Neurologic Prognosis in Cardiac Arrest Patients Treated With Therapeutic Hypothermia

Nicholas A. Blondin, MD and David M. Greer, MD, MA, FCCP

Background: Therapeutic hypothermia is now commonly used to improve neurologic outcomes in eligible patients after cardiac arrest. The physiologic effects of cooling and pharmacologic effects of sedatives and neuromuscular blocking agents can affect the clinical exam and neurophysiologic findings. This can lead to uncertainty in neurologic prognostication. In this article, we review data on assessing prognosis in patients treated with therapeutic hypothermia.

Review Summary: Features of the clinical examination, neurophysiologic testing (including somatosensory-evoked potentials and electroencephalography), serum/cerebrospinal fluid biomarkers and neuroimaging can be used to help predict prognosis. However, no single test can predict poor prognosis with absolute certainty. Given the features that help to predict poor, indeterminate, or good outcome, we provide practical advice in assessing neurologic prognosis after cardiac arrest in patients treated with therapeutic hypothermia.

Conclusions: The American Academy of Neurology practice parameters for assessing prognosis after cardiac arrest may not be accurate for patients treated with therapeutic hypothermia. Application of these guidelines may lead to overly pessimistic prognostication and premature withdrawal of care. If uncertainty exists regarding the prognosis in a given patient after cardiac arrest, additional time should be allowed to pass, as patients may ultimately recover with good neurologic outcome.

Key Words: hypothermia, prognosis, cardiac arrest

Within the past decade, therapeutic hypothermia has emerged as the standard of care for eligible patients resuscitated after cardiac arrest.[1] Therapeutic hypothermia has been found to decrease morbidity and mortality, and has led to improved neurologic outcomes.[2–5] However, hypothermia has also introduced new challenges to the prediction of outcome in survivors of cardiac arrest. This review will examine new evidence for assessing neurologic prognosis in patients treated with therapeutic hypothermia.

In a standard therapeutic hypothermia protocol, patients undergo cooling for 24 hours to a target temperature of 33°C (range, 32°C-34°C) using either surface-based or catheter-based cooling methods. During the cooling period, patients are sedated, typically with benzodiazepines, opioids, propofol, or a combination of these agents. Neuromuscular blockade to prevent shivering is also frequently given with a nondepolarizing neuromuscular blocking agent such as vecuronium.

After 24 hours from the time of induction of hypothermia, controlled rewarming takes place over the next 8 to 12 hours. Paralytic agents, followed by sedatives and analgesics, are tapered off after the patient is rewarmed. After rewarming, efforts are made to minimize sedation, which is then typically used for purposes of patient comfort. However, some patients are maintained on anticonvulsant medications owing to concerns for, or evidence of, seizures.

The sedation and neuromuscular blockade used during hypothermia result in pharmacologic effects that can make the clinical examination unreliable. Although these medications may be weaned by 48 hours after cardiac arrest, sedatives are commonly used up to 72 hours and beyond.[6] The pharmacokinetic and pharmacodynamic properties of sedatives, analgesics, and neuromuscular blocking agents are altered during hypothermia. Hypothermia can also decrease hepatic and renal drug clearance.[7–9] Significant increases in serum midazolam, fentanyl, and propofol concentrations may occur during hypothermia.[8,10,11]

Owing to the persistent presence and effects of sedatives and paralytic agents, as well as the physiologic effects of hypothermia, caution needs to be exercised when attempting to interpret the clinical examination and neurophysiologic findings. Abnormalities in the pupillary light response, other brainstem reflexes, and the motor aspects of the neurologic examination may be significant. The results of electrophysiologic tests, such as electroencephalography (EEG) and somatosensory-evoked potentials (SSEPS), can also be affected by drugs and systemic metabolic derangements.

Neurologists are often asked to assess prognosis and predict functional outcome. A commonly used outcome measure is the Glasgow-Pittsburgh Cerebral Performance Categories (CPC) scale.[12,13] A CPC of 1 indicates full recovery, CPC 2 indicates moderate disability, and CPC 3 indicates severe neurologic disability but preserved consciousness. Patients with CPC 4 are comatose or in a persistent vegetative state, and those with CPC 5 have died. In this review, a "good outcome" reflects a CPC of 1 or 2 and a "poor outcome" reflects a CPC of 4 or 5, where a patient never regains consciousness. Whether to assign a CPC score of 3 as good outcome or poor outcome is controversial; a severe disability may not be considered a poor outcome in the setting of a patient who has been in coma from cardiac arrest, as some would wish to survive even with significant neurologic disabilities but with preservation of consciousness.

The current American Academy of Neurology (AAN) practice parameters do not take the potential influence of induced therapeutic hypothermia into consideration.[14] Recently, the American Heart Association (AHA) acknowledged that traditional data used to determine a poor neurologic prognosis are less reliable in patients treated with therapeutic

hypothermia.[14] As hypothermia is now in widespread practice, new guidelines will be needed to address the influence of therapeutic hypothermia in the accurate assessment of neurologic prognosis after cardiac arrest.

This review focuses on assessment of prognosis in patients treated with hypothermia using evidence from recently published reports and studies. Most studies are small, as no Class I evidence exists for predicting poor prognosis in this patient population. Below, the predictive ability of the clinical examination, SSEPs, EEG, myoclonic status epilepticus (MSE), biomarkers, and imaging are discussed based on the currently available data.

CLINICAL EXAMINATION

Key components of the standard clinical neurologic examination, including the pupillary light response, corneal reflexes, and motor response to painful stimuli are typically performed in a serial manner on patients resuscitated after a cardiac arrest. The current AAN practice parameters state that at 72 hours after cardiac arrest, absent pupillary responses, absent corneal reflexes, or absent motor responses or extensor posturing predict poor prognosis with a high degree of certainty in patients not treated with hypothermia.[15] It should be noted that on motor testing, no movement or extensor posturing to noxious stimulation is regarded as a poor motor response, while flexor posturing or better may be associated with a good outcome.

Available data on patients treated with hypothermia suggest that the clinical examination in this population may have decreased accuracy in predicting poor prognosis. In a study of 37 patients, 2 out of 14 patients with poor motor responses 72 hours after cardiac arrest regained consciousness, and both had poor motor responses until day 6.[16] However, upper cranial nerve function retained predictive value, as none of the 6 patients with absent pupillary reactivity or absent corneal reflexes at 72 hours regained consciousness.

In a study of 44 patients, no patients with an absent pupillary light response at 72 hours regained consciousness.[6] However, 1 patient with absent corneal reflexes and 2 patients with poor motor responses at 72 hours did regain consciousness. In another study of 45 patients, 2 patients with an absent pupillary response or absent corneal reflexes between 36 and 72 hours after cardiac arrest ultimately regained consciousness and achieved a good outcome.[17] Eleven of the patients in this study had a poor motor response at 72 hours and survived, and 4 patients achieved a good outcome.

Overall, evidence suggests that an absent motor response at 72 hours post-arrest does not reliably predict poor prognosis in patients who have undergone therapeutic hypothermia. However, the presence of a motor response may suggest a good outcome. In a study of 72 patients, the presence of a motor response within 24 hours after the discontinuation of sedation predicted a good outcome with 100% specificity.[18] In summary, the absence of brainstem reflexes at 72 hours strongly suggests a poor prognosis, but cannot be used with absolute certainty. Future studies should be performed to confirm the absolute prognostic ability of the pupillary light response and corneal reflex examination in patients who have undergone therapeutic hypothermia.

SSEP

SSEPs are commonly used to assess prognosis after cardiac arrest, and the current AAN practice parameters state that the bilateral absence of the N20 response between 24 and 72 hours after cardiac arrest can accurately predict poor prognosis in patients who have not undergone hypothermia.[15,19] Additional studies in normothermic patients with SSEPs performed from 4 to 24 hours after cardiac arrest found that an absent N20 response invariably predicted poor prognosis.[20,21] However, reports do exist of patients who initially have absent N20 responses who proceed to recover these responses, as well as achieve a good recovery.[22]

The cortical N20 response is measured after electrical stimulation of the median nerve. Hypothermia affects the N20 response, as conduction velocity in the median nerve decreases by 2 m/s for every 1°C decrease, resulting in an increased N20 latency.[23,24] Below body temperatures of 30°C, the cortical N20 response disappears.[25,26] However, at temperatures of 32°C to 34°C, the N20 latency may be prolonged but should remain present.[25,27] Thus, the N20 response should be a reliable finding at body temperatures of 32°C to 34°C.

The role of SSEP for prognostication in patients undergoing hypothermia has recently been examined. An earlier study of 3 patients with bilaterally absent N20 responses 24 to 48 hours after cardiac arrest found that none of the patients regained consciousness.[28] Another study of 77 patients identified 13 patients with bilaterally absent N20 responses during hypothermia, and none regained consciousness.[29] In another study of 14 patients with an absent N20 response more than 72 hours after cardiac arrest, none regained consciousness.[6] A study of 100 patients in whom the N20 response was assessed at least 24 hours after the completion of rewarming and the discontinuation of sedation found that no patients with bilaterally absent N20 responses survived.[17]

However, the bilateral absence of an N20 response does not appear to invariably predict poor prognosis. In a study of 185 patients, 36 patients had bilaterally absent N20 responses at 72 hours, but 1 patient did survive and ultimately achieve a good recovery.[30] Another patient had severe bilateral reductions of N20 amplitudes, but also survived and achieved normal cognitive functioning. In both patients, the SSEP was performed 2 days after the institution of rewarming. The available data suggest that an absent N20 response after rewarming or even during hypothermia likely predicts poor prognosis, but owing to this isolated case of recovery, a bilaterally absent N20 response at 72 hours may not predict poor prognosis with absolute certainty.

EEG

EEG has been used for decades to assess neurologic prognosis. Various classification systems and time intervals of recording after resuscitation have confounded the utility of EEG to accurately predict prognosis. The common background EEG patterns observed after cardiac arrest (Fig. 1) include extremely low voltage (flat; maximum voltage <5 μV), continuous, discontinuous suppression-burst (SB) pattern, or electrographic status epilepticus (ESE) with recurrent epileptiform activity.

In the target temperature range of 32°C to 34°C during hypothermia, the EEG should not be significantly affected.[31] However, extremely low-voltage EEGs are not uncommon during hypothermia. This may be secondary to the pharmacologic effects of the benzodiazepines, opioids, and propofol used for sedation, or owing to a decrease in the cerebral metabolic rate and in electrical activity overall. Hypothermia has been found to be independently protective against seizures.[32]

The most recent AHA guidelines recommend a "spot" EEG as early as possible, or continuous EEG monitoring for
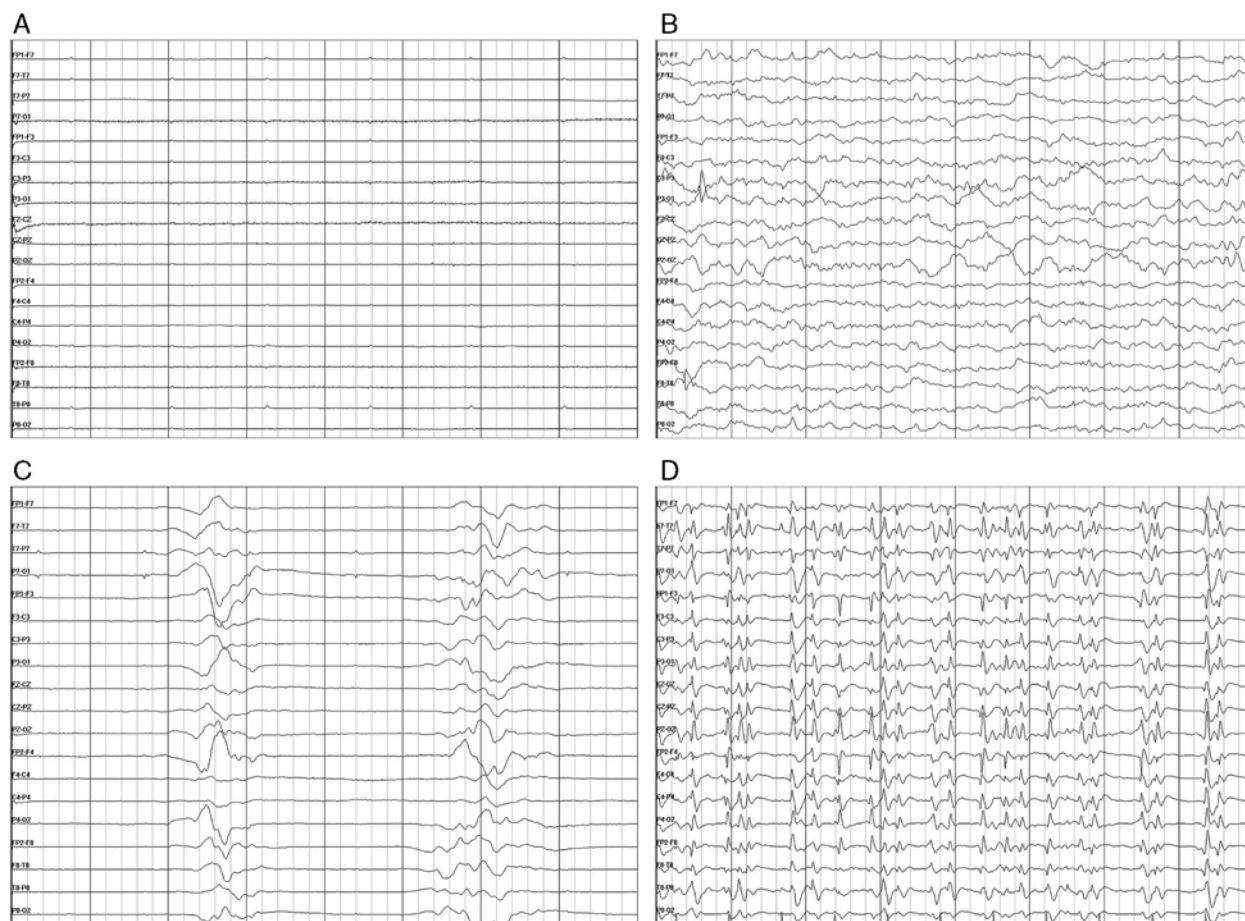
FIGURE 1. Common EEG patterns. The common EEG patterns observed after cardiac arrest include extremely low voltage (A), continuous (B), discontinuous suppression-burst pattern (C), or electrographic status epilepticus with recurrent epileptiform activity (D). EEGs are being displayed at a speed of 30 mm/s and amplitude of 70 to 100 μV. EEG indicates electroencephalography.

patients treated with therapeutic hypothermia.[14] An EEG is essential, as neuromuscular blockade will mask clinical seizures. In a study of 51 patients undergoing hypothermia, EEG detected ESE with epileptiform activity persisting for greater than 30 minutes in 5 patients, and none of these patients ultimately regained consciousness.[33] However, it should be noted

that a standard treatment of ESE was not performed in these patients, introducing the possibility of inadequate treatment.

Several studies have examined the utility of EEG for assessing prognosis in patients treated with hypothermia. Continuous amplitude integrated EEG (aEEG) is a technique that can be used to classify ongoing EEG patterns, as patterns
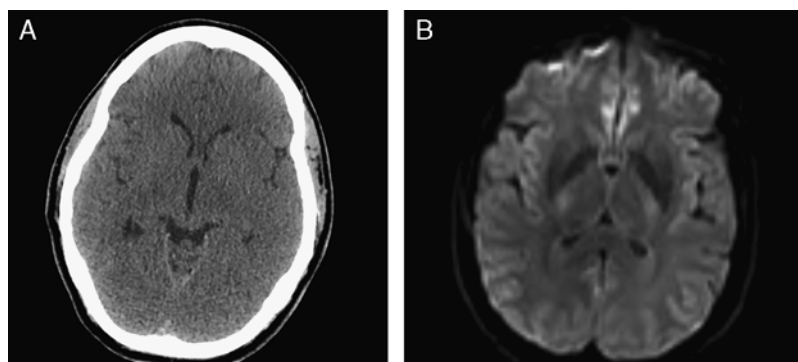
FIGURE 2. Imaging characteristics of anoxic injury. A, Noncontrast head CT showing diffuse cerebral edema, sulcal effacement, and loss of gray-white differentiation; (B) Diffusion-weighted imaging MRI demonstrating hyperintensity in the gray matter, particularly in the mesial frontal lobes, representing widespread restricted diffusion in the cerebral cortex. CT indicates computed tomography; MRI, magnetic resonance imaging.

can change during the course of hypothermia treatment. An initial study of aEEG was carried out on 34 patients with continuous EEG recordings during hypothermia.[34] Two patients were found to have an SB pattern and 1 patient had an alpha coma pattern, and none of these 3 regained consciousness. Seven patients developed clinical seizures, correlated with ESE during hypothermia, which was refractory to anticonvulsant therapy, and none of these patients regained consciousness. All patients with an initially continuous EEG regained consciousness, whereas the outcome was mixed in 24 patients who had an initially flat pattern; 11 evolved to a pattern other than continuous upon returning to normothermia, and none of these 11 regained consciousness.

A larger aEEG study was also undertaken on patients undergoing therapeutic hypothermia. Monitoring was initiated in 100 patients at a median of 8 hours after cardiac arrest.[35] During hypothermia, 14 patients had an initial SB pattern, and all ultimately died without regaining consciousness. An initially flat pattern during hypothermia was not predictive of prognosis, whereas a continuous pattern had a positive predictive value for regaining consciousness of 91%. Normothermia was achieved at a median of 36 hours after cardiac arrest; 7 patients had an SB pattern and 17 patients had ESE, and all 24 died during the hospitalization without regaining consciousness. All 17 patients with ESE received standard treatment with an anticonvulsant. Nine patients initially had a flat pattern, and 3 ultimately regained consciousness.

The bispectral index (BIS) is another EEG modality that has been studied for the assessment of prognosis in patients who have suffered cardiac arrest. BIS was originally developed to assess depth of anesthesia during surgery.[36] In a study of 45 patients, continuous BIS monitoring was performed for the initial 72 hours after cardiac arrest.[37] Fourteen patients had a BIS score of 0 during the first 24 hours. At 6 months, 11 of these patients had died, 1 remained in a vegetative state, and 2 had severe neurologic deficits but had regained consciousness. Thus, a BIS score of 0 does not invariably predict poor prognosis.

Despite the findings in the studies using an aEEG, ESE during hypothermia does not have a uniformly poor prognosis. In a study of 110 patients, 3 had ESE during hypothermia but ultimately recovered and achieved a good outcome after they were aggressively treated with anticonvulsants.[16] It was noted that all 3 of these patients had reactive EEG backgrounds. In this same study, 3 patients who were found to have no EEG background reactivity regained consciousness but all had severe neurologic impairment. This suggests that EEG reactivity may be helpful to assessing prognosis, and the presence of reactivity may suggest a good outcome.

EEG should be performed as soon as possible during hypothermia to assess for ESE and also identify the background pattern. An SB pattern during hypothermia quite commonly heralds a poor prognosis. ESE also indicates some likelihood of poor outcome; however, seizures should be treated aggressively as poor outcome is not certain, and no studies have examined the efficacy of aggressive anticonvulsant medication treatment in this population.

Case reports do exist of patients with ESE while undergoing hypothermia who ultimately had a good outcome after aggressive treatment of their seizures. The identification of a continuous EEG background during hypothermia may correlate with a good prognosis. Future research will need to evaluate the role of both "spot" EEG as well as continuous EEG monitoring before the optimal use of EEG to prognosticate can be determined.

MYOCLONUS

Historically, MSE has been proposed as a clinical feature strongly suggestive of poor prognosis.[38,39] MSE is a clinical entity commonly observed after cardiac arrest, and various EEG patterns may coexist such as flat, SB, and ESE.[40] MSE appears clinically as spontaneous, repetitive, unrelenting, generalized, and multifocal myoclonus involving the face, limbs, and axial musculature in the presence of coma.[14]

Several case reports exist of normothermic patients with MSE who recovered consciousness.[41–44] Myoclonus may be more commonly seen in patients who suffer a primary hypoxic event, even without a concomitant loss of perfusion, and in this setting is often associated with a good outcome.[41,45,46]

In a study of 44 patients who underwent therapeutic hypothermia, 2 patients developed MSE within 72 hours, and neither regained consciousness.[6] However, in another study of 181 patients, 3 patients who developed MSE during hypothermia regained consciousness.[47] These 3 patients had preserved pupillary and corneal reflexes, intact bilateral N20 responses, and reactive EEG backgrounds, and all were treated with benzodiazepines, anticonvulsants, and propofol. Other case reports also exist of isolated patients who developed MSE during hypothermia and later regained consciousness with good outcome.[16,48,49]

It is important to recognize that MSE may develop during weaning of neuromuscular blockade, as 23 out of 51 patients in 1 study developed MSE at a median time of 29 hours after cardiac arrest.[33] Should MSE appear, it should be evaluated aggressively with EEG, and anticonvulsants used to treat electrographic seizures, as MSE does not appear to be invariably associated with poor outcome. Furthermore, MSE likely does not have a role as a prognostic sign in patients treated with therapeutic hypothermia.

BIOMARKERS

In addition to the clinical examination and neurophysiologic tests, biochemical markers have been studied to predict prognosis. Neuron-specific enolase (NSE) is the neuronal form of the intracytoplasmic glycolytic enzyme enolase. NSE is found in neurons, and neuronal injury can be detected by the presence of increased levels of NSE in the cerebrospinal fluid or blood.[50,51] However, NSE is also found in platelets and red blood cells, and hemolysis can increase serum NSE values.[52] Several studies in normothermic cardiac arrest patients have demonstrated that high serum NSE levels are associated with poor outcome.[53–56] Current guidelines state that a serum NSE level greater than 33 μg/L between 24 and 72 hours after cardiac arrest can accurately predict poor prognosis.[14]

The usefulness of NSE levels to predict prognosis in patients undergoing therapeutic hypothermia has also been examined. NSE levels are typically attenuated in hypothermic patients compared with normothermic patients.[57,58] Serum cutoff values for NSE and the trend of NSE levels over time have been investigated. In general, treatment with hypothermia can result in rapidly decreasing levels of serum NSE, and decreasing NSE values over time have been found to be associated with recovery of consciousness, good neurologic outcome, and decreased mortality.[57] However, 1 study found that an increasing serum NSE level between 24 and 48 hours was invariably associated with a poor outcome.[57] This study found that a serum NSE level of 31.2 μg/L at 24 hours post-arrest had a 96% specificity for predicting poor outcome, and a level of 25.0 μg/L at 48 hours had a 96% specificity for predicting poor outcome.

Another study also found that a rise in serum NSE level of >2 μg/L between 24 and 48 hours, or a serum NSE level greater than 28 μg/L at 48 hours post-arrest, had a 100% specificity for predicting no better recovery than severe neurologic disability, but some patients did have recovery of consciousness.[59] Oksanen et al[60] found that an increase in the NSE level by 6.4 μg/L or more from 24 to 48 hours could accurately predict an outcome of severe neurologic disability or worse, but in their study the NSE cut-off values were higher, at 41 μg/L at 24 hours and 33 μg/L at 48 hours. A study by Steffen et al[58] found even higher cut-off values. In this study, serum NSE was measured 72 hours after cardiac arrest, and a value of 78.9 μg/L was found to have 100% specificity for predicting no better outcome than severe neurologic disability.

In patients treated with hypothermia, absolute NSE cut-off values for the prediction of neurologic prognosis appear to be unreliable. One study reported that 4 out of 42 patients with an NSE level greater than 33 μg/L regained consciousness and achieved a good outcome, with 1 patient having an NSE level of 85 μg/L.[6] The serum NSE levels can be affected by time to NSE measurement, laboratory immunoassay, hemolysis, circumstances surrounding the cardiac arrest, and probably hypothermia treatment itself. Although a rising NSE level between 24 and 48 hours may suggest poor prognosis, there does not appear to be a NSE cut-off value that can be used reliably to predict poor prognosis in patients who have undergone therapeutic hypothermia.

IMAGING

With recent advances in imaging technology, the role of neuroimaging to assess prognosis has been explored. Initial experience with neuroimaging after cardiac arrest was based on computed tomography (CT). Early CT performance can help to rule out acute neurologic injuries, such as an intracranial hemorrhage, but CT performed soon after cardiac arrest is most often normal. CT findings can later evolve to demonstrate edematous changes in brain parenchyma over the next several days, but these changes may be of limited predictive value. More recent work in normothermic patients has suggested that certain CT imaging findings, such as changes in Hounsfield units in specific brain regions, may be useful for prognosis.[61] However, in current guidelines, there continues to be inadequate data to support CT imaging as a prognostic tool.[14]

Magnetic resonance imaging (MRI) is commonly used after cardiac arrest, as it is more sensitive than CT in illustrating the degree of anoxic brain injury (Fig. 2). An early study using conventional MRI after cardiac arrest found that MRI findings were not helpful for use in prognostication.[62] However, patients underwent only T2-weighted imaging, performed within a range of 1 to 47 days after the cardiac arrest in an ultra-low-field magnet operating at 0.02 Tesla. Since the time of that study, imaging technology has changed dramatically, and diffusion-weighted imaging (DWI) MR sequences are now being used to detect structural neurologic abnormalities after cardiac arrest.

Several studies have shown that significant differences exist in DWI between ischemic infarction and anoxic injury, such as evolving regions of restricted diffusion and changing apparent diffusion coefficient (ADC) values over time.[63–67] These changes in DWI and ADC indicate that imaging within hours after cardiac arrest may not demonstrate the full extent of ischemic brain injury, and ADC depression caused by global hypoxia can be significantly delayed

compared with that caused by focal ischemia.[68–70] This may be secondary to delayed apoptosis, or a delayed CNS hypoperfusion state after resuscitation, causing secondary ischemic injury hours to days after the cardiac arrest.[71] Studies in normothermic patients have found that patients with absent or mild DWI and ADC changes typically have a good outcome.[72–75]

A small number of imaging studies have been performed on patients undergoing hypothermia. In therapeutic hypothermia, ADC values change linearly and directly with declining brain temperatures, with an approximate 1.6% change in ADC intensity for every 1°C decrease in brain temperature.[76]

In 1 study of 20 patients who underwent therapeutic hypothermia, in the 4 patients who survived none had restricted diffusion in the parietal or temporal lobes.[77] Another study of 33 patients (21 of whom underwent therapeutic hypothermia) who underwent MRI at a median of 88 hours following cardiac arrest found that patients in the good outcome group with minimal or mild DWI abnormalities had a good outcome, while those with moderate or severe abnormalities had a poor outcome.[70]

Several quantitative measures, such as mean brain ADC value and the percentage of brain parenchyma below certain ADC value thresholds, have been examined. In a study of 80 patients (14 of whom underwent therapeutic hypothermia) who underwent MRI at a median of 2 days after cardiac arrest, no patients with a median brain ADC value less than 665×10^{-6} mm^2/s had recovery better than a moderate-to-severe neurologic disability, although some did regain consciousness.[78]

In another study of 51 patients (31 of whom underwent therapeutic hypothermia) who underwent MRI at a mean of 88 hours, the finding of greater than 10% of brain volume with an ADC value less than 650×10^{-6} mm^2/s between 2 and 4.5 days after the cardiac arrest was invariably associated with a poor prognosis.[79] In this study, the ADC changes were variable over time and found to only provide prognostic information when MRI was obtained between 49 and 108 hours after cardiac arrest. This indicates that the timing of imaging must be taken into account when imaging results are used to assess prognosis.

MRI does have limitations. Imaging cannot easily be performed on patients with implanted devices, such as a pacemaker or Automated Implantable Cardioverter-Defibrillator, or other metallic objects. Historically, there has been concern about clinically unstable patients being unable to safely undergo MRI.[61,73] Most patients can now safely undergo MRI with portable ventilators, monitors and IV pumps that are MRI compatible. Unless there is an unstable cardiac rhythm or severe hemodynamic or respiratory instability, transport and acquisition of MRI can be performed safely in most cases.

The finding of a normal or near-normal MRI after cardiac arrest should lead to continued supportive care, as these patients may awaken with an ultimately good outcome. Conversely, the presence of widespread diffusion-weighted abnormalities or ADC depression may correlate with poor outcome, but MRI has not yet been validated as a predictive tool. Future prospective trials should further evaluate the role of neuroimaging in prognosis.

SUMMARY

Accurate prognostication after cardiac arrest is often challenging. Neurologists are frequently consulted to provide expertise on the chances of a meaningful recovery. Criteria for a poor outcome should have a high degree of certainty before

TABLE 1. Features Suggesting a Poor, Indeterminate, or Good Prognosis in Patients Treated With Therapeutic Hypothermia

Features that likely suggest a poor prognosis
    Absence of a pupillary light response at 72 h[6,16]
    Absence of corneal reflexes at 72 h[17]
Features that may suggest a poor prognosis
    Bilateral absence of the cortical N20 response[6,17,28,29]
    Suppression-burst EEG pattern during hypothermia[34,35]
    Rising NSE level between 24 and 48 h post-arrest[57,60]
    Significant depressions of MRI ADC values at 72 h[79]
Features that are considered indeterminate
    Absence of motor function at 72 h[16]
    Flat EEG pattern during hypothermia[34,35]
    Presence of myoclonic status epilepticus at any time[47]
    NSE level greater than 33 μg/L at 72 h[6,58]
Features that may suggest a good prognosis
    Presence of a motor response of withdrawal or better within 48 h
        post-arrest[18]
    Continuous EEG pattern without epileptiform activity during
        hypothermia[34,35]
    Absent or minimal abnormalities in ADC values at 72 h[70,77]

Features are the opinion of the authors, based on available data (cited). No features appear to be able to absolutely predict a poor prognosis, and no features have been proven to predict a good prognosis.

ADC indicates apparent diffusion coefficient; EEG, electroencephalography; MRI, magnetic resonance imaging; NSE, neuron-specific enolase.

TABLE 2. Recommendations for Prognostication

Perform EEG as early as possible
Treat electrographic seizures aggressively
Apply clinical examination findings 72 h after normothermia achieved
Perform SSEP 48 h after normothermia achieved
Assess NSE 48-72 h after normothermia achieved
Perform CT 24-48 h after normothermia achieved, if above data
    inconclusive
Perform MRI 3-5 days after normothermia achieved, if above data
    inconclusive

CT indicates computed tomography; EEG, electroencephalography; MRI, magnetic resonance imaging; NSE, neuron-specific enolase; SSEP, somatosensory-evoked potential.

being used routinely in clinical practice. With the introduction of therapeutic hypothermia, neurologic prognosis has become even more difficult. On review of published data, there does not appear to be any single criteria that can predict no recovery of consciousness with absolute certainty. Rather, providing prognosis must now rest on integrating the results of several clinical and diagnostic tests.

On the basis of review of the literature, we propose features that may suggest poor, indeterminate, or good prognosis in patients treated with therapeutic hypothermia (Table 1). These statements reflect our opinion based on the references cited in the table, as no consensus guidelines currently exist for individual parameters stated in the most recent AAN guidelines. The most recent AHA guidelines do recommend aggressive treatment and observation for at least 72 hours post-arrest in patients treated with therapeutic hypothermia before predicting poor outcome.[14]

In our opinion, for patients who undergo hypothermia, features that strongly suggest a poor prognosis include the absence of a pupillary light response or corneal reflexes at 72 hours post-arrest, the bilateral absence of the cortical N20 response, a SB EEG pattern or ESE during hypothermia, rising NSE levels between 24 and 48 hours post-arrest, and significant depressions of MRI ADC values 3 days post-arrest. Features that are now considered indeterminate in patients who undergo hypothermia include the absence of motor function on clinical examination 72 hours post-arrest, a flat EEG pattern during hypothermia, the presence of myoclonic status epilepticus at any time, and a serum NSE level greater than 33 μg/L 72 hours post-arrest. Features that may predict a good prognosis include the presence of a motor response of withdrawal or better within 48 hours post-arrest, a continuous EEG pattern without epileptiform activity during hypothermia, and absent or minimal abnormalities on DWI 3 days after cardiac arrest. However, these features were only examined in small studies, and further investigation must be undertaken before definitive conclusions are drawn.

It is important to remember that a common bias in trials of prognosis after cardiac arrest is the self-fulfilling prophecy created by early withdrawal of care. Over the next several years, larger studies should be undertaken to assess the accuracy of predictive tools specifically in the population that undergoes therapeutic hypothermia after cardiac arrest. These studies should be designed with an acceptable waiting period in cases in which the prognosis is uncertain, as delayed recovery can occur. Furthermore, given the possibility of delayed recovery, the time points at which the current prognostic tools are employed may need to be adjusted.

On the basis of the review of the literature, we suggest the following practical advice (Table 2): (1) EEG should be performed as early as possible, preferably continuously, and electrographic seizures (and particularly ESE) should be treated aggressively; (2) clinical examination findings, including pupillary, corneal, and motor responses, should be applied 72 hours after the patient has achieved normothermia; (3) SSEP should be performed at 48 hours after the patient has achieved normothermia; (4) the utility of biomarkers in this population is unclear, and NSE should be assessed 48 to 72 hours after normothermia is achieved; (5) the utility of neuroimaging in this population is unclear, and CT for prognostication should be performed 24 to 48 hours after the patient has achieved normothermia, and MRI should be performed 3 to 5 days after the patient has achieved normothermia.

Application of the current AAN guidelines to patients undergoing therapeutic hypothermia may lead to overly pessimistic prognostication and premature withdrawal of care. If uncertainty exists in the prognosis in a given patient after cardiac arrest, additional time should be allowed to pass, as clinical features may recover, neurophysiology may normalize, and neuroimaging may show injury in a delayed fashion. Overall, with continued widespread adoption of therapeutic hypothermia after cardiac arrest, more patients will survive resuscitation with good neurological outcomes, and thus one should always err on the side of caution in assessing prognosis.

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