Chapter 17
Hypoxic-Ischemic Injury After Cardiac Arrest

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17.1 Introduction

There are 350,000–450,000 out-of-hospital cardiac arrests each year in the United States [1]. Cardiopulmonary resuscitation (CPR) is attempted in 100,000 of these cases, and 40,000 are admitted to the hospital [2]. Cardiac arrest is often related to a primary cardiac arrhythmia but may also result from respiratory arrest or profound hypotension. Neurological injury, such as a devastating acute brain injury, traumatic brain injury, or aneurysmal subarachnoid hemorrhage, may also result in cardiac arrest.

Unfortunately, survival to discharge after cardiac arrest is less than 10%, and prognosis is unknown with patients remaining comatose for weeks [1]. Patients that survive cardiac arrest may have numerous consequences including brain injury, cardiac dysfunction, and systemic ischemia. The pathophysiology of brain injury caused by cardiac arrest is understood; however,

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less is known about the biological mechanisms and cellular pathways mediating recovery in this population. Once return of spontaneous circulation (ROSC) has occurred, the chances of survival may be determined by several clinical observations. Patients hospitalized following cardiac arrest will be admitted to an intensive care unit and will frequently be in refractory cardiogenic shock, requiring multiple vasopressors.

This chapter addresses the pathophysiology, clinical assessment, and identification of poor prognostic indicators in patients with anoxic-ischemic brain injury after cardiac arrest. Expert consultations for assessment of comatose patients after CPR are quite common. The assessment and management of patients with anoxic-ischemic injury after ROSC is a major clinical task for the interdisciplinary team caring for these patients in the intensive care unit.

17.1.1 Pathophysiology of Anoxic-Ischemic Injury: The Basic Principles

The brain is able to tolerate anoxia for approximately 2–4 min before irreversible neuronal damage occurs. In cardiac arrest, whether it is due to asystole or ventricular fibrillation, there is no measurable blood flow to the brain. With standard CPR techniques, only one third of the pre-arrest cerebral blood flow can be achieved. Cardiac arrest is the most profound injury to the brain, even worse than traumatic brain injury. Hypoxic injury alone may result in temporary synaptic dysfunction, but when asystole, hypotension, and minimal cerebral perfusion occur during chest compression, ischemic brain injury results. Ischemia leads to the dysfunction of cell membrane ion pumps and a rapid unraveling of the cellular machinery causing the opening of calcium channels and release of excitatory amino

acids, particularly glutamate and aspartate, which causes calcium overload and cellular death. Restoration of the systemic blood circulation does not automatically result in reperfusion of cerebral tissue. There are several areas in the brain that are not reperfused, which is related to endothelial edema caused by ischemia, blood sludging, early intravascular coagulation, and leukocyte adhesion [1–3].

Ischemia results in activation of the N-methyl-D-aspartate (NMDA) and *a*-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, causing the opening of calcium and sodium channels and an apoptosis pathway [4]. This biochemical pathway happens very quickly and is not preventable, thus allowing the neurons to be very susceptible to hypoxic-ischemic injury. Selected regions of the brain are specifically susceptible to global ischemia including the hippocampus, neocortex, cerebellum, corpus striatum, and thalamus [1, 2].

After reestablishment of circulation, reperfusion and reoxygenation can cause further neuronal damage over a period of hours to days, which is often referred as "reperfusion injury." Alterations in the inflammatory response can cause endothelium activation, leukocyte infiltration, and further tissue injury. Other contributing factors include hypotension, hypoxemia, impaired cerebrovascular autoregulation, and brain edema, which can further impede the delivery of oxygen to the brain [2].

Therapeutic hypothermia is initiated to limit neurologic injury by slowing down brain metabolism. This aids in decreasing the amount of oxygen and adenosine triphosphate (ATP) being consumed [2]. Apoptosis is prevented by means of calcium overload and glutamate release, as well as the initiation of antiapoptotic Bcl-2 and the destruction of the proapoptotic factor BAX [5]. Therapeutic hypothermia has also been shown to suppress inflammation that appears after global cerebral ischemia and to decrease hyperemia and delayed hypoperfusion [1].

17.2 Case Presentation

A 40-year-old female with past medical history of diabetes mellitus type II, hyperlipidemia, hypertension, smoker who was in her usual state of health during the day developed chest pain on and off over the late afternoon and early evening, presented to the local emergency department (ED). Soon after arrival in the ED, she went into ventricular fibrillation and required 45 min of CPR, with a total of 12 shocks delivered. Patient received a total of 450 mg of amiodarone, followed by initiation of an amiodarone drip. The patient was intubated, 12 lead ECG completed that revealed ST elevation. The patient received aspirin and clopidogrel. Patient was transferred to the CCU and underwent cardiac catheterization, resulting in stent placement of the LAD coronary artery. Upon neurological examination, the patient had pupils 4 mm and reactive to light bilaterally, cough, gag and corneal reflexes intact, no facial droop, and moved all four extremities to painful stimuli mostly flexion. Targeted temperature management to 36 °C was initiated. CT scan of the brain showed no evidence of brain edema. Neurological examination following the rewarming period demonstrated the patient did not open eyes to voice or tracking, roving eye movements, withdrawal in all four extremities or possibly decorticate posturing, intact brainstem reflexes, and triggering the ventilator. EEG shows diffuse suppression with questionable reactivity but no epileptiform activity. SSEP shows normal N20 responses. Serum neuron-specific enolase is normal. We are asked to assess the neurologic injury and prospects of improvement. Several days were allowed before prognostic neurological exam to allow sedative medications to metabolize. The patient did not improve neurologically and remained comatose. MRI was performed 4 days after CPR which showed diffuse cortical infarction. After failure to improve neurologically 14 days after CPR, family made the decision to withdraw support.

17.3 Management and Interventions

17.3.1 Targeted Temperature Management and Its Practice

Induced hypothermia, or targeted hypothermia, aims to reduce the body's core temperature. Recent randomized clinical trials enrolling out-of-hospital cardiac arrest patients demonstrated that aggressive hypothermia (33C) does not provide additional benefit over mild hypothermia (36C). Detailed hypothermia protocols are usually developed by each institution, and providers may see substantial variation from hospital to hospital.

Cooling requires reduction in core temperature with ice packs, rapid infusion of cold intravenous fluids, and the use of external cooling devices or endovascular cooling systems [6]. Therapeutic hypothermia should be initiated as soon as possible following cardiac arrest and continued for 24 h prior to the rewarming phase. Shivering is expected and should be treated with sedatives, opioids, or neuromuscular blockade (see section in Chap. 23 for shivering management recommendations). The absence of shivering during hypothermia treatment indicates severe brain injury in the hypothalamus and purports a poor prognosis [1, 7]. During therapeutic hypothermia treatment, hyperglycemia may occur and result in a decreased urine output. Other complications that may occur include pneumonia, cardiac arrhythmias, and pancreatitis. Vasopressors may be needed, but this is likely for treatment of cardiogenic shock from myocardial stunning [3]. Therapeutic hypothermia may also result in electrolyte imbalances such as hypokalemia, hypomagnesemia, hypophosphatemia, and hyperglycemia. Therefore, monitoring of serum electrolytes at regular intervals will be pertinent to guide the appropriate therapies [2]. Seizures may also occur during therapeutic hypothermia and the rewarming phase of the treatment. Typically, subclinical seizures are not identified, so it

would be recommended to monitor patients with continuous electroencephalographics (EEG) monitoring and treat the seizures if they transpire to improve patient outcomes.

Following the therapeutic hypothermia period, the patient will need to be rewarmed slowly to normal core body temperature. Clinical trials have demonstrated an improved patient outcome of 55% in the therapeutic hypothermia group, when compared to 39% in the control group [4]. It is important to know that patients may persist in a coma for a period of time following cardiac arrest and still have neurological recovery.

17.3.2 Neurologic Evaluation of the Comatose Patient After Cardiac Arrest

How do we interpret a comatose patient? How do we assess the clinical consequences of acute loss of multiple cortical layers, loss of watershed areas as a result of no flow, and loss of neurons in extremely susceptible areas such as the global pallidus?

First, no blood flow to the brain or a fraction of blood flow during resuscitation first damages the deep basal ganglia and thalami, followed by the cortical mantle, and finally the brainstem. Few patients become brain dead (which requires involvement of brainstem reflexes clinically) after CPR because the brainstem is resilient to major systemic injury. Pathology shows ischemic injury to the cortical laminae, globus pallidus, and cerebellum, and these changes can be found on MR imaging. Thus, most patients will have clinical signs of bi-hemispheric damage with no localizing signs. Common exam findings include increased tone, no motor response to pain or reflexive responses, gaze preference up or down (indicative of thalamic injury), and normal brainstem reflexes. If cortical areas (including most vertical cortical layers) are damaged, myoclonus status could appear. Myoclonus status epilepticus is an unusual presentation, often seen after prolonged cardiopulmonary

resuscitation or exsanguination and is vigorous, forceful with jerks involving all four limbs and with significant facial distortions, all in association with upward eye jerks. Shivering, rigor, or non-sustained clonus is often misinterpreted as myoclonus. Myoclonus status may be associated with continuous seizures on EEG, a burst suppression pattern, or marked decrease in amplitude. Myoclonus status epilepticus is also more frequently associated with CT scan abnormalities. Thus it is a telltale sign of a major severity of injury. Patients with different degrees of cortical injury are more difficult to prognosticate.

Second, patients with dilated pupils, loss of pupil reflexes, and corneal reflexes indicating pontomesencephalic involvement will do very poorly (unless these reflexes are muted by drugs used to manage shivering as a result of targeted temperature management protocol). Loss of brainstem reflexes may occur from prolonged anoxic injury allowing more injury or may occur as a result of brain edema also a result of more severe injury to the cortex. These core fundamentals of correlating pathophysiology in conjunction with clinical findings help in understanding the spectrum of anoxic-ischemic injury.

A complete neurologic evaluation should occur following the ROSC post-cardiac arrest. It will be vital to assure that no extenuating factors will confound the examination such as (obviously) paralytic or sedative medications and persistent hypotension (SBP less than 90 mmHg). Early awakening after cardiac arrest, ability to localize to painful stimulus, or the ability to follow simple commands are indicators of a positive outcome. However, a significant percentage of post-cardiac arrest patients will have a poor neurologic outcome, and it becomes important to sort out who might have a probable chance to survive cognitively intact. Devastating neurologic outcomes leave providers and families to be burdened with hard decisions related to goals of care, acceptable outcomes, and end-of-life decisions [1].

The most important concept is to understand that particular elements of the neurologic examination are vital when determining the severity of anoxic-ischemic injury. Clinical neurological examination should follow a standard procedure. The standard examination should include motor response to pain, with specific attention to myoclonus and spontaneous or elicited eye movement abnormalities and brainstem reflexes [6–8]. When performing brainstem reflex testing, it is important to include pupillary light reflex, corneal reflex, and cough and gag reflexes if the patient has spontaneous respirations. The brainstem is far more resilient to anoxic-ischemic injury than the cortex, so when evaluating the brainstem reflexes and the pupil response to light, it is frequently found to be within normal limits. If you find an absent pupil response, consider that it may be a result of high doses of atropine used during resuscitation. Fixed and dilated pupils examined several hours post-cardiac arrest is a clinical indicator of a poor outcome. Fixed and dilated pupils would rarely be an isolated examination finding but more commonly seen with brainstem involvement. Corneal reflexes may be absent initially but often return over time. Identifying eye movement abnormalities provides more clinical information; for example, having a persistent upward gaze indicates significant global bi-hemispheric injury that may also include involvement of the thalamus. Persistent upward gaze is often a clinical indicator of a poor functional outcome but in 10% of cases was found to be consistent with survival. When eliciting the vestibulo-ocular reflex or rapid head movement, the examiner may see a downward gaze. Other eye abnormalities may include the ping pong gaze, lateral gaze deviations, or continuous blinking which are not examined for prognostic value [6].

An essential clinical indicator is myoclonus status epilepticus or more clearly explained as continuous and forceful jerking movements involving facial muscles, limbs, and abdominal muscles [6]. These jerks can be provoked by touch or hand clapping and may include the diaphragm which affects ventilation of the patient [6]. Myoclonus status epilepticus signifies a poor prognosis [7].

17.3.3 Ancillary Diagnostics

Other diagnostic tests can be considered to assist in the neurologic examination including electroencephalogram (EEG), somatosensory evoked potentials (SSEPs) biochemical markers, computed tomography (CT), and magnetic resonance imaging (MRI). The most common EEG finding is episodic low-amplitude events (ELAE). ELAEs are often correlated with medication effect and therefore not suggestive of hypoxic-ischemic cerebral injury. When there is background EEG motion that reveals generalized slow wave motion, the patient has an increased chance of a better outcome. When a burst suppression pattern is identified on EEG that is often suggestive of a fatal outcome or vegetative state, EEG with the existence of faster frequency with spontaneous fluctuation and reactivity to stimuli provides the indication of a better neurologic recovery [4]. When EEG indicates seizures, the consideration of continuous EEG and treatment of the seizures will need to be considered.

SSEPs are another test used to assist with identifying neurological recovery. SSEPs are not confounded by medications, temperature, or metabolic abnormalities and therefore are a reliable tool for aiding neurologic prognostication [6]. SSEP involves the peripheral stimulation of the median nerve that results in a potential at the brachial plexus, cervical spinal cord, and bilateral cortex potentials (N20), evaluated with scalp electrodes. In order for the SSEP to be considered trustworthy, the cervical spine potential has to be acknowledged, as this could be a possible concern in patients with severe anoxic-ischemic injury involving the cervical spinal cord. The bilateral absence of cortical potentials (N20 component) is approximately 100% definite in calculating poor outcomes when completed between day one and day three post-cardiac arrest [6, 7]. Nevertheless, the existence of cortical N20 responses does not assure awakening from a coma will transpire. SSEP along with the clinical examination does offer adequate and reliable information for prognostication of neurologic recovery [8].

Biochemical markers that have been identified to detect cerebral damage post-cardiac arrest include serum neuron-specific enolase (NSE) and S100 [9]. NSE is a gamma isomer of enolase that is found in the neurons, and S100 is a calcium-binding astroglial protein [6]. Elevated levels of NSE and S100 are linked to hypoxic-ischemic brain injury and poor neurologic outcomes; however, we need to keep in mind that there is absence of standardization in how we measure these markers. Therapeutic hypothermia may also play a role in the effects of metabolism and clearance of these biomarkers, thus hindering the prognostic value [6].

17.3.4 Imaging

A majority of CT scans post-cardiac arrest will be normal; however, additional CT scans over the next couple of days may demonstrate changes. CT changes that may occur are related to widespread cerebral edema. Often these patients have several additional clinical indicators signifying a poor neurologic outcome. MRI imaging is more reliable in prognosticating for outcome and provides details such has diffuse cortical injury that involves bithalamic and putaminal injury [4]. A normal MRI does not necessarily indicate a better outcome because clinicians have seen numerous patients in a persistent vegetative state or minimally conscious states with normal MRI scans, with brain atrophy seen months following initial injury [4].

There are numerous diagnostic tests, including neuroimaging, electrophysiology, and laboratory testing, that may aid in evaluating neurologic recovery, but there is no one stand-alone test that is satisfactory in prognostication [7]. Some guidance is shown in Fig. 17.1. Timing of tests is not known, but we can expect MRI, EEG, and SSEP abnormalities within 24 h after the event.

MRI may become abnormal if repeated, but there are patients with repeatedly normal MRI who never awaken only to demonstrate generalized brain atrophy later.

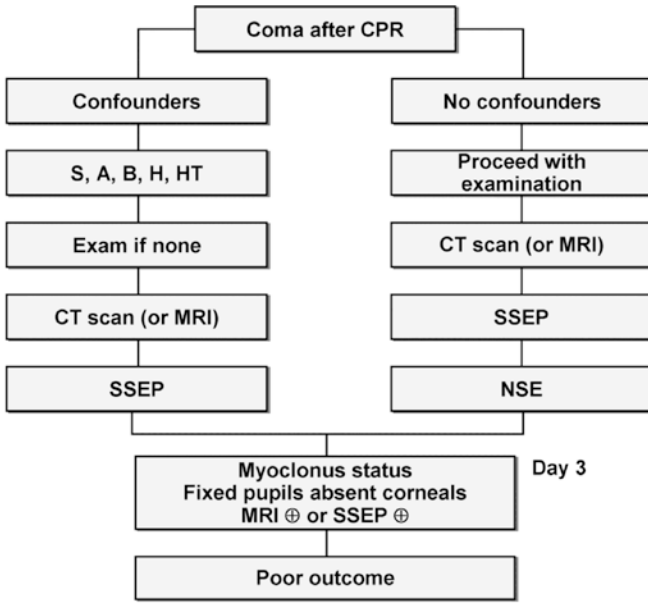

Fig. 17.1 Evaluation of hypoxic ischemic injury algorithm. *S* sedatives, *A* analgesics, *B* neuromuscular junction blockers, *H* hypothermia

17.3.5 Prognostication Summary

Anoxic-ischemic injury remains the primary cause of disability post-cardiac arrest [10]. Targeted hypothermia is standard of care in many hospitals with modern ICUs, but the practice varies. Uncertainties about the timing of initial therapy, duration of therapy, best means to cool, and target temperature during therapeutic hypothermia exist. Prognostication in these comatose patients remains unreliable if there is (1) no myoclonus status, (2) present brainstem reflexes, (3) no suppression of EEG background or burst suppression pattern, (4) normal or near normal MRI, and (5) normal SSEPs. This means that in the majority of patients, outcome cannot be clearly established in the first

weeks. Failure to improve motor response to localization implies longstanding cognitive deficits and even failure to awaken beyond a minimally conscious state. Neurologic assessment remains key and cannot be replaced by any ancillary test. Thus, neurologists and neurology specialty trained providers will continue to be consulted to perform thorough neurological examinations on patients post-cardiac arrest and provide their expertise in treating and prognostication to guide the primary care providers and families in determining goals of care.

Summary Points

- Targeted hypothermia is the primary treatment strategy following cardiac arrest to preserve neurological function.
- Shivering is expected with therapeutic hypothermia and should be treated with sedatives, opioids, or neuromuscular blockade agents.
- Repeat neurologic examination without confounders often predicts poor outcome.
- MRI and SSEP are helpful for determining degree of injury.
- The absence of brainstem reflexes indicates poor outcome.
- Uncertainty remains regarding the presence of seizures or seizure activity in comatose patients following cardiac arrest in identifying if it is a treatable complication or indicator of substantial brain injury.

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