Management of Anoxic Brain Injury

41

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Case Presentation

A 46 year old male with a history of tobacco dependence and uncontrolled diabetes is brought in to the emergency department after a resuscitated cardiac arrest. He had been in his usual state of health and after waking up this morning collapsed at the side of the bed and was noted to be apneic by his wife. When the paramedics arrived, he had received no bystander CPR and he was in ventricular fibrillation and he ultimately regained return of spontaneous circulation (ROSC) after 7 shocks and was intubated in the field.

On arrival to the ED unresponsiveness was confirmed, he was connected to a ventilator after verifying endotracheal tube positioning and obtaining labs and 12 lead ECG. He was given a 30 mL/Kg bolus of chilled (4 °C) normal saline solution, packed in ice and rushed to the cardiac catheterization lab. There he was found to have no significant obstructive coronary artery disease but was noted to have biventricular failure with elevated filling pressures. Transthoracic echocardiography showed a severely reduced left ventricular ejection fraction of ~10 %. On his way to the Intensive Care Unit, he had a CT scan of the brain which was read as concerning for early loss of gray-white matter differentiation (Fig. 41.1). He arrives in the ICU intubated, sedated, paralyzed and ice packed.

Question What approach should guide this patient's management?

Answer Targeted Temperature Management (TTM) with initial Mild Therapeutic Hypothermia followed by Maintenance of Normothermia.

Most adult patients, with few exceptions, that suffer anoxic brain injury should be treated with targeted temperature management in order to minimize secondary brain injury. On arrival to the ICU the patient was connected to an automated closed-loop intravascular cooling system. Target temperature of 33 °C was achieved within four hours from return of spontaneous circulation (ROSC). In order to facilitate cooling to goal temperature, shivering was countered by sedation with midazolam and fentanyl infusions as well as paralysis with cis-atracurium. Target temperature was maintained for 24 h, after which controlled active rewarming of 0.25 °C per hour was undertaken with the closed loop TTM system until the patient was rewarmed to the new target temperature of 37 °C. At this point the

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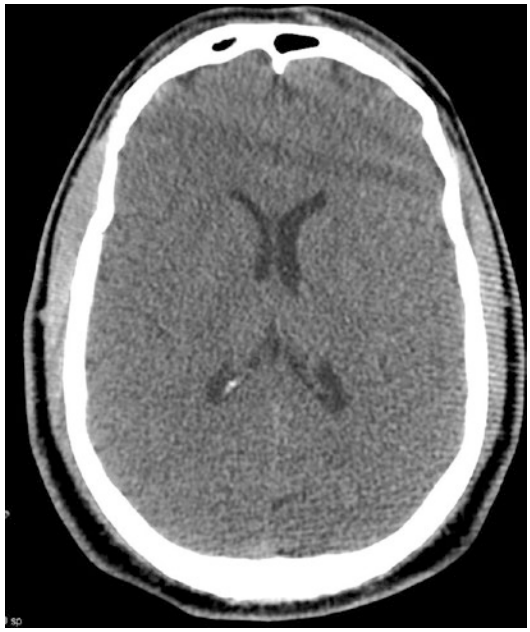

Fig. 41.1 A representative image from the CT of the brain is shown

TTM system was set to maintain normothermia, cooling the patient if necessary to maintain a temperature of 37 °C for the next 72 h. During this entire time patient was monitored with continuous EEG; he had follow up MRI of the brain which did not demonstrate evidence of focal or diffuse damage, serum neuron specific enolase levels drawn at 48 and 72 h were 26 ng/mL and 19 ng/mL respectively. He remained comatose on minimal sedation for 118 h from ROSC prior to improvement in his neurologic examination. He was extubated on hospital day 8 and was quite delirious, but had a non-focal neurologic exam and was able to participate actively with physical and occupational therapy. He was transferred out of the ICU on hospital day 10 and discharged to home on hospital day 13. Neurocognitive testing at 90 day follow up showed normal function with very mild short term memory impairment that was not impacting his performance at work (Fig. 41.2).

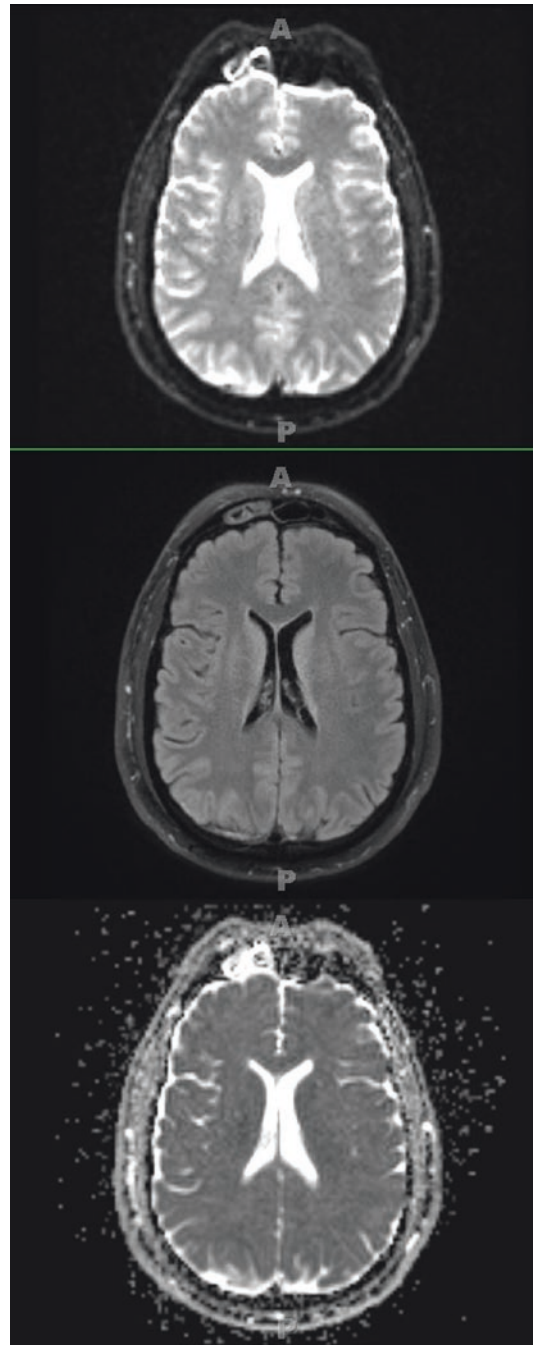

Fig. 41.2 A representative image from the MRI of the brain is shown

Principles of Management

Diagnosis

Anoxic brain injury, also known as hypoxic encephalopathy, ischemic-hypoxic encephalopathy is a fairly heterogenous entity. It best conceptualized as a spectrum of brain injury ranging from brain death, minimally conscious states, to recovery of consciousness with cognitive impairment and movement disorders to mild transient loss of consciousness with or without transient neurologic deficits. The diagnosis is made after loss of consciousness after an episode of global cerebral hypoxia or hypoperfusion. It is in essence a clinical diagnosis, as no radiological, laboratory or electrophysiologic test can fully diagnose it; these ancillary exams are often negative even in cases of severe anoxic encephalopathy.

Therapeutic Hypothermia

The use of hypothermia in the treatment of injuries dates back to antiquity, with one of the earliest applications being attributed to Hippocrates, who recommended covering wounded combatants in snow to enhance survival and recovery. In modern times, the observation that hypothermia mitigates acute neurological injury and improves outcomes was made decades ago. The first documented use of hypothermia for neuroprotection after in-hospital cardiac arrest consists of a 1958 case series of 4 patients [1]. One of the first human clinical studies on induced hypothermia for out-of hospital cardiac arrest survivors was a pilot safety and feasibility study performed by Bernard et al. in 1997 [2], this was followed in 1998, by another small study by Yanagawa et al. [3]. These two studies suggested a potential therapeutic benefit from induced hypothermia in comatose post-cardiac arrest survivors, and paved the way for subsequent definitive trials.

In the following two decades, there have been three landmark trials in TTM for hypoxic ischemic brain injury. In 2002 the two initial trials were published simultaneously, one in Australia and the other in Europe. The Australian study was Bernard et al.'s follow up study that enrolled comatose survivors of ventricular fibrillation arrests [4]. This study randomized 77 patients to receive mild therapeutic hypothermia of 33 °C or normothermia (no temperature intervention). The hypothermia arm included 43 patients while the normothermia arm had 34 patients. In this trial, cooling was initiated by paramedics prior to hospital arrival and cooling was achieved and maintained with ice packs. The target temperature was maintained for 12 h and patients were sedated and paralyzed with repeated boluses of midazolam and vecuronium as needed to prevent shivering, followed by active rewarming with a heated-air blanket beginning at 18 h after hospital arrival, with continued sedation and neuromuscular blockade to suppress shivering. Discharge to home or to a rehabilitation facility was regarded as a good outcome, whereas in-hospital mortality and discharge to a long-term nursing facility were regarded as poor outcomes. The study found that 21 of 43 patients (49 %) treated with hypothermia had good outcomes and were discharge to home or to a rehabilitation facility, compared with 9 of 34 (26 %) in the normothermia group (relative risk (RR) of good outcome, 1.85, 95 % confidence interval (CI) 0.97–3.49, number needed to treat (NNT) = 4). Mortality at discharge was 22 of 43 (51 %) in the hypothermia group and 23 of 34 (68 %) in the normothermia group (RR 0.76, 95 % CI 0.52–1.10, NNT = 6).

The second, larger trial by the European Hypothermia after Cardiac Arrest (HACA) group, randomized 273 comatose survivors of ventricular fibrillation arrests to mild therapeutic hypothermia (32–34 °C) beginning after hospital arrival versus normothermia [5]. One hundred and thirty-seven patients were randomized to the hypothermia arm, while 138 patients were randomized to the normothermia arm. Patients in the hypothermia group were cooled by via forced air mattresses and blankets, and were maintained at target temperature for 24 h. Patients were subsequently rewarmed passively over a period of 8 h. Sedation with midazolam and paralysis with vecuronium was administered to prevent shivering. Seventy-five of the 136 patients (55 %) in the

hypothermia group had a favorable neurological outcome (able to live independently and work at least part-time) at 6 months compared with 54 of 137 (39 %) in the normothermia group (RR 1.40, 95 % CI 1.08–1.81, NNT = 6). At 6 months there were 56 deaths among the 137 participants (41 %) in the hypothermia group versus 76 of 138 (55 %) in the normothermia group (RR 0.74, 95 % CI 0.58–0.95, NNT = 7).

The third, largest and most recent trial is the Therapeutic Temperature Management (TTM 33–36) trial [6]. This prospective multicenter study undertaken in Europe and Australia randomized 939 comatose OHCA survivors to cooling to 33 or 36 °C, with protocolized sedation, rewarming and prognostic evaluation. In this study the method of cooling was left at the discretion of each study site; however the intention was to reach goal temperature as quickly as possible. Rewarming was initiated at 28 h from randomization and done with controlled active rewarming of 0.5 °C per hour. Mandatory sedation was only able to be stopped or tapered at 36 h from randomization. This study found no significant difference in outcomes or complications between the two temperature groups.

Maintenance of Normothermia

Active, controlled rewarming at a rate of 0.25 °C per hour is recommended until a core temperature of 36–37 °C is achieved [7]. Once the patient has been rewarmed, the therapeutic temperature management system should remain in place for a further 48–72 h to ensure normothermia, protecting the brain from the detrimental effects of hyperthermia [8]. Rebound pyrexia is a common phenomenon occurring in about 40 % of patients post therapeutic hypothermia only temperatures >38.7 °C appear to be associated with worse neurologic outcomes in patients who survive to discharge [9]. It must be noted that current guidelines suggest preventing hyperpyrexia >37.7 °C based on data from data from focal cerebral ischemia [7]. The mechanism for this common presentation of fever after therapeutic hypothermia is not well understood, however several factor are thought to contribute to its presence: altered thermoregulation from damage to thalamic structures, rebound hyperthermia, infection and pro-inflammatory states all are likely contributors.

Supportive Care

During targeted temperature management the prevention of shivering is a crucial intervention to allow for rapid induction of therapeutic hypothermia, and to avoid the metabolic stress required to generate body heat through shivering. The use of sedation, paralysis and other adjuvant measures is necessary for adequate TTM. Factors such as age, weight, hemodynamic status, renal and hepatic function, effects of hypothermia on pharmacokinetics and dynamics and the ability to preserve the neurologic examination are factors that weigh on the choice of drugs. At this time no definitive evidence supporting a particular drug regimen exists, however short acting and rapidly cleared drugs with neutral hemodynamic profiles are ideal. Adjuvant measure to control shivering include targeting serum magnesium levels of 3–4 mg/dL, the use of buspirone and meperidine, skin counter warming and heat applied to feet and hands can also be helpful.

Cerebral edema has been reported on the initial cranial CT in approximately 30 % of patients following cardiac arrest [10], however there is no evidence supporting the use of invasive measurement of intracranial pressure to manage this patient population [11]. Basic neurocritical care nursing measures such as maintaining the head of the bed elevated to 30° and in a neutral midline position should be maintained to improve cerebral venous drainage and minimize elevations in intracranial pressure. In HE secondary to cardiac arrest, the incidence of non-convulsive status epilepticus (NCSE) is estimated to be as high as 24 % [12, 13], and is associated with worse outcomes [14, 15]. Post hypoxic myoclonus occurs in roughly 20 % of patients, and traditionally the presence of seizures or myoclonus has been regarded as predictors for poor neurologic outcomes. However, this has been shown to not

always be the case [16, 17]. There is insufficient evidence to recommend prophylactic use of antiepileptic drugs in patients with anoxic-ischemic encephalopathy; however if possible, continuous electroencephalographic monitoring provides the opportunity for early detection and aggressive treatment of NCSE which may impact outcomes and survival.

The ventilator management of patients undergoing therapeutic hypothermia for hypoxic-ischemic encephalopathy should follow a few simple parameters as outlined in current guidelines [7]: arterial partial pressure of oxygen should be approximately 100 mmHg and pulse oxymetry saturations should be equal or greater than 94 %; partial pressures of carbon dioxide should be 40–45 mmHg. The management of common respiratory problems following cardiopulmonary arrest is addressed elsewhere in this book. Cardiovascular care including management of myocardial ischemia, arrhythmias and shock are beyond the scope of this chapter. However, the following basic principles should be regarded: euvolemia should be targeted to accommodate cardiac, pulmonary and renal concerns. An adequate intravascular volume is crucial for cerebral perfusion and to allow for expected cold diuresis during hypothermia. Blood pressure goals should be individualized based on cardiac function, end organ perfusion and taking into account an approximation of the status of cerebral autoregulation. Usually a mean arterial pressure (MAP) of 65 mmHg is adequate and recommended by current guidelines [7]; however a MAP of 70–100 mmHg may be considered in particularly to augment cerebral perfusion pressure in cases of cerebral edema and elevated ICP. There is no quality data on hemodynamic parameters for this population. Empiric antibiotics are encouraged in situations when a clinical infection is suspected, as early initiation of antibiotic therapy has been associated with better outcomes following TTM for cardiopulmonary arrests [18].

Hypothermia causes alterations in endogenous insulin release as well as decreasing insulin sensitivity, therefore great care must be taken to avoid hypoglycemia during rewarming as insulin sensitivity increases back to baseline. As in other forms of brain injury, normoglycemia should be maintained with insulin infusions to avoid the potentially erratic absorption of subcutaneous insulin secondary to peripheral vasoconstriction with changes in temperature as well as the fluctuations of glycemia during therapeutic hypothermia. Current guidelines recommend keeping blood glucose levels between 144 and 180 mg/dL as well as aggressively correcting hypoglycemia <80 mg/dL [7].

Evidence Contour

The mainstay of management in patients with anoxic brain injury involves neuroprotective strategies and supportive critical care management. The only proven effective neuroprotective intervention is mild therapeutic hypothermia, though current evidence leaves questions regarding the optimal depth and duration of therapy. The prognostication of neurologic outcomes is a major area of focus for clinicians and researchers, as there is no optimal paradigm to date.

Therapeutic Hypothermia

Following the initial two landmark trials, the International Liaison Committee on Resuscitation (ILCOR), and the American Heart Association (AHA) published an interim scientific statement in 2003 with recommendations on the use of therapeutic hypothermia in comatose survivors of cardiac arrest [19]. This was followed in 2005 and updated in 2010 in the AHA Guidelines for CPR and Emergency Cardiovascular Care [7], which included the following treatment recommendations: (a) Unconscious adult patients resuscitated after in- or out-of-hospital cardiac arrest should be cooled to 32–34 °C for 12–24 h when the initial rhythm was ventricular fibrillation (Class Ib). (b) Similar therapy may be beneficial for patients with in-hospital cardiac arrest or out-of-hospital arrest associated with an initial rhythm other than ventricular fibrillation (Class IIb). To further assess the impact of hypothermia

on neurologic outcomes, a Cochrane systematic review of hypothermia for neuroprotection after cardiac arrest was published by Holzer et al. [20], and concluded that with conventional cooling methods, patients receiving TTM were more likely to reach a good neurologic outcome (RR 1.55; 95 % CI 1.22 to 1.96) and were more likely to survive to hospital discharge (RR 1.35; 95 % CI 1.10 to 1.65) compared to standard care. It also showed no difference in adverse events between hypothermia and control patients. International guidelines have not been published or updated since the publication of the TTM trial, however ILCOR did issue a statement after the publication of the TTM trial urging clinicians to continue to guide themselves with the existing recommendations pending consensus on the implications of the TTM trial [21]. Some clinicians and institutions have interpreted the results of the TTM trial as evidence against mild therapeutic hypothermia, given the lack of difference in outcomes between the two groups and the fact that 36 °C does not constitute mild therapeutic hypothermia (defined as 32–35 °C). What remains as an unanswered question is how this data applies to populations where the rate of bystander CPR is far lower than the excellent rates reported in the TTM trial, and if more severe anoxic-ischemic injury derives a greater benefit than those with milder injury. Pending clarification of this crucial question, we recommend continuing to use temperatures of 32–34 °C, and reserving the use of temperatures of 36 °C for patients that cannot tolerate lower temperatures.

It is generally accepted that prompt initiation of hypothermia and rapid achievement of target temperature is ideal [22]. Clinical evidence in humans undergoing intra-arrest therapeutic hypothermia is limited, but has been shown to be safe [23–26], improve rates of return of spontaneous circulation, neurologic outcomes and survival [27]. Most evidence indicates that the sooner TTM is initiated, the better; however animal data indicates that initiating hypothermia after 12 h has no benefit [28]. This must be tempered with the realization that the most recent (and best) evidence for induction of pre-hospital therapeutic hypothermia, has shown that despite reaching target temperature sooner, this intervention failed to translate into improved survival or neurologic outcomes [29].

Rewarming and Maintenance of Normothermia

The recommendations for the speed of rewarming and avoidance of hyperthermia after rewarming are still somewhat controversial. They are based on assumptions and observations from both laboratory research and clinical studies indicating a correlation between worse outcomes, markers of neuronal damage or dysfunction and damage in the setting of pyrexia [30–34]. However, some limited clinical data do not support the notion of slower rewarming resulting in improved neurologic outcomes [35]. The recommendation to rewarm at 0.25 °C per hour is based more on pre-clinical data and the concept that there are no significant gains from rapid rewarming and there may be some clinical benefit.

Neurologic Prognostication

The 2006 practice parameters of the American Academy of Neurology provide specific recommendations for the prognostication of neurologic outcomes for cardiac arrest survivors; however these recommendations are based mainly on dated observations from the pre-therapeutic hypothermia era. This practice parameter is endorsed by both the 2008 ILCOR [36] and the 2010 AHA guidelines for CPR and emergency cardiovascular care [7] for use in patients not treated with hypothermia. They also caution on its use in patients treated with hypothermia as available parameters are less reliable for predicting poor outcome in these cases, and waiting at least 72 h before making prognostication attempts is recommended. Delayed neurologic recovery beyond 72 h has been well documented [37, 38].

Traditionally the clinical exam was 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 false positive rate (FPR) of zero with a 95 % confidence interval (CI) of 0–3 for predicting a poor neurologic outcome. However, in the post therapeutic hypothermia setting, several studies have challenged the reliability of clinical testing [16, 39–41]. It was also common to equate the presence of post anoxic status myoclonus in the first 24 h 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 [16, 17].

Neuron specific enolase is the most commonly used and studied biomarker of brain injury for prognostication in the setting of hypoxic-ischemic encephalopathy. In the AAN guidelines, a NSE value >33 μg/L obtained within the first 72 h is assigned a FPR of zero with a CI of 0–3. Steffen et al. [42] have questioned the cutoff value in patients who have undergone hypothermia, where in order to have 100 % specificity the cutoff needed to be raised to 78.9 μg/L. They did however find a similar cutoff value to that quoted by the AAN guidelines for patients who were not treated with therapeutic hypothermia.

Electroencephalography (EEG) and SSEP are the most common electrophysiologic study modalities employed in neuroprognostication. EEG has been evaluated in the prognostication of cardiac arrest survivors [16, 43–45], and has also led to some important clinical discoveries and emerging data seems to support its growing utility [46]. 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. [47] pooled four existing studies [16, 43, 44, 48] on EEG in hypoxic-ischemic encephalopathy patients who had undergone therapeutic hypothermia and found that 29 % of these patients had acute electrographic non-convulsive status epilepticus (NCSE). This has important clinical repercussions and illustrates the need for continuous electroencephalographic (cEEG) monitoring of these patients until they recover consciousness, as aggressive antiepileptic treatment should be instated to avoid falling into self fulfilling prophecies equating NCSE to a poor outcome [49]. This is important, as 6 % of patients in Abend et al.'s [47] pooled sample recovered consciousness including several with minimal residual neurologic deficits.

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 cEEG by Cloostermans et al. [50] found EEG to be superior in terms of its sensitivity to predict poor neurologic outcomes in hypoxic-ischemic encephalopathy treated with therapeutic hypothermia. Leithner et al. [51] demonstrated that neurologic recovery is possible despite absent or minimally present median nerve N20 responses (>24 h) after cardiac arrest. In the study by Bouwes et al. [39], the absence of N20 responses on SSEP during the hypothermia therapy had a FPR of 3 %.

Imaging studies have also been employed for prognostication mainly in the form of brain computed tomography (CT) and Magnetic Resonance Imaging (MRI). The use of imaging has not yet been formally incorporated into any guidelines however, and has been used based on individual clinician practice. At this stage these tools simply can provide 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. With regards to a multi-modal prognostication algorithm, there is no clear international consensus regarding how to best implement such a process [52, 53]. At this time we recommend the use of a multimodal approach based on individual center experience, expertise and available resources taking into account the limitations of all existing methods.

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