## *Chapter 13*

# HYPOXIC-ISCHEMIC ENCEPHALOPATHY IN ADULTS

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## CLINICAL CASE

A 42 year old woman has a witnessed collapse at a gym while exercising on a treadmill. Bystanders provide basic life support (BLS) and apply an automated external defibrillator (AED) which delivers two shocks. When emergency medical services (EMS) personnel arrive, the patient remains in cardiac arrest with persistent ventricular fibrillation. After 20 minutes of advanced cardiovascular life support (ACLS) including endotracheal intubation, further defibrillation attempts and intravenous drug therapy, the patient recovers spontaneous circulation but remains unresponsive and is transported to the nearest emergency department.

In the ambulance en route to the hospital, a 12-lead electrocardiogram is consistent with an acute lateral myocardial infarction. On arrival in the hospital emergency department, the patient is noted to be unresponsive, in sinus tachycardia and hypotensive. Paramedics confirm that the patient has been pulseless for 30 minutes. In the emergency department she receives boluses of normal saline chilled to 4°C, external cooling pads are applied and the patient is given an aspirin and clopidogrel load. Labs are sent, the patient is connected to a ventilator and a chest x-ray is obtained. The patient is sent for a head CT scan en route to the cardiac catheterization lab. Head CT showed no acute pathology, and the patient goes to the catheterization lab where she is found to have a plaque rupture with complete occlusion of a coronary artery that is treated with thrombectomy and placement of a drug eluting stent.

The patient is admitted to the ICU where she completes a 24 hour course of therapeutic hypothermia at 33°C, during which she received fentanyl and propofol infusions, intermittent boluses of cisatracurium to suppress shivering as well as enteral buspirone. The patient is then actively rewarmed at 0.25°C per hour to 36.5°C and is actively maintained normothermic for the following 72 hours. During this time, the patient remains comatose despite being off all sedatives. She has non-reactive pupils, weak corneal reflexes, present cough and gag reflexes and is able to breathe spontaneously during pressure support trials. Follow up head CT on day 3 shows some loss of gray-white matter differentiation and mild sulcal effacement. A continuous electroencephalogram shows diffuse slowing with no ictal activity; N20 median nerve somatosensory evoked potentials showed mild increase in latency but are present bilaterally. Serum neuron specific enolase level was elevated at 47µg/L. After discussions with family, they opted for continued ICU care for the patient. On post arrest day 6 she was awake, following commands and was extubated two days later. The patient was eventually transferred to inpatient rehabilitation. Six months after the arrest, the patient had returned to live with her family and resume her employment as a florist, with only mild short term memory impairment.

## OVERVIEW

Hypoxic-ischemic encephalopathy (HIE) is a syndrome of acute global brain injury resulting from critical reduction or loss of blood flow and supply of oxygen and nutrients. Some of the terms used to describe this clinical syndrome include anoxic encephalopathy, post-cardiac arrest brain injury and other terms denoting a diminution of blood or oxygen to the whole brain. The most common clinical presentations include disorders of consciousness (e.g. coma or vegetative state), seizures and myoclonus. The clinical conditions leading to HIE include cardiopulmonary arrest, asphyxia, and drowning. The pathological injury to the brain results in cell injury and death from an intracellular energetic crisis that selectively affects vulnerable areas such as the CA-1 region of the hippocampus, caudate, putamen and neocortex, with relative sparing of the brainstem. High quality cardiopulmonary resuscitation with prompt restoration of spontaneous circulation is crucial to survival. The mainstay of post-resuscitation care for the global ischemic brain injury is targeted temperature management (TTM). ICU management also includes optimizing hemodynamic status, diagnosing and treating seizures and other supportive care. Prognostication of poor outcome in patients not treated with hypothermia has been defined by practice guidelines but caution is recommended in the use of prognostic parameters for those treated with hypothermia.

## EPIDEMIOLOGY

The most common cause of HIE is cardiac arrest, which is commonly secondary to cardiac etiologies such as infarction or arrhythmia. Other causes of cardiac arrest include respiratory, neurological and metabolic conditions as well as trauma, intoxication and environmental exposure. Each year over half a million cardiac arrests (CA) occur in the United States. Approximately 380,000 of these occur outside of health care facilities, and another 210,000 occur in hospitals each year [1]. Based on prospective studies from North America, Europe and Asia the incidence of cardiac arrest is estimated to be somewhere between 50-100 per 100,000 in the general population [2].

Asphyxia is classically defined as the mechanical disruption of airflow, resulting in hypoxia and hypercapnea with subsequent cardiac arrest and death. This term usually encompasses hanging, drowning, strangulation, suffocation, and choking. The incidence of asphyxia varies regionally, temporally and according to the underlying mechanism. In 2010, there were approximately 38,000 suicides in the US, which is a 16% increase over the rate per 100,000 population from the year 2000. During this time period, most of the increase in suicide was due to an increase in hanging and suffocation, which increased from 19% to 26% of all suicides [3]. Drowning is one of the leading causes of accidental death in the United States, where approximately 6000-8000 deaths occur yearly, and over 150,000 deaths occur due to drowning around the world. It is estimated that globally there are 2 million survivors of a drowning event per year [4].

## PATHOPHYSIOLOGY

The various causes of HIE share an overall common pathophysiologic mechanism where the global brain injury is a result of lack of oxygen and glucose supply. Brain injury in primary cardiac arrest results from a sudden reduction or cessation of blood flow that is followed by hypoxemia as respiratory

failure sets in. In drowning and asphyxia, the primary injury results from a reduction in oxygen levels that typically precede the decrease in blood flow leading to cardiac arrest. Hence some difference may be considered between primary cardiac versus respiratory events as the cause of the arrest.

In HIE, neuronal injury is mediated by oxygen deprivation which results in a decrease of adenosine-triphosphate (ATP) production and cellular energy starvation as well as loss of cellular integrity. This process results in uncontrolled glutamate release, which leads to injury from excitotoxicity mediated principally through NMDA receptors. As part of this cascade of cellular injury, inhibitory neurotransmitters that normally minimize glutamate excitotoxicity such as GABA and glycine, are decreased as well. NMDA mediated glutamate excitotoxicity creates an intracellular calcium influx that activates a number of second messengers that amplify cellular injury by increasing calcium permeability and increasing glutamate release. This complex chain of events from circulatory arrest to intracellular calcium overload occurs rapidly, and results in the activation of neuronal nitric oxide synthase. Oxygen free radical species are also responsible for cellular injury by direct DNA fragmentation, protein oxidation, lipid peroxidation and disruption of the mitochondrial respiratory chain. Reactive oxygen species are released by calcium mediated mitochondrial disruption and as well as during reperfusion when renewed oxygen supplies act as a substrate for enzymatic oxidative reactions. Oxidative stress leads to further inflammation and injury through complement activation and subsequent degradation, cytokine production (IL-1, IL-6, IL-8 and TNF-α), expression of leukocyte adhesion molecules, and microvascular dysfunction. Secondary brain injury is a delayed phenomenon, and is mediated by cerebral edema with resulting elevations in intracranial pressure, non-convulsive seizures and blood-brain-barrier (BBB) disruption. Cytotoxic edema is a result of excitotoxicity and ionic pump failure, as well as cellular water shift across cell membranes with impaired aquaporin function. Matrix metalloproteinases are implicated in disruption of the BBB. Oxidative DNA damage resulting from reperfusion induces both necrotic and apoptotic processes in the brain at the cellular level; examples include DNA fragmentation as well as negative intracellular signaling events such as NAD depletion, p53 activation, and intra-mitochondrial processes.

## CLINICAL FEATURES

The predominant presenting clinical features of HIE are alteration of consciousness, most commonly a comatose state, in addition to cardiovascular instability, respiratory insufficiency and loss of protective airway reflexes. The clinical features common to HIE of varying etiologies are presented in Table 13-1. A detailed discussion of the wide range of possible injuries is beyond the scope of this chapter, however a comprehensive review on this topic has been published as a consensus statement on Post-Cardiac Arrest Syndrome (PCAS) by the American Heart Association [5].

Disorders of consciousness and various degrees of neurologic disability account for the majority of complications in survivors of the HIE. The most vulnerable areas of the brain are the cortical projection neurons, the posterior cingulate cortex/precuneus, medial prefrontal cortex, and bilateral temporo-parietal junctions (collectively termed Default Mode Network)[6], the cerebellar Purkinje cells [7] and the CA-1 area of the hippocampus [8, 9]; they are also some of the those most heavily involved in consciousness and arousal. Damage to the basal ganglia and cerebellum is sometimes also present and is responsible for the movement disorders and ataxia seen occasionally following HIE [10] The brainstem appears to be somewhat more resistant to hypoxic-ischemic injury [11].

**Table 13-1.** List of Possible Clinical Features by Organ System

| | Early | Delayed |
|---|---|---|
| **Neurological** | Coma<br>Seizures and myoclonus<br>Dysautonomia | Persistent vegetative state, minimally conscious state<br>Seizure disorders<br>Movement disorders<br>Cognitive impairment<br>Post traumatic stress disorder<br>Depression<br>Dysautonomia |
| **Cardiovascular** | Arrhythmias<br>Myocardial dysfunction | Myocardial dysfunction |
| **Respiratory** | ARDS<br>Loss of respiratory drive<br>Loss of adequate airway reflexes | Chronic respiratory failure with possible need for tracheostomy and ventilator dependence |
| **Gastrointestinal** | Bowel ischemia<br>Ischemic hepatopathy ("shock liver") | If surgical intervention was necessary, may have complications: ostomies, short bowel syndrome, malabsorption, etc. |
| **Renal** | Acute kidney injury with or without acute tubular necrosis | Chronic renal failure with or without dialysis |
| **Endocrine** | Disordered glucose regulation | |

*This table does not include clinical manifestations specific to particular etiologies of hypoxic-ischemic encephalopathy such as drowning or hanging, nor does it take into consideration the effects of therapeutic hypothermia.

In patients with HIE, careful evaluation and management of systemic injuries is necessary in addition to management of neurological concerns. Post-cardiac arrest myocardial dysfunction is common, and may be due to a variety of factors, which may be primary contributors to the arrest such as myocardial infarction or a primary arrhythmia, or secondary myocardial dysfunction following ischemia and reperfusion of the heart. This dysfunction is characterized by decreased left ventricular function, which may manifest as cardiogenic shock or stress induced cardiomyopathy. Respiratory problems encountered in HIE may range from pulmonary contusions as well as costal and sternal fractures resulting from cardiopulmonary resuscitation (CPR) and can lead to hypoxia from alterations in chest wall compliance, aspiration pneumonia/pneumonitis due to loss of airway reflexes or emergent intubation, and pneumothorax. All of these may lead to respiratory failure with or without acute respiratory distress syndrome (ARDS). Intestinal ischemia can also complicate the post-resuscitation course by resulting in refractory lactic acidosis or in some cases bowel perforation. The kidneys and the liver are two other organs commonly injured in ischemia-reperfusion or low-flow states; however, little objective data exists on these entities in the setting of PCAS. Hypoxic hepatitis is sometimes seen accompanying HIE, and carries a high mortality in survivors; on the other hand acute kidney injury following cardiac ar-

rest seems to have been overestimated, particularly if cardiogenic shock is not present. Patients suffer multiple endocrine derangements including changes in anti-diuretic hormone (ADH), cortisol, ACTH, insulin, and glucagon levels as part of the post resuscitation course and little is yet known or understood about these conditions. Hematologic and coagulation disorders are also recognized; however, they too are not well described or fully understood. There is activation of coagulation factors as well as hyperfibrinolysis that are sometimes compounded by the effects of therapeutic hypothermia when employed. Recognizing these problems and promptly addressing them enhances the chances for patients to achieve better outcomes.

## DIAGNOSIS

The diagnosis of HIE is a clinical one, as it requires the presence of an inciting event leading to reduction or cessation of blood flow and oxygen supply to the brain. The onset of acute alteration in consciousness presents an extensive list of differential diagnoses. A complete neurologic assessment is still essential in the immediate management of HIE. The neurologic examination should be considered in the context of ongoing systemic processes, such as hemodynamic instability, the use of pharmacological agents such as paralytics, and therapeutic hypothermia. In the unresponsive patient, assessment of the best clinical response is key to determining the level of consciousness; assessment of brainstem and motor reflexes help define severity and prognosis. In the vast majority of patients, the neurological assessment will be non-localizing. However, findings of focal neurological abnormalities on examination may direct the work-up to specific etiologies such as stroke or hemorrhage. Observations of spontaneous motor activity may also require early electrophysiological test to differentiate seizures from movement disorders and myoclonus.

There are no tests or procedures specific for the diagnosis of HIE. Diagnostic work-up using laboratory tests, neuro-electrophysiologic studies and neuroimaging are needed to help establish the etiology of HIE, stage the severity of injury, help define prognosis, and rule out other pathologies that may present similarly to HIE. Biomarkers of brain tissue injury such as neuron-specific enolase(NSE) for neurons, protein s100 for astrocytes, and neurofilament heavy chain (NfH) protein among others are generally elevated in serum or CSF during the acute phase of injury. These biomarkers may be used to define the severity of injury and some may be useful as adjuncts in prognostication. Early head CT may be normal, but subsequent tests or MRI may demonstrate areas of brain tissue injury in areas with selective vulnerability, diffuse cerebral edema, loss of gray white matter differentiation among other findings that are indicative of HIE. The typical findings related to HIE on neuroimaging with head CT or MRI may be noted early but require a few days to define the full extent of injury [12, 13]. Emergency neuroimaging at the time of presentation of alteration in level of consciousness is important to rule-out other causes of acute brain injury which may require specific interventions, such as subarachnoid hemorrhage, intracerebral hemorrhage, and acute ischemic stroke. Considering that seizures may be common and can occur early in the post-resuscitation period, early electroencephalography (EEG) is important in diagnosis and management of seizures. Other neurophysiologic testing, such as with somatosensory evoked potentials (SSEP), is typically used for prognostication, and will be discussed later in this chapter.

## TREATMENT

### Emergent Medical Stabilization

After successful resuscitation with return of spontaneous circulation (ROSC) per ACLS guidelines, patients who remain unresponsive and are presumed to have HIE, should be rapidly evaluated for therapeutic hypothermia and ongoing care [14]. If not yet done, the airway should be definitively secured with endotracheal intubation and mechanical ventilation should be instituted. All patients should have a 12-lead ECG performed immediately after resuscitation. Hemodynamic stability has to be maintained and consideration for cardiac reperfusion interventions must be undertaken in all appropriate patients. Patients should be kept NPO and enteral access should be obtained via orogastric tube. Urinary catheters should be inserted in all patients for close monitoring of urinary output. After adequate peripheral intravenous access, central venous access should be considered. The indications for central access are for administration of vasopressors, need for additional venous access, hemodynamic monitoring and endovascular temperature management when available and applicable. Arterial access should also be obtained expeditiously to enable hemodynamic monitoring and serial arterial blood gas measurements. Finally, patients should have an initial emergency cranial CT scan to rule out complicating conditions with potential to alter immediate management such as subarachnoid or intraparenchymal hemorrhage, ischemic stroke and cerebral herniation or conditions that may affect the use of antiplatelet agents or anticoagulants should there be a concomitant myocardial infarction. Please refer to Figure 13-1 for additional details on the initial stabilization of patients with HIE post ROSC.

### Therapeutic Hypothermia

Since the development of modern CPR techniques in the 1950s, numerous pharmacological trials with putative neuroprotective agents have failed to improve survival and quality of life of patients resuscitated from cardiac arrest [15–18]. In 2002, two randomized clinical trials showed that therapeutic hypothermia to 32-34°C for 12-24 hours provided to comatose survivors of cardiac arrest improved both survival and quality of life of survivors [19, 20]. Therapeutic hypothermia has demonstrated a robust benefit with a number needed to treat (NNT) of six. While these two landmark studies focused on out of hospital cardiac arrest with ventricular tachycardia (VT) or ventricular fibrillation (VF) as initial rhythms, subsequent studies showed likely survival and quality of life benefits for victims of cardiac arrest with initial rhythms of asystole or pulseless electrical activity (PEA) with therapeutic hypothermia (TH) [21]. At this time, it is reasonable to provide TH to all comatose cardiac arrest victims regardless of presenting ECG rhythm in accordance with the ILCOR (International Liaison Committee on Resuscitation) guidelines (American Heart Association [AHA] class I recommendation for out of hospital arrest with VT/VF as the initial rhythm, and IIB for those with PEA and asystole as initial rhythm or in-hospital cardiac arrest) [14].

Recently, a larger prospective randomized clinical trial of temperature management that included comatose survivors of out of hospital cardiac arrest with pulseless VT/VF and PEA/asystole was published [22]. This study compared two temperatures interventions: 33°C or 36°C for 24 hours followed by rewarming to normothermia, with maintenance of normothermia for a total treatment of 72 hours. This study found no statistically significant difference in both outcomes and complications between the 33°C or 36°C treated groups. With these findings, ILCOR in a statement issued in December 2013, still recommends use of the 33°C for 24 hours but also provides that 36°C may be provided as an alternative until a formal consensus can be issued [23]. Some caveats to remember: 1) the recent study employed 36°C for 24 hours, and was followed by rewarming and active maintenance of normothermia, with the entire intervention lasting 72 hours; 2) treatment with 36°C is not equivalent to normothermia or no TTM intervention; and 3) the temperature interventions were undertaken as part of an ICU care bundle that included glucose control, fever control, systemic blood pressure management and protocolized end-of-life decision making that delayed withdrawal of life support for several days after the intervention in most cases [22].

Multiple clinical studies, including case series, registry reports and uncontrolled trials with historical controls, have shown mixed results regarding the benefit of TH in patients with PEA or asystole. Some showed improvement in survival and in the quality of neurologic recovery [24–26]; while others showed a lack of outcome benefit in those treated with TH that had PEA and asystole [27–30]. While the benefits were mixed, these studies also showed that the adverse effects of TH were not significantly different from non-TH treated groups. However, as previously noted in the large randomized controlled study by Nielsen which included both PEA and asystole as well as pulseless VT/VF, outcome benefits for patients treated with 33°C or 36°C were reported in both groups [22].

Despite its benefits to CA survivors, some considerations need to be noted for the possible adverse effects of TH. The clinical trials showed a non-significant rate of adverse events between TH and control group. The more common adverse conditions to be vigilant for include pneumonia, sepsis, bleeding, electrolyte abnormalities, cardiac arrhythmias and glucose dysregulation [5]. Establishing treatment protocols of care for induction and maintenance of hypothermia and rewarming, as well as for tracking potential adverse events have enhanced the delivery of care and contributed to the success of TH.

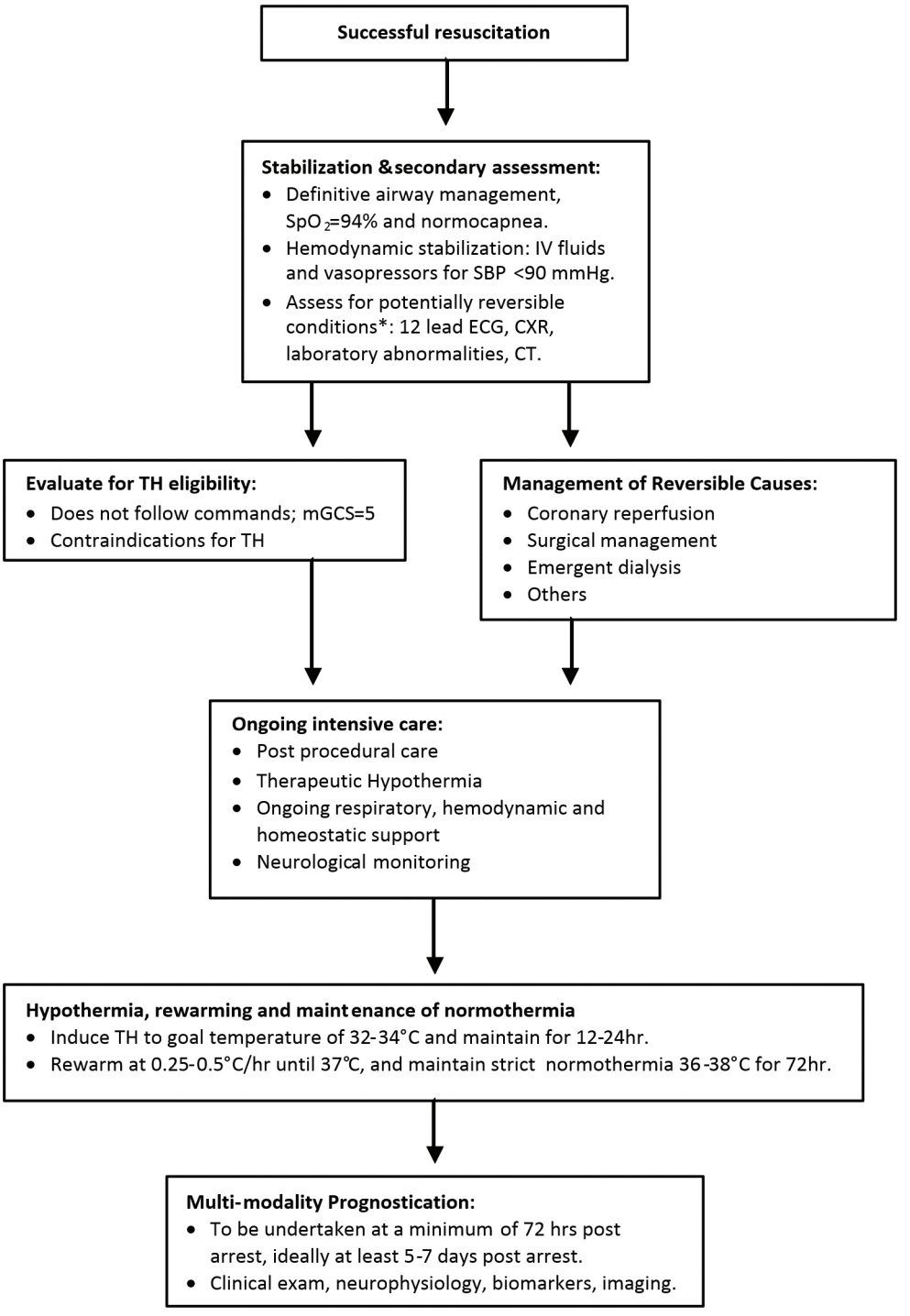
There are many methods to induce hypothermia, ranging from physical surface cooling (e.g. ice packs, cold baths, special pads, helmets), intravenous infusion of chilled fluids, endovascular temperature control devices, intraperitoneal, and endonasal cooling systems. Some evidence favors tighter control of temperature to 33°C, and automated temperature feedback systems (endovascular or surface) are ideal to maintain target temperature in TH. In general the main determinants of the ability to cool patients, regardless of the method, are the initial ambient and patient temperatures, body surface area, age and the level of impairment of the endogenous thermoregulatory mechanisms [31]. With regards to the timing of induction of TH, it is generally accepted that prompt initiation of hypothermia and achievement of target temperature is optimal [32].

Clinical evidence in humans undergoing intra-arrest therapeutic hypothermia (IATH) is limited, but has been shown to be both safe and feasible, and in one study it showed improvements in ROSC, survival to hospital discharge, and neurologic outcomes [33–35]. The duration of the maintenance phase of TH is another area that is not well studied or fully understood. In the original 2002 trials, the European study maintained hypothermia for 24 hours [20], whereas the Australian study did so for 12 hours [19]. There are ongoing studies looking to address the question of the optimal duration of TH. There are additional unanswered questions pertaining to the ideal rate of rewarming. The optimal duration of TH and the most appropriate method and rate of rewarming are still in need of clarification.

**Shivering**

Another important consideration when treating with therapeutic hypothermia is the management and prevention of shivering. Shivering is a centrally mediated thermoregulatory response that normally sets in at around 35.5°C, and is usually overcome below 34°C. However, these reference temperatures apply to healthy individuals and may not be the same in all CA patients. The absence of shivering after induction of hypothermia, or spontaneous hypothermia prior to induction of hypothermia has been associated with worse outcomes [36]. It is possible that damage to the hypothalamus impairing thermoregulation may be a marker for more severe injury. On the other hand, the presence of shivering is known to increase body temperature which has been shown to worsen brain injury and negatively impact outcomes [37].

A clinical scale to quantify and assess shivering has been developed [38] and can be used to suppress shivering in a stepwise fashion. After securing the airway, non-depolarizing neuromuscular blocking agents (NMBA) with no histamine release potential and short to intermediate duration may be necessary to abolish shivering, especially during induction of TH. There has been a shift from continuous infusion of NMBA to intermittent bolus dosing, to control shivering. Concomitant sedation is necessary with the use of NMBA. Along with preventing shivering and thereby facilitating induction of hypothermia, sedation and analgesia also play an important role in optimizing ventilator synchrony and minimizing endogenous stress induced by catecholamine surges. Ideally sedation and analgesia would be used initially, with NMBA paralysis added if initial measures fail.




** ECG: electrocardiogram. CXR: chest x-ray. CT: computed tomography. TH: therapeutic hypothermia. GCS: Glasgow Coma Scale. mGCS: motor GCS component score. TTM: targeted temperature management system. STEMI: ST-elevation myocardial infarction. AMI: acute myocardial infarction.*

**Figure 13-1.** Post-Resuscitation Algorithm

There is great variability in the practice and methods for both sedation and analgesia in TH for the PCAS [39], and this is due to the lack of clear evidence for the ideal choice of agents. Options for sedation include fentanyl, remifentanyl, or propofol infusions, the latter being added if necessary to

achieve adequate analagosedation that is quickly titratable and has a favorable context-sensitive half-life profile. There is also some experience with the use of benzodiazepines such as midazolam or lorazepam. Dexmedetomidine is another promising agent as it has little propensity for respiratory depression and sedation, has been found in brain injured patients to have superior cognitive impairment profile, has some potential neuroprotective properties [40, 41] and decreases shivering [42, 43]. Additionally an initial 4-6 gram load of intravenous magnesium sulphate to achieve serum magnesium levels of 3-4 mg/dL can be given to correct potential hypomagnesemia and to facilitate hypothermia by decreasing shivering as part of the initial stabilization and induction of hypothermia. There are a variety of interventions to control shivering and in the absence of high quality studies, practitioners need to individualize treatment based on patient response and medical conditions. The use of meperidine has also been advocated to aid in controlling shivering, but concerns regarding the accumulation of metabolites and their impact on lowering the seizure threshold make this a less appealing agent. Buspirone has been shown to be effective and is a favored adjunct in the management of shivering as is the use of skin counter-warming measures [44].

**Seizure and Myoclonus Management**

In HIE secondary to cardiac arrest, the incidence of non-convulsive status epilepticus (NCSE) is estimated to be as high as 24% [45, 46] and is associated with worse outcomes [47, 48]. Therefore, neuromonitoring with continuous surface EEG should be strongly considered. It is important to recognize that the presence of NCSE in this patient population should be viewed as an opportunity to aggressively treat this condition in hopes to modify the natural history of the condition instead of succumbing to self-fulfilling prophecies of poor outcomes and therapeutic nihilism [49]. There is insufficient evidence to recommend pro-phylactic use of antiepileptic drugs at this time. Also, the optimal antiepileptic medication for the treatment of NCSE is not clear. It is reasonable to use of less sedating agents or those with a short half-life (midazolam, levetiracetam, fosphenytoin or valproic acid) to avoid clouding the neurologic evaluation for purposes of neurological prognostication once the patient has been rewarmed and adequate time for observation has been provided. In HIE patients with status epilepticus, existing management guidelines should be followed [50]. Acute post hypoxic myoclonus (PHM) occurs in about 30% of CA patients with HIE, and can be divided into status myoclonus and multifocal myoclonus. Though little evidence exists regarding the optimal therapy for PHM, subcortical myoclonus usually responds best to clonazepam. Propofol, though not an antiepileptic drug per se, does suppress myoclonic as well as electrographic activity but longer term control after weaning of propofol is problematic. Alternatively, valproate, phenytoin, phenobarbital or other benzodiazepines seem to be less effective [51].

**ICP Management**

Cerebral edema is thought to play a major role in the pathophysiology of brain injury following cardiac arrest. Cerebral edema is apparent on the initial cranial computed tomography (CT) in approximately 30% of patients following cardiac arrest [52]. Therapeutic hypothermia has an effect in decreasing cerebral edema; however, additional measures such as osmotherapy and barbiturate coma have not been well studied and at this time are not recommended for routine use. In cases of cerebral herniation, the use of hypertonic saline and osmotherapy in an attempt to reverse

herniation could be considered [53]. However, if a patient develops cerebral herniation due to diffuse brain swelling in the setting of HIE, this is an ominous sign.

**General Intensive Care Management**

*Hemodynamic Management*

Goal directed hemodynamic parameters for PCAS victims undergoing therapeutic hypothermia should generally include euvolemia and a mean arterial pressure (MAP) of 60 mmHg or systolic pressure (SBP) of 90 mmHg to maintain organ perfusion [54]. However, a MAP of 70-100 mmHg may be considered to augment cerebral perfusion pressure (CPP) in cases of cerebral edema and elevated intracranial hypertension (Table 13-2). These goals may need to be individualized and depend on the availability of monitoring equipment. A multimodal approach to the assessment of intravascular volume with dynamic indices of volume, fluid responsiveness, and organ perfusion can include focused bedside ultrasonography, as well as invasive measurements of continuous cardiac output, stroke volume variation, pulse pressure variation, global end-diastolic volume, and other hemodynamic variables. In cases of hypotension, norepinephrine is the recommended vasopressor. However, early and thoughtful consideration should be given to mechanical support via intraaortic balloon counterpulsation, cardiopulmonary bypass, ventricular assist devices, or extracorporeal circulatory support systems.

*Mechanical Ventilation*

In the management of HIE, mechanical ventilation should be aimed at maintaining tissue normoxia and normocapnea (Table 13-2). Arterial oxygen concentration or saturation goals have not been studied rigorously, but there seems to be some indication that supranormal values may be counterproductive [55–57]. Current guidelines for post resuscitation care suggest discontinuation of 100% inspired oxygen once ROSC is achieved and that oxygen delivery be titrated to maintain an arterial oxygen saturation of 94-98% as soon as possible in the post resuscitation phase [14], as hyperoxia seems to have detrimental effects [58]. Normocapnea with $P_aCO_2$ values between 40-45 mmHg and end-tidal $CO_2$ values of 35-40 mmHg, should be targeted. Hyperventilation can decrease cardiac output via increased intrathoracic pressure, and decreases in cerebral blood flow via cerebral vasoconstriction. Low tidal volume lung protective ventilation strategies are standard of care for patients with ARDS and acute lung injury; similar tidal volumes of 6ml/kg of ideal body weight in patients without evidence of ARDS might be considered. It is recommended that continuous pulse oximetry and end-tidal carbon dioxide concentration be monitored, with frequent correlation to measured arterial blood gases. Both techniques have been used extensively in the setting of resuscitation, however transcutaneous pulse oximetry can be potentially confounded in a linear fashion by hypothermia, and both oximetry and capnography can be further affected by poor perfusion states.

**Table 13-2.** Post-Resuscitation Goal Directed Therapy

| Parameter | Value or Indication |
|---|---|
| Goal Temperature | 32-34°C |
| Cooling Duration | 24 hours |
| Emergent PCI | If STEMI, new LBBB or RWMA. Delayed PCI in other cases as clinically indicated. |
| Volume Status | Euvolemia |
| Mean Arterial Pressure | 60 mmHg, may consider 70-100 mmHg in individual cases if concerns for CPP. |
| Oxygenation | ABG $P_aO_2$ of 80-100 mmHg with 94-98% saturation. |
| Ventilation | ABG $P_aCO_2$ 40-45 mmHg. Adjust minute ventilation to keep tidal volume of 6 mL/kg ideal body weight. |
| Glycemia | Serum glucose 144-180 mg/dL. Aggressively correct hypoglycemia <80 mg/dL. |
| Hemoglobin/Hematocrit | 7-10 g/dL, carefully individualized goals depending on clinical situation. |
| Sodium | 140-145 mEq/L |
| Potassium | 4-4.5 mEq/L |
| Magnesium | 3-4 mEq/L |
| EEG | Monitoring for presence of seizures (convulsive and nonconvulsive status epilepticus), background rhythm and reactivity. |

*Temperature Modulation*

After maintaining TH of 32-34°C for 24 hours, active, controlled rewarming at a rate of 0.25-0.5°C per hour is recommended until a core temperature of 36-37°C is achieved. After rewarming, active temperature management should continue for a further 48-72 hours to ensure normothermia, protecting the brain from the detrimental effects of fever. Rebound fever is a common phenomenon occurring in about 40% of patients post therapeutic hypothermia; one study found that only temperatures >38.7°C were associated with worse neurologic outcomes in patients who survived to discharge [37]. The mechanism for this common presentation of fever after therapeutic hypothermia is not well understood; however, several factors are thought to contribute to its presence including altered thermoregulation from damage to thalamic structures, rebound hyperthermia post warming, infection, and pro-inflammatory states.

*Renal, Endocrine, Hematologic and Gastrointestinal Management*

Therapeutic hypothermia induces important changes in metabolism and homeostasis, resulting in changes to urine output (i.e. cold diuresis) with alterations in potassium, magnesium and phosphate. The importance of control over potassium and magnesium levels is related to their importance in cardiac conduction and role in arrhythmogenesis. Potassium levels of >4 mEq/L and magnesium levels >2.0 mEq/L should be maintained, with levels in the 3-4 mEq/L range to reduce shivering being preferred.

Serum sodium concentrations should be maintained in the normal range whenever possible, however in cases of cerebral edema, elevated intracranial pressure and herniation, increased sodium goals could be considered. Hypotonic intravenous fluids should be avoided. Normoglycemia should be maintained with insulin infusions to avoid the potential for erratic absorption of subcutaneous insulin with changes in temperature as well as the fluctuations of serum glucose levels which may occur across the phases of therapeutic hypothermia. Hypothermia decreases insulin secretion and insulin sensitivity and great care must be taken to avoid hypoglycemia during rewarming as insulin sensitivity increases back to baseline. While there is no evidence that ultra-tight glycemic control improves outcomes, has been implicated with worse outcomes and increased mortality. Current guidelines suggest maintaining blood glucose levels between 144-180 mg/dL as well as aggressively treating levels below 80 mg/dL [14].

Patients undergoing TH post cardiac arrest should receive stress ulcer prophylaxis, as they are at high risk for developing significant gastrointestinal bleeding due to ischemia, hypoperfusion, physiologic stress, and coagulopathy. There is no clear evidence regarding optimal hemoglobin or hematocrit goals, nor transfusion thresholds for resuscitated cardiac arrest victims with HIE. Though much controversy remains on this subject, patients with acute coronary syndromes should be carefully evaluated in terms of risk-benefit, and consideration may be given to transfuse to a goal hematocrit >30%. It must be noted that the most recent systematic literature reviews and transfusion guidelines specifically state that a restrictive transfusion cannot be recommended in high risk patients [59–61]. DVT prophylaxis is indicated with pneumatic compression devices and subcutaneous heparin administration. A summary of these recommendations can be found in Table 13-2.

## PROGNOSTICATION

Neuroprognostication is vital and yet continues to be one of the most controversial topics in post resuscitation care. Specifically in relation to HIE, the 2006 practice parameters of the American Academy of Neurology provide specific recommendations for the prognostication of neurologic outcomes for cardiac arrest survivors not treated with TH [62]. To date there is no adequate paradigm for prognostication in HIE treated with TH. Clinical examination including the presence or absence of brainstem reflexes, motor responses and absence of myoclonus were traditionally used to predict a favorable prognosis. Electrophysiologic testing in the form of somatosensory evoked potentials (SSEP), the serum biomarker neuron specific enolase(NSE), as well as neuroimaging have been employed as additional tests to attempt to improve the predictive accuracy of neuroprognostication. However, what limited certainty these tests and parameters provided has become even more questionable in the setting of therapeutic hypothermia. The use of sedatives and analgesics adds a degree of uncertainty given unpredictable drug effects on patients' neurologic status. Samaniego et al [63] illustrate the fact that neurologic examination and testing for prognostication purposes is commonly performed in close proximity to the administration of confounding medications. The limited size and quality of the studies in this vital field are further hampered by the very real and significant phenomenon of the "self-fulfilling prophecy", where the outcomes of the study (death as an indicator of poor neurologic outcome) are influenced by the results of the diagnostic modality not being blinded to the treating physicians [63–66]. This generally occurs in the form of a patient having care withdrawn based on the results of imaging, neurophysiologic or other forms of testing biasing those involved (physicians and family). Though multimodality prognostication employing several or all of the available modalities certainly makes clinical sense, we have no prospective validation of such an approach with a false-positive rate (FPR) that approaches zero and has an acceptably narrow confi-

dence interval for patients treated with TH. It is worth noting that the most recent trial of multimodality prognostication [67] was not blinded and contrasts many other studies on the utility of somatosensory evoked potentials [65, 68]. The most current systematic reviews and meta-analyses agree that existing studies involving patients treated with TH are suboptimal optimal and warned of dangers of self-fulfilling prophecies [69, 70]. One meta-analysis also shows that predictive value of prognostic tests increases when performed after the first 72 hours [69, 70].

The clinical neurological examination has traditionally been the cornerstone of neuroprognostication, an exam with absent pupillary or corneal reflexes as well as extensor or absent motor response on post arrest day three is considered by the AAN guidelines to have a FPR of zero with a 95% confidence interval (CI) of 0-3 for predicting a poor neurologic outcome in patients who were not cooled. However, in the post therapeutic hypothermia setting, several studies have challenged the reliability of clinical testing [65, 66, 71, 72]. It was also common to equate the presence of post anoxic status myoclonus in the first 24 hours with a universally poor outcome; AAN guidelines assigned this finding a FPR of zero with CI of 0-8.8. However, more recent studies have also questioned these values in patients who received TH [66, 73].

Neuron specific enolase is the most commonly used and studied biomarker of brain injury for prognostication in the setting of the PCAS. In the AAN guidelines, a NSE value >33µg/L obtained within the first 72 hours is assigned a FPR of zero with a CI of 0-3 in patients who did not receive TH. Steffen et al [74] have questioned the cut-off value in patients who have undergone hypothermia, where in order to have 100% specificity the cut-off needed to be raised to 78.9µg/L. Two other studies raise important concerns regarding the applications of NSE in neuroprognostication after therapeutic hypothermia where FPR were as high as 10 with CI of 6-16 [64, 65].

EEG and SSEP are the most common electrophysiological modalities utilized in neuroprognostication. EEG has been evaluated in the prognostication of cardiac arrest survivors [66, 75–82], and has also led to some important clinical discoveries. The 2006 AAN practice parameters assign EEG a FPR of 3% with a CI of 0.9-11; making it the least predictive method to predict neurologic outcomes. Abend et al [83] pooled four existing studies on EEG in CA patients who had undergone therapeutic hypothermia and found that 29% of these patients had acute electrographic non-convulsive status epilepticus (NCSE).

In contrast to the established guidelines and practice where SSEP is considered the most accurate ancillary method to aid clinical diagnosis of poor neurologic outcome (FPR 0.7% CI 0-3.7), a recent study comparing SSEP and continuous EEG by Cloostermans et al [80] found EEG to be superior in terms of its sensitivity to predict poor neurologic outcomes in CA patients treated with hypothermia. Leithner et al [84] demonstrated that neurologic recovery is possible despite absent or minimally present median nerve N20 responses greater than 24 hours after cardiac arrest. In the study by Bouwes et al [65], the absence of N20 responses on SSEP during hypothermia therapy had a FPR of 3%.

Imaging studies have also been employed for prognostication mainly in the form of brain computed tomography (CT) where loss of gray-white matter differentiation and obvious infarction have also been used to bolster clinical prediction. The use of imaging has not yet been formally incorporated into any guidelines, however, and has been used based on individual clinician practice. More recently, quantitative measurements of signal change on both CT and MRI have attempted to improve the predictive

abilities of imaging studies in the PCAS. At this time imaging can only provide limited supporting information in an overall multi-modal prognostication strategy, no decisions should be made based on solely one modality, but particularly not based on imaging alone.

Given the aforementioned uncertainties in prognostication of neurological outcome in patients with HIE following cardiac arrest treated with therapeutic hypothermia, the following points should be kept in mind. There is no good evidence from well-designed studies to support substantial accuracy of early prognostication (< 72 hours post-arrest) in cardiac arrest survivors treated with therapeutic hypothermia. Given our lack of understanding of how therapeutic hypothermia improves outcomes, as well as its effects on emergence from coma and its well described effects in altering drug metabolism and clearance, it is prudent to be more conservative in approaching prognostication. Patients should be observed for a minimum of 72 hours post arrest. However, 5-7 or more days of observation may be necessary to fully account for the effects of therapeutic hypothermia.

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## HYPOXIC-ISCHEMIC ENCEPHALOPATHY QUESTIONS

1. What are the most common clinical manifestations of HIE?
    a) Coagulopathies
    b) Seizure disorders
    c) Disorders of consciousness
    d) Stroke
    e) Autonomic instability

2. According to the AHA guidelines for post resuscitation care, what should the systolic blood pressure (SBP) goal be for post cardiac arrest patients?
    a) SBP >100 mmHg
    b) SBP >60 mmHg
    c) SBP<100 and >60 mmHg
    d) SBP <180 mmHg
    e) SBP>90

3. Which of the following factors allows for accurate prognostication of neurologic outcomes in patients with HIE post cardiac arrest treated with therapeutic hypothermia in the first 24 hours post arrest?
    a) N20 median nerve somatosensory evoked potentials
    b) Clinical neurologic examination
    c) Multimodality prognostication combining imaging, clinical examination and electroencephalography
    d) Neuron specific enolase levels
    e) None of the above

4. Based on the landmark 2002 trials on therapeutic hypothermia for comatose survivors of witnessed cardiac arrest with initial rhythms of VT/VF (Bernard et al and HACA Study Group), what is the number needed to treat to achieve a good neurologic outcome?
    a) NNT = 6
    b) NNT = 13
    c) NNT = 16
    d) NNT = 22
    e) None of the above

5. What is the principal pathophysiologic mechanism of injury at the cellular level resulting from global cerebral hypoxia-ischemia?
    a) Cellular peroxidation
    b) Excitotoxicity
    c) DNA fragmentation
    d) Mitochondrial failure
    e) Errors in transcription

6. What is the current utility of the 2006 Practice Parameter from the Quality Standards Subcommittee of the American Academy of Neurology: *Prediction of Outcome in Comatose Survivors after Cardiopulmonary Resuscitation*?
    a) These guidelines are outdated and no longer applicable
    b) They only apply to comatose survivors of cardiac arrest treated with therapeutic hypothermia
    c) They only apply to comatose survivors of cardiac arrest who are not treated with therapeutic hypothermia
    d) They still apply to all comatose survivors of cardiac arrest regardless of use of therapeutic hypothermia
    e) None of the above

7. Which of the following statements is **false**?
    a) Cardiac arrest is the most common precipitating factor of HIE in adults
    b) HIE can result from cardiac, respiratory, traumatic and a variety of other causes that result in inadequate oxygen and blood flow to the entire brain
    c) After successful resuscitation, cardiac arrest survivors should be maintained with an $SpO_2$ of ≥94%
    d) Initiation of therapeutic hypothermia is absolutely contraindicated in comatose cardiac arrest survivors with acute myocardial infarction that are going for emergent coronary revascularization.
    e) None of the above

8. Which of the following precipitating mechanisms of HIE carries the best prognosis?
    a) Primary cardiac arrest
    b) Drowning
    c) Partial hanging
    d) Primary respiratory arrest
    e) No mechanism of HIE has been definitively proven to confer an improved likelihood of a good outcome

9. Which of the following is used to diagnose HIE?
    a) MRI
    b) History and clinical examination
    c) Transcranial Doppler ultrasonography
    d) EEG
    e) Radionuclide cerebral blood flow study

10. Which of the following are evidence-based interventions in post cardiac arrest care?
    a) Therapeutic hypothermia of 30-32°C for 12-24 hours
    b) Routine intracranial pressure monitoring
    c) The use of calcium channel blockers to limit excitotoxicity
    d) Therapeutic hypothermia of 32-34°C for 12-24 hours
    e) Routine seizure prophylaxis with anti-epileptic drugs

## HYPOXIC-ISCHEMIC ENCEPHALOPATHY ANSWERS

1. **The correct answer is C.** Disorders of consciousness are the most characteristic feature of HIE; this may eventually resolve, however, and patients may recover full consciousness. Seizure disorders and autonomic instability may also be present in HIE, however, they are not as common. Stroke is not associated with HIE and coagulopathy may be seen as a complication of TH; however, it is not a feature of HIE.

2. **The correct answer is E.** According to the AHA post resuscitation guidelines the systolic blood pressure should be maintained greater than 90 mmHg.

3. **The correct answer is E.** In comatose survivors of cardiac arrest treated with therapeutic hypothermia there is no evidence supporting the use of early (prior to 72 hours post arrest) prognostication. In fact none of the options presented (imaging, electrophysiology, clinical examination or biomarkers), have sufficiently low false positive rates with narrow confidence interval to recommend their independent use in prognostication.

4. **The correct answer is A.** Based on the Bernard et al. and the Hypothermia After Cardiac Arrest (HACA) Study Group data, the number needed to treat to obtain a good neurologic outcome in witnessed, comatose survivors of VT/VF arrests with less than 30 minutes to return of spontaneous circulation (ROSC) is six (NNT = 6).

5. **The correct answer is B.** Cellular oxygen deprivation, results in decreased ATP production with resulting cellular energy starvation. This results in excitotoxicity, an uncontrolled release of glutamate, which leads to injury mediated through NMDA receptors. NMDA mediated glutamate excitotoxicity creates intracellular calcium influx that activates second messengers which amplify cellular injury by increasing calcium permeability and increasing glutamate release leading to a vicious cycle and the activation of nitric oxide synthase. Secondary to excitotoxicty, oxygen free radical species are also responsible for cellular injury by direct DNA fragmentation, protein oxidation, lipid peroxidation and disruption of the mitochondrial respiratory chain.

6. **The correct answer is C.** The current utility of the 2006 Practice Parameter from the Quality Standards Subcommittee of the American Academy of Neurology: *Prediction of Outcome in Comatose Survivors after Cardiopulmonary Resuscitation* is to provide a prognostic algorithm for patients who have not undergone therapeutic hypothermia. These recommendations have not been well validated in patients treated with hypothermia.

7. **The correct answer (only false statement) is D.** The need for emergent cardiac revascularization is not an absolute contraindication to the initiation of therapeutic hypothermia. Evidence has shown that initiation of hypothermia prior to percutaneous coronary intervention does not delay door to balloon time, or increase complication rates. All other statements are correct.

8. **The correct answer is E.** Though some authors have postulated that primary cardiac events have the best outcomes, this statement is not definitively proven and remains controversial. At this time no etiologic mechanism can be considered to have a better pre-test probability of a good outcome compared to other causes of HIE.

9. **The correct answer is B**. The diagnosis of HIE is made on the basis of clinical examination consistent with an encephalopathy, and a history consistent with a precipitating event that could result in a global cerebral hypoxic or ischemic event. The other options (MRI, EEG, TCD) are useful adjuncts in ruling out other processes and can provide relevant information, but they are not necessary to make the diagnosis of HIE. A radionuclide cerebral blood flow test would only be necessary as a confirmatory exam in cases of brain death.

10. **The correct answer is D**. Therapeutic hypothermia of 32-34°C for 12-24 hours is the only evidence based intervention listed. There is no evidence for moderate (<32°C) therapeutic hypothermia or routine use of seizure prophylaxis after cardiac arrest. Studies evaluating the possible benefit of calcium channel blockade with agents such as lidoflazine failed to show any benefit.