2012;40(3):747-753.
16. Lopez-de-Sa E, Rey JR, Armada E, et al. Hypothermia in comatose survivors from out-of-hospital cardiac arrest: pilot trial comparing 2 levels of target temperature. *Circulation*. 2012; 126(24):2826-2833.
17. The Italian Cooling Experience (ICE) Study Group. Early- versus late-initiation of therapeutic hypothermia after cardiac arrest: preliminary observations from the experience of 17 Italian intensive care units. *Resuscitation*. 2012;83(7):823-828.
18. Finley Caulfield A, Rachabattula S, Eyngorn I, et al. A comparison of cooling techniques to treat cardiac arrest patients with hypothermia. *Stroke Res Treat*. 2011;2011:690506.
19. Scirica BM. Therapeutic hypothermia after cardiac arrest. *Circulation*. 2013;127(2):244-250.
20. Tortorici MA, Kochanek PM, Poloyac SM. Effects of hypothermia on drug disposition, metabolism, and response: a focus of hypothermia-mediated alterations on the cytochrome P450 enzyme system. *Crit Care Med*. 2007;35(9):2196-2204.
21. Van den Broek MPH, Groenendaal F, Egberts ACG, Rademaker CM a. Effects of hypothermia on pharmacokinetics and pharmacodynamics: a systematic review of preclinical and clinical studies. *Clin Pharmacokinet*. 2010;49(5):277-294.
22. Fritz HG, Holzmayr M, Walter B, Moeritz K-U, Lupp A, Bauer R. The effect of mild hypothermia on plasma fentanyl concentration and biotransformation in juvenile pigs. *Anesth Analg*. 2005; 100(4):996-1002.
23. Leslie K, Sessler DI, Bjorksten AR, Moayeri A. Mild hypothermia alters propofol pharmacokinetics and increases the duration of action of atracurium. *Anesth Analg*. 1995;80(5):1007-1014.
24. Levy DE, Caronna JJ, Singer BH, Lapinski HF. Predicting outcome from hypoxic-ischemic coma. *J Am Med Assoc*. 1985; 253(10):1420-1426.
25. Booth CM, Boone RH, Tomlinson G, Detsky AS. Is this patient dead, vegetative, or severely neurologically impaired? assessing outcome for comatose survivors of cardiac arrest. *J Am Med Assoc*. 2004;291(7):870-879.
26. Zandbergen EGJ, Hijdra A, Koelman JHTM, et al. Prediction of poor outcome within the first 3 days of postanoxic coma. *Neurology*. 2006;66(1):62-68.
27. Rossetti AO, Oddo M, Logroscino G, Kaplan PW. Prognostication after cardiac arrest and hypothermia: a prospective study. *Ann Neurol*. 2010;67(3):301-307.
28. Al Thenayan E, Savard M, Sharpe M, Norton L, Young B. Predictors of poor neurologic outcome after induced mild hypothermia following cardiac arrest. *Neurology*. 2008;71(19): 1535-1537.
29. Agarwal P, Frucht SJ. Myoclonus. *Curr Opin Neurol*. 2003; 16(4):515-521.
30. Swanson PD, Luttrell CN, Magladery JW. Myoclonus – a report of 67 cases and review of the literature. *Medicine*. 1962;41: 339-356.
31. Lance J, Adams R. The syndrome of inattention or action myoclonus as a sequel to hypoxic encephalopathy. *Brain*. 1963;86: 111-136.
32. Khot S, Tirschwell DL. Long-term neurological complications after hypoxic-ischemic encephalopathy. *Semin Neurol*. 2006; 26(4):422-431.
33. Hallett M. Human posthypoxic myoclonus. *Mov Disord*. 2000; 15(suppl 1):8-13.
34. Mani R, Schmitt SE, Mazer M, Putt ME, Gaieski DF. The frequency and timing of epileptiform activity on continuous electroencephalogram in comatose post-cardiac arrest syndrome patients treated with therapeutic hypothermia. *Resuscitation*. 2012;83(7):840-847.
35. Lucas JM, Cocchi MN, Salciccioli J, et al. Neurologic recovery after therapeutic hypothermia in patients with post-cardiac arrest myoclonus. *Resuscitation*. 2012;83(2):265-269.
36. Wijdicks EF, Parisi JE, Sharbrough FW. Prognostic value of myoclonus status in comatose survivors of cardiac arrest. *Ann Neurol*. 1994;35(2):239-243.
37. Krumholz A, Stern BJ, Weiss HD. Outcome from coma after cardiopulmonary resuscitation: relation to seizures and myoclonus. *Neurology*. 1988;38(3):401-405.

38. Rossetti AO, Oddo M, Liaudet L, Kaplan PW. Predictors of awakening from postanoxic status epilepticus after therapeutic hypothermia. *Neurology*. 2009;72(8):744-749.
39. Rittenberger JC, Brenner RP, Guyette FX, Callaway CW. Frequency and timing of nonconvulsive status epilepticus in comatose post-cardiac arrest subjects treated with hypothermia. *Neurocrit Care*. 2013;16(1):114-122.
40. Miller JW, Henry JC. Solving the dilemma of EEG misinterpretation. *Neurology*. 2013;80(1):13-14.
41. Ronner HE, Ponten SC, Stam CJ, Uitdehaag BMJ. Inter-observer variability of the EEG diagnosis of seizures in comatose patients. *Seizure*. 2009;18(4):257-263.
42. Scollo-Lavizzari G, Bassetti C. Prognostic value of EEG in postanoxic coma after cardiac arrest. *Eur Neurol*. 1987;26(3):161-170.
43. Crepeau AZ, Rabinstein A a, Fugate JE, et al. Continuous EEG in therapeutic hypothermia after cardiac arrest: prognostic and clinical value. *Neurology*. 2013;80(4):339-344.
44. Hockaday JM, Potts F, Epstein E, Bonazzi A, Schwab RS. Electroencephalographic changes in acute cerebral anoxia from cardiac or respiratory arrest. *Electroencephalogr Clin Neurophysiol*. 1965;18(1962):575-586.
45. Synek V. Value of a revised EEG coma scale for prognosis after cerebral anoxia and diffuse head injury. *Clin Electroencephalogr*. 1990;21(1):25-30.
46. Chen R, Bolton CF, Young BG. Prediction of outcome in patients with anoxic coma: a clinical and electrophysiologic study. *Crit Care Med*. 1996;24(4):672-678.
47. Rossetti a O, Logroscino G, Liaudet L, et al. Status epilepticus: an independent outcome predictor after cerebral anoxia. *Neurology*. 2007;69(3):255-260.
48. Geocadin RG, Ritzl EK. Seizures and status epilepticus in post cardiac arrest syndrome: therapeutic opportunities to improve outcome or basis to withhold life sustaining therapies? *Resuscitation*. 2012;83(7):791-792.
49. Bender A, Howell K, Frey M, Berlis A, Naumann M, Buheitel G. Bilateral loss of cortical SSEP responses is compatible with good outcome after cardiac arrest. *J Neurol*. 2012;259(11):2481-2483.
50. Bouwes A, Binnekade JM, Zandstra DF, et al. Somatosensory evoked potentials during mild hypothermia after cardiopulmonary resuscitation. *Neurology*. 2009;73(18):1457-1461.
51. Fugate JE, Wijdicks EFM, Mandrekar J, et al. Predictors of neurologic outcome in hypothermia after cardiac arrest. *Ann Neurol*. 2010;68(6):907-914.
52. Leithner C, Ploner CJ, Hasper D, Storm C. Does hypothermia influence the predictive value of bilateral absent N20 after cardiac arrest? *Neurology*. 2010;74(12):965-969.
53. Tirschwell DL, Longstreth WT, Rauch-Matthews ME, et al. Cerebrospinal fluid creatine kinase BB isoenzyme activity and neurologic prognosis after cardiac arrest. *Neurology*. 1997;48(2):352-357.
54. Zingler VC, Krumm B, Bertsch T, Fassbender K, Pohlmann-Eden B. Early prediction of neurological outcome after cardiopulmonary resuscitation: a multimodal approach combining neurobiochemical and electrophysiological investigations may provide high prognostic certainty in patients after cardiac arrest. *Eur Neurol*. 2003;49(2):79-84.
55. Steffen IG, Hasper D, Ploner CJ, et al. Mild therapeutic hypothermia alters neuron specific enolase as an outcome predictor after resuscitation: 97 prospective hypothermia patients compared to 133 historical non-hypothermia patients. *Crit Care (London, England)*. 2010;14(2):R69.
56. Wu O, Batista LM, Lima FO, Vangel MG, Furie KL, Greer DM. Predicting clinical outcome in comatose cardiac arrest patients using early noncontrast computed tomography. *Stroke*. 2011;42(4):985-992.
57. Torbey MT, Selim M, Knorr J, Bigelow C, Recht L. Quantitative analysis of the loss of distinction between gray and white matter in comatose patients after cardiac arrest. *Stroke*. 2000;31(9):2163-2167.
58. Torbey MT, Bhardwaj A. MR imaging in comatose survivors of cardiac resuscitation. *Am J Neuroradiol*. 2002;23(4):738.
59. Greer D, Scripko P, Bartscher J, et al. Serial MRI changes in comatose cardiac arrest patients. *Neurocrit Care*. 2011;14(1):61-67.
60. Topcuoglu MA, Oguz KK, Buyukserbetci G, Bulut E. Prognostic value of magnetic resonance imaging in post-resuscitation encephalopathy. *Intern Med*. 2009;48(18):1635-1645.
61. Wijman C a C, Mlynash M, Caulfield AF, et al. Prognostic value of brain diffusion-weighted imaging after cardiac arrest. *Ann Neurol*. 2009;65(4):394-402.
62. Heradstveit BE, Larsson E-M, Skeidsvoll H, et al. Repeated magnetic resonance imaging and cerebral performance after cardiac arrest–a pilot study. *Resuscitation*. 2011;82(5):549-555.
63. Mlynash M, Campbell DM, Leproust EM, et al. Temporal and spatial profile of brain diffusion-weighted MRI after cardiac arrest. *Stroke*. 2010;41(8):1665-1672.
64. Greer DM, Scripko PD, Wu O, et al. Hippocampal magnetic resonance imaging abnormalities in cardiac arrest are associated with poor outcome [published online September 17, 2012]. *J Stroke Cerebrovasc Dis*. 2012.
65. Järnum H, Knutsson L, Rundgren M, et al. Diffusion and perfusion MRI of the brain in comatose patients treated with mild hypothermia after cardiac arrest: a prospective observational study. *Resuscitation*. 2009;80(4):425-430.
66. Benson C. Comment: EEG monitoring after cardiac arrest — the cold facts. *Neurology*. 2013;80(4):339-344.
67. Holloway RG, Benesch CG, Burgin WS, Zentner JB. Prognosis and decision making in severe stroke. *J Am Med Assoc*. 2005;294(6):725-733.