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Management of Brain Injury After Resuscitation From Cardiac Arrest

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About 460,000 sudden cardiac deaths from a total of 728,743 cardiac-related deaths were reported in 1999 in the United States [1]. Thirty-six percent of the sudden deaths were in-hospital cardiac arrest and 64% were out-of-hospital arrest [1]. About 18% of patients survive to discharge following in-hospital cardiac arrest [2,3], whereas only 2% to 9% of patients who experience out-of-hospital cardiac arrest survive to discharge [4–6]. Functional outcomes of survivors are variable, but poor-quality survival is common [7], with only 3% to 7% able to return to their previous level of functioning [8]. The prevalence of coma or persistent vegetative state among survivors represents an enormous burden on patients, their families, health care personnel, and resources. The economic impact of cardiac arrest was the subject of a cost-effectiveness study that compared continuing versus withholding cardiopulmonary resuscitation (CPR) and ventilatory support after day 3. The estimated incremental cost of the more aggressive care strategy was $140,000 (1998 dollars) per quality adjusted life year (QALY) for high-risk patients (three to five risk factors, 93% 2-month mortality) and $87,000/QALY for low-risk patients (zero to two risk factors, 49% mortality) [9]. The economic burden of survivors of anoxic brain injury also is great, with in-patient rehabilitation lasting a mean of 41.5 days and costing $44,181 per patient [10].

The devastating neurologic injury that is caused by cardiac arrest has been recognized since the early development of modern resuscitation techniques. The persistence of unfavorable neurologic outcomes, despite advances in CPR, led the American Heart Association to recognize brain injury after cardiac arrest as an important area for clinical research. In its 2000 Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, the term “cardiopulmonary-cerebral resuscitation” was proposed to emphasize brain injury in relation to cardiac arrest [11]. After more than 2 decades of clinical trials failed to demonstrate benefit from a host of putative neuroprotective strategies, two clinical trials that were published in 2002 showed that induced mild hypothermia can ameliorate brain injury, improving survival and functional neurologic outcome in comatose survivors of out-of-hospital cardiac arrest. Comprehensive reviews on brain injury and cardiac arrest are available elsewhere [12,13]. This article is an update of a previous publication [14] and

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provides a focused review on the advances in the care of brain injury after cardiac arrest, highlighting therapeutic hypothermia as a treatment for global ischemic brain injury.

Mechanisms of neuronal injury after cardiac arrest

During total circulatory arrest, lack of cerebral oxygenation results in loss of ATP production and dysfunction of membrane ATP–dependent Na-K pumps. Subsequent loss of cellular integrity triggers the release of glutamate, which causes excitotoxic injury [15] that is mediated largely through N-methyl-D-aspartate (NMDA) receptors [16]. Other neurotransmitters that dampen the excitotoxicity of glutamate, such as glycine and g-aminobutyric acid (GABA), are decreased concomitantly [17]. Activation of NMDA receptors by glutamate leads to an influx of calcium into the intracellular space. Elevated intracellular calcium activates a series of second messengers, which amplifies injury by increasing calcium permeability and glutamate release [18]. Elevated intracellular calcium also increases oxygen-free radicals by interfering with the mitochondrial respiratory chain [18,19]. During re-perfusion, excitotoxicity can be enhanced by providing oxygen as a substrate for several enzymatic oxidation reactions that produce free radicals in the setting of mitochondrial dysfunction [20]. These reactive oxygen species are known to cause damage through lipid peroxidation, protein oxidation, and DNA fragmentation, all of which contribute to cell death [21]. The complexity of the injury cascade is not limited to the above processes. A more detailed description of the mechanisms of neuronal injury that are related to global ischemia is provided in several reviews [22–25]. This injury cascade begins with hypoxia and reperfusion, but it can continue for hours to days after the initial insult.

Numerous clinical studies have tested therapies that are directed at specific steps of the injury cascade, and have failed to show an outcome benefit [12,13]. Conversely, recent randomized trials demonstrate that therapeutic hypothermia is associated with improved survival and functional outcome following cardiac arrest. Although the mechanism underlying the neuroprotective effect of hypothermia is not fully understood, numerous hypotheses have been suggested [26]. The ability of hypothermia to affect multiple points of the injury cascade may contribute significantly to its success as an intervention. These effects include retarding the initial rate of ATP depletion [27,28], reducing excitotoxic neurotransmitter release [29], altering intracellular messenger activity [30], limiting breakdown of the blood–brain barrier [31], reducing inflammatory responses [32], altering gene expression and protein synthesis [33,34], reducing intracellular calcium, and changing glutamate receptor regulation [35].

Neurologic injury and clinical manifestations

Global cerebral ischemia during cardiac arrest results in heterogeneous injury to the brain. Large projection neurons of the cerebral cortex, cerebellar Purkinje cells, and the CA-1 area of the hippocampus are the most vulnerable areas [36]. The subcortical areas, such as the brainstem, thalamus, and hypothalamus, are more resistant to injury than the cortex [37,38]. If the thalamocortical complex or extensive bilateral cortical regions are injured, dysfunction in arousal and consciousness may result [39]. The impairment in arousal remains the most predominant neurologic problem during the early post-resuscitative period. A review on neuroanatomic and physiologic considerations of coma related to brain injury after cardiac arrest was recently published by Hoesch and colleagues in 2008 [40]. Other areas that are prone to ischemic injury include the basal ganglia and cerebellum, which account for movement disorders and dyscoordination that are seen often after cardiac arrest. The brainstem can tolerate a greater degree of global ischemia. This is manifested as preservation of cranial nerve and sensory motor reflexes. Significant impairment of the

cortex and thalamus with relative preservation of the brainstem results in vegetative and comatose states.

Neurologic evaluation

The clinical evaluation of survivors of cardiac arrest in this article focuses on patients who remain unresponsive or unable to follow verbal commands after return of spontaneous circulation (ROSC). With the exception of a few recent studies, all of these observations were made on patients who were not subjected to treatment with mild therapeutic hypothermia [41–45]. Because most cardiac arrest survivors do not receive therapeutic hypothermia, it is important to review the evaluation of the survivor who is not treated with hypothermia. A complete neurologic evaluation must be undertaken following ROSC. It is important to exclude factors that may obscure the neurologic examination, such as paralytic and sedative medications, illicit drugs used before arrest, ongoing cerebral hypoperfusion, seizures or postictal encephalopathy, electrolyte abnormalities, and metabolic derangements. The evaluation should assess mental status by documenting the patient's ability to arouse and interact meaningfully with the examiner. Evaluation of the brainstem includes the testing of cranial nerve function and reflexes, most importantly the pupillary light reflex, corneal reflex, grimacing to noxious stimulation, cough and gag reflexes, and the presence of spontaneous respirations. In a comatose patient, the motor and sensory examination relies on the evaluation of the patient's response to a noxious stimulus, which may be purposeful (warding off the stimulus), reflexive (extensor or flexor posturing), or absent. It is also helpful to note the autonomic responses such as respiratory pattern, temperature lability, and heart rate and blood pressure variability. Diagnostic tests may be performed to enhance the neurologic assessment of these patients. The diagnostic tests that have been studied best include electroencephalography (EEG), median nerve somatosensory evoked potentials (SSEPs), serum testing for elevated neuron-specific enolase, and neuroimaging [43]. Recently, the American Academy of Neurology published an evidence-based review and generated practice parameters on the prediction of poor outcome in comatose survivors of cardiac arrest [43]. The practice parameters defined specific indicators of poor outcome on bedside examination: absent pupillary light response and corneal reflexes and extensor or no motor response to pain after 3 days of observation (level A), and myoclonic status epilepticus (level B). Based on neuroelectrophysiologic testing, the bilateral absence of cortical responses (N20 potentials) on somatosensory evoked potential recordings 3 days after CPR also predicted poor outcome (level B). Serum neuron-specific enolase greater than 33 mg/L also was specific for poor outcome (level B). Neurologic prognosis cannot be determined by the circumstances of CPR alone. Although neuroimaging may be helpful in characterizing structural brain injury, its role in outcome prediction in cardiac arrest survivors remains uncertain [43]. Outcome prediction data have been shown to influence physicians and families' decision regarding withdrawal of life support in patients with poor outcome after resuscitation from cardiac arrest [46].

Neuroprotective trials after cardiac arrest

The landmark controlled clinical trials that primarily targeted brain injury after cardiac arrest span from the Brain Resuscitation Clinical Trial (BRCT) of barbiturates in 1986 [47] to the more recent trials of therapeutic hypothermia [48,49]. The barbiturate thiopental was the first agent used in a controlled clinical trial. Thiopental reduced metabolism, edema formation, intracranial pressure (ICP), seizure activity, and damage by focal and incomplete ischemia [47]. Although successful in a primate model of global ischemia [50] and successful pilot studies in humans [51], it failed to show a therapeutic benefit over placebo in the BRCT 1 trial [47]. The BRCT 1 trials also allowed for the addition of glucocorticoid treatment to the study agent (thiopental or placebo) at the discretion of the treating

physician. The glucocorticoid treatment doses did not show additional benefit [52]. A follow-up study (BRCT 2) found no benefit in the treatment with the calcium channel blocker lidoflazine [53]. Based on the observation that the nimodipine reduced death or severe ischemic deficits in subarachnoid hemorrhage, a clinical trial using nimodipine was conducted [54,55]. This study found no difference in mortality or other outcomes between nimodipine and placebo treatment at 1 year [54]. Following the observation by Longstreth and colleagues [56] that hyperglycemia was associated with poor recovery after cardiac arrest, a randomized controlled trial performed by the same group did not find an outcome difference between patients who were resuscitated with solutions that did (5% glucose) or did not (0.45% NaCl) contain glucose [56]. Another controlled clinical trial found no outcome benefit with intravenous magnesium, despite its antiarrhythmic effects and ability to block excitatory neurotransmitters [57]. A subsequent study that combined magnesium with diazepam, an inhibitor of neuroexcitotoxic injury, also reported outcomes that were not different from treatment with placebo [58]. Most of these agents showed preclinical benefit in animal models of focal and global ischemia or clinical benefit in human studies of other neurologic diseases. With the notable exception of induced hypothermia, none of these trials demonstrated significant neurologic or functional outcome benefit.

The failed clinical trials did provide critical insight into the epidemiology, pathophysiology, preclinical modeling, and clinical trial design that may have contributed to the success of recent trials in hypothermia.

Clinical trials in hypothermia and cardiac arrest

Induced hypothermia as a therapy for acute brain injury was described in the 1940s by Fay [59]. In 1950, Bigelow and colleagues [60] reported the usefulness of hypothermia during cardiac surgery. Over the following decade, Rosomoff [61] designed the landmark experimental models of therapeutic hypothermia in brain injury. In the 1980s, researchers in Pittsburgh [24,25] and Miami [26,62] approached induced hypothermia for brain injury after cardiac arrest in a more systematic manner. This led to extensive pre-clinical studies that showed functional and survival benefit in rodent [63,64] and canine models [65,66]. The first human clinical study on induced hypothermia for survivors of out-of hospital cardiac arrest was performed by Bernard and colleagues [67] in 1997. In this pilot safety and feasibility study, hypothermia was induced in 22 patients using surface cooling with ice packs and maintained for 12 hours in the ICU. In 1998, Yanagawa and colleagues [68] reported a study of 13 cardiac arrest survivors who were cooled to a target temperature of 33°C for 48 hours using cooling blankets and convective heat loss through alcohol evaporation. Both studies suggested a potential therapeutic benefit to hypothermia after cardiac arrest and paved the way for definitive trials.

Australian hypothermia study

The Australian study that was undertaken by Bernard and colleagues [49] enrolled comatose patients after successful resuscitation with an initial cardiac rhythm of ventricular fibrillation. This study randomly assigned 77 patients to receive hypothermia or normothermia using an alternating-day methodology. The hypothermia treatment arm included 43 patients and the normothermia arm had 34 patients. Paramedics in the field initiated early hypothermia by applying cold packs to the patients' head and torso. Upon arrival at the hospital, vigorous cooling was performed by application of ice packs around the head, neck, torso, and limbs to reduce the core temperature to 33°C, as monitored by a tympanic or bladder thermometer. The target temperature was maintained for 12 hours, and patients were sedated and paralyzed with repeated boluses of midazolam and vecuronium as needed to prevent shivering. The patients were actively rewarmed with a heated-air blanket beginning at 18 hours after arrival, with continued sedation and neuromuscular blockade to

suppress shivering. Similar sedation and paralysis protocols were provided to patients assigned to the normothermic group, but the target core temperature was maintained at 37°C. Passive rewarming was used in these patients if there was mild spontaneous hypothermia on arrival. The primary outcome measure was place of discharge: home, rehabilitation facility, or long-term nursing facility. Discharge to home or to a rehabilitation facility was regarded as a good outcome, whereas in-hospital mortality or discharge to a long-term nursing facility was regarded as a poor outcome. Neurologic outcome batteries were not analyzed as outcome measures. The study found that 21 (49%) of 43 patients who were treated with hypothermia had good outcomes compared with 9 (26%) of 34 patients in the normothermia group (relative risk [RR] of good outcome, 1.85; 95% confidence interval [CI], 0.97–3.49;). Mortality at discharge was 51% (22 of 43) in the hypothermia group and 68% (23 of 34) in the normothermia group (RR, 0.76; 95% CI, 0.52–1.10;).

European study: hypothermia after cardiac arrest

A larger, multicenter European study was conducted by the Hypothermia After Cardiac Arrest (HACA) group [48]. The study screened 3551 potential subjects and included 273. The study randomized patients to induced hypothermia beginning after arrival at the hospital versus standard normothermia after resuscitation. There were 137 patients in the hypothermia arm and 138 patients in the normothermia arm. Patients in the hypothermia group were cooled to a target temperature of 32°C to 34°C. Hypothermia was achieved using external cooling by a mattress and blanket that delivers cold air over the body. The goal was to reach the target temperature within 4 hours of resuscitation. Core temperature was monitored with a bladder thermometer and maintained within the target range for 24 hours. Patients were rewarmed passively over a period of 8 hours. Sedation with midazolam and paralysis with vecuronium were used to prevent temperature increases due to shivering. Seventy-five (55%) of the 136 patients in the hypothermia group had a favorable neurologic outcome at 6 months compared with 54 (39%) of 137 in the normothermia group (RR, 1.40; 95% CI, 1.08–1.81). At 6 months, there were 56 deaths among the 137 participants (41%) in the hypothermia group and 76 death among the 138 patients (55%) in the normothermia group (RR, 0.74; 95% CI, 0.58–0.95).

Following these two studies, the International Liaison Committee on Resuscitation (ILCOR) and the American Heart Association published an interim scientific statement with recommendations on the use of therapeutic hypothermia in comatose survivors of cardiac arrest [69]. This was followed, in 2005, by the American Heart Association Guidelines for CPR and Emergency Cardiovascular Care, which included the following treatment recommendations [70,71]: Unconscious adult patients resuscitated after out-of-hospital cardiac arrest should be cooled to 32°C to 34°C (89.6°F–93.2°F) for 12 to 24 hours when the initial rhythm was ventricular fibrillation (Class IIa) 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).

Clinical impact of therapeutic hypothermia

To further assess the impact of hypothermia on neurologic outcomes, a systematic review of hypothermia for neuroprotection after cardiac arrest was undertaken by Holzer and colleagues [72]. This review evaluated three controlled clinical trials of adult cardiac arrest survivors who were treated with hypothermia within 6 hours of arrival at the emergency department. In addition to the study by Bernard and colleagues [49] and the HACA trial [48], a feasibility study by Hachimi-Idrissi and colleagues [73] was included. This study included 30 comatose cardiac arrest survivors with initial rhythms of asystole and pulseless electrical activity who were randomized to a target bladder temperature of 34°C for a maximum of 4 hours using a helmet device containing an aqueous glycerol solution. The

meta-analysis of the three studies, using an intention-to-treat methodology, determined that favorable neurologic recovery occurred more often in the hypothermia groups (RR, 1.68; 95% CI, 1.29–2.07) [72]. This observation translates into a number needed to treat of 6 patients, even after controlling for several variables, such as age, gender, arrest duration, CPR time, and CPR technique. In 2006, a meta-analysis by Cheung and colleagues [74] added another study to the three studies above for a total of 436 patients, with 232 cooled to a core temperature of 32°C to 34°C. Their analysis showed that mild hypothermia decreased in-hospital mortality (relative risk [RR] 0.75; 95% CI, 0.62–0.92) and reduced the incidence of unfavorable neurologic outcome (RR 0.74; 95% CI, 0.62–0.84). This shows that the numbers needed to treat were 7 patients to save 1 life, and 5 patients to improve neurologic outcome. They did not find evidence of treatment-limiting side effects.

Post-clinical trial experience

After the completion of the therapeutic hypothermia trial in Europe, the European Resuscitation Council Hypothermia After Cardiac Arrest Registry (ERC HACA-R) was formed to monitor developments in medical practice after the ILCOR recommendations on hypothermia in cardiac arrest were published [75]. Data on 650 cardiac arrest patients with successful restoration of spontaneous circulation from 19 sites within Europe were entered between March 2003 and June 2005. The decision to cool patients was made by the treating physicians in 462 (79%) of patients. The method of cooling in 347 (59%) was by an endovascular device, and in 114 (19%) was by other methods such as ice packs, cooling blankets, and cold fluids. The beneficial effects of hypothermia in the clinical trials were reflected in this registry result. Of those that had unfavorable outcome, 55% were in the hypothermia-treated group compared with 68% of the non–hypothermia-treated group ($P = .02$). Of those who died during the hospital stay, 43% were in the hypothermia-treated group compared with 68% of the non–hypothermia-treated group ($P < .001$). The adverse events reported were minimal with 15 (3%) episodes of hemorrhage and 28 patients (6%) with 1 episode of arrhythmia within 7 days after cooling. No fatalities as a result of cooling were reported [75]. This registry data show that therapeutic hypothermia is feasible and can be used safely and effectively outside a randomized clinical trial.

Timing of cooling and rewarming

The best time to initiate hypothermia after resuscitation and the optimal duration of hypothermia have not been defined. It is reasonable to believe that the benefits may be maximized if hypothermia is initiated as soon as possible after resuscitation. In the European study, the interval between resuscitation and attainment of target temperature had an interquartile range of 4 to 16 hours, with a mean of approximately 8 hours [48,69,76]. Despite some delay, hypothermia still provided benefit. Rewarming should be undertaken slowly to avoid worsening neurologic injury, sudden vasodilatation, and shock [77,78]. The European study rewarmed patients passively over 8 hours after 24 hours of hypothermia, whereas the Australian study reported active rewarming for 6 hours using a heated-air blanket, beginning 18 hours after ROSC [48,49]. Preclinical studies have shown that delayed cooling negates the beneficial effect of hypothermia [79], and its beneficial effects may be enhanced even if it is initiated during the intra-arrest or resuscitation period [80,81] or immediately after return of spontaneous circulation [82]. There is a need to translate this preclinical research into human studies to help determine the optimal onset and duration of therapeutic hypothermia, and rates of cooling and rewarming.

Complications of hypothermia

Potential complications of mild induced hypothermia include renal insufficiency, bleeding, sepsis, and pancreatitis; however, these complications have been seen in control groups. The

study by Bernard and colleagues [49] and the HACA group [48] reported no statistically significant difference in complications between groups. In the HACA study, there was a trend toward increased bleeding and sepsis in the hypothermia group, but this was not statistically significant. In the study by Bernard and colleagues [49], the hypothermia group had a trend toward lower cardiac index, higher systemic vascular resistance, and more hyperglycemia. The proportion of patients with any complication was high in both groups: 70% in the normothermia group and 73% in the hypothermia group. Relative hypokalemia and metabolic acidosis are other potential metabolic derangements that are associated with hypothermia [83]. Close monitoring and appropriate correction of these conditions is important, with the understanding that potassium increases the rewarming phase as it shifts to the extracellular space. From a neurologic perspective, seizures have been noted in normothermia and hypothermia-treated patients, and likely are secondary to the global ischemic injury that was sustained during the cardiac arrest and reperfusion [84,85]. It is advisable to have a low threshold for performing an electroencephalogram (EEG) on patients who are suspected to be seizing, especially those who are paralyzed or heavily sedated, because this can mask the clinical manifestation.

The effect of therapeutic hypothermia on cognitive functioning and neurophysiological outcome was also recently studied in a subset of patient in the HACA study [48,86]. In this cohort, neuropsychological examination was performed in 45 of the 47 conscious survivors of CA (27 in hypothermia and 18 in normothermia group) 3 months after the injury. The investigators found no differences in demographic variables, depression, or delays related to the resuscitation. They also found no differences in any of the cognitive functions tested; with 67% of patients in hypothermia and 44% patients in normothermia group were cognitively intact or had only very mild impairment. Severe cognitive deficits were found in 15% with hypothermia and 28% with normothermia [86]. This study shows that that use of therapeutic hypothermia was not associated with cognitive decline or neurophysiological deficits in this subset of patients studied.

Management of shivering

Shivering in response to hypothermia may cause significant disruption of therapy by heat generation leading to an increase in core temperature and increased oxygen consumption [69,76]. Shivering is most prominent during induction; therefore, more attention needs to be provided on the use of sedatives and paralytics during this period. The European and Australian studies used vecuronium as a paralytic agent and intravenous midazolam for sedation [48,49]. The use of sedation and paralysis requires full mechanical ventilatory support; however, these patients are comatose and likely require this level of ventilatory assistance anyway. A detailed neurologic evaluation is essential before initiation of paralysis and sedation, and it should be repeated once the drugs have been discontinued, remembering that patients will clear these agents in variable timeframes. Although no comparison studies exist that formally compared the degree of shivering with the different methods of inducing hypothermia, more patients have been noted to shiver with rapid surface cooling systems [87]. Other agents that have been effective in controlling shivering are meperidine [88–90] and buspirone, which has synergistic properties with meperidine; however, the side-effect profile of the latter drug makes it a poor candidate for use in neurologically impaired patients [91]. In another study the combination of dexmedetomidine and meperidine was also shown to reduce the shivering threshold [92].

Methods of achieving hypothermia

Cooling can be achieved externally or internally, and methods vary from simple techniques using ice bags and iced lavage, to devices that are designed specifically to induce, maintain,

and reverse hypothermia. The technologies used to induce therapeutic hypothermia were recently reviewed [93]. The technologies include various surface cooling devices and intravascular cooling catheters. The surface cooling devices can be divided into selective regional brain cooling and generalized cooling that involves most of the body with a systemic temperature response. Some studies have been undertaken comparing the effectiveness of newer technologies to standard surface cooling. One prospective study comparing a specialized pad for surface cooling [94] and another retrospective study using endovascular cooling catheter [95] found significant stability at maintaining temperature within therapeutic range. Both studies, however, did not provide definite faster cooling rate compared with standard surface cooling. In the absence of definitive studies showing the best method of inducing hypothermia, the decision on the means of cooling is dependent on the treating team. Factors to consider in relation to the technology are the following: the place where hypothermia is initiated (in the field, emergency department, or intensive care unit [ICU]), the capacity of first responders to initiate hypothermia, the rapidity of induction and stability of temperature during treatment, the ability to control rewarming, the portability of the device, specific adverse effects, whether the device hampers provision of care in the critical care environment, and cost.

The ability of infused cold intravenous solutions to decrease core temperature provides another opportunity to induce hypothermia. Several studies have shown the feasibility and safety of cold fluid infusions to reduce core temperature after resuscitation from cardiac arrest. Bernard and colleagues [96] infused 30 mL/kg of ice-cold (4°C) Ringer's lactate solution to cardiac arrest survivors, with a reduction in median core temperature from 35.5°C to 33.8°C. The investigators reported no hemodynamic, renal, or acid-base complications. No patient developed pulmonary edema. Kim and colleagues [97] showed that an infusion of 2 L of normal saline at 4°C to 17 survivors of out-of-hospital cardiac arrest was safe and effective in decreasing body temperature rapidly by 1.4°C within 30 minutes after the initiation of infusion. This rapid infusion did not affect ejection fraction or increase central venous pressure, pulmonary pressures, or left atrial filling pressures. Intravenous infusion of cold saline is effective in decreasing core temperature, but is not as effective in maintaining it over time; thus, a secondary method to maintain hypothermia is needed. A study of 134 patients by Polderman and colleagues [98] examined the combined effect of a water-circulating cooling blanket and intravenous infusion of 2.3 L (mean) of 4°C saline over 50 minutes. They noted a mean reduction of core temperature from 36.9°C at baseline to 32.9°C at 1 hour. This study showed that induction and maintenance of hypothermia by means of combined cold-fluid infusion and ice-water cooling blankets is quick, safe, and efficacious.

Therapeutic hypothermia and neurologic prognostication

The recent practice parameters that were issued by the American Academy of Neurology focused on predictors of poor outcome in patients who were not treated with hypothermia [43]. Although this publication is an important synthesis clarification, critical aspects in the care of these patients remain unresolved. What is the best way to assess brain injury during the early period when it may still be amenable to treatment with hypothermia? Are there neurologic parameters that can identify which patients are most likely to benefit from therapy? Do the prognostic indicators discussed in the practice parameter apply to patients who are treated with hypothermia? For patients who were treated with hypothermia, the existing studies of prognostic indicators have focused on biochemical markers and evoked potentials. A substudy of the HACA trial compared two serum markers, neuron-specific enolase (NSE) and S-100b, in 34 hypothermic and 32 normothermic patients after cardiac arrest [99]. NSE is an enzyme specific to neurons and neuroectodermal cells that is not ordinarily found in serum; it has a half-life of approximately 24 hours. The S-100b protein is

a calcium-binding protein that is found predominantly is astroglia and Schwann cells; it has a serum half-life of approximately 0.5 hours. The investigators reported that the NSE concentration was lower in hypothermia-treated patients, but there was no difference in S-100b levels. Survival, recovery of consciousness, and good outcome correlated significantly with decreasing levels of NSE between 24 and 48 hours. Although the investigators identified cut-off values for NSE concentrations that were predictive of poor outcomes, these values differed significantly between the hypothermia and normothermia groups [99].

The effects of hypothermia on SSEPs were studied previously in patients who did not experience cardiac arrest, because SSEP is used often for intra-operative monitoring of patients who are treated with hypothermia during neurosurgical procedures [72]. The median nerve cortical (N20) potential amplitude is unaffected, but the latency is prolonged, in hypothermic patients compared with normothermic patients. A substudy of the European HACA trial examined the prognostic accuracy of SSEPs in 57 patients 24 to 28 hours after cardiac arrest [100]. Thirty patients were treated with hypothermia, and the N20 latency was prolonged in all of these patients. Eleven patients had absent N20 responses (3 hypothermic and 8 normothermic patients), none of which regained consciousness. Despite the small number of patients, this study suggests that SSEP performed 24 to 28 hours after cardiac arrest retains specificity for poor outcomes, even in hypothermic patients [100]. The ability to predict poor outcome after therapeutic hypothermia using SSEPs needs to be confirmed in a larger, prospectively designed study.

Enhancing neuromonitoring in cardiac arrest survivors

Therapeutic hypothermia demonstrates that brain injury after cardiac arrest can be ameliorated. The implementation of hypothermia as a brain-directed therapy might be slowed by the unavailability of a readily interpretable bedside real-time brain function monitor. The temperature reduction provided empirically is monitored from the bladder or the heart; the actual effect on the brain as the target organ is not monitored directly. This is a stark contrast to the availability and ease of interpretation of cardiac function using ECG, or pulmonary function using the pulse oximetry in the ICU. While available, bedside neurologic tests, such as the EEG and SSEP, are limited to centers with specialized neuroelectrophysiologic expertise. The importance of brain injury and the need to interpret these tests properly necessitates a closed collaboration with a neurointensivist or neurologists. To truly advance the care of these patients, technologies need to be developed to allow the non-neurologists and other health workers to evaluate the evolution of brain injury. Therefore, SSEP and EEG technologies need to be simplified, automated, and quantified in a manner that is easily interpretable. Recently, the ability of quantitative EEG to track the brain recovery with hypothermia therapy has been investigated in animal studies [101,102] and in humans [103–105]. Continued research is required to determine whether other prognostic indicators retain accuracy in patients who are treated with hypothermia. Recently, much interest has centered on SSEPs to prognosticate in normothermia- and hypothermia-treated patients after cardiac arrest, and suggest the need to adapt and simplify this technology for wider application.

Other neuroprotective measures in the ICU

Cerebral perfusion

Hypotension after ROSC can worsen cerebral ischemia, and it should be avoided [70]. Microvascular dysfunction and autoregulatory failure are the two main factors that impair cerebral perfusion after cardiac arrest. The identification of cerebral microvascular thrombi following cardiac arrest has suggested the possibility of benefit from thrombolytic therapy,

and this has been tested in clinical trials [106,107]. Cerebral perfusion can be compromised further by altered autoregulation of the cerebral vasculature, which has been described as absent or right-shifted in the acute phase in many survivors of cardiac arrest [108]. The clinical implication of this finding is that a patient's mean arterial blood pressure (MAP) may need to be maintained at higher levels to ensure adequate cerebral blood flow [108]. Notwithstanding, there are little data to suggest an optimal blood pressure goal to maintain cerebral perfusion following cardiac arrest. One study indicated that a MAP of greater than 65 mm Hg, which may support adequate coronary perfusion, probably is not sufficient to provide adequate blood supply to the brain, unless other therapies that are designed to decrease cerebral metabolic demand are implemented (eg, sedation, hypothermia) [108]. A MAP of 80 to 100 mm Hg has been suggested to be beneficial, at least for the first 24 hours after arrest [109].

Cerebral edema and increased intracranial pressure

Usually, ICP is not elevated after cardiac arrest [110], but high ICP can compromise cerebral blood flow, and cerebral herniation can cause structural brain damage and death. In comatose patients with evidence of increased ICP, such as clinical signs of herniation or cerebral edema on CT scan, ICP monitoring may be helpful to guide therapies for optimization of ICP and cerebral perfusion pressure [111]. Hypoxia, hypotension, and hypercapnia can worsen brain damage and should be avoided [70]. In the absence of ongoing ICP elevation, prophylactic and long-standing hyperventilation aggravated a wide range of brain injury [70,112]. Therefore, it is suggested that comatose patients be mechanically ventilated to achieve normocapnia [70].

Fever management

Fever may worsen secondary brain damage after cardiac arrest. Each degree over 37°C was correlated with an increased risk for severe disability, coma, or persistent vegetative state [113]. Evidence that temperature elevation worsens outcome makes the need to provide therapeutic hypothermia after cardiac arrest even more significant. In patients who are not deemed candidates for therapeutic hypothermia as a cerebral protective mechanism, antipyretics and surface or invasive cooling measures should be used aggressively to ensure that the body temperature is less than 38°C.

Hyperglycemia management

Hyperglycemia after ischemic brain injury has been associated with worse outcome [56,114]. Recent studies have shown that tight glucose control in critically ill patients can lead to better outcome [115]. A recent study found a strong association between blood glucose levels at 12 hours after restoration of spontaneous circulation and neurologic recovery over 6 months (Losert and colleagues, 2008 [116]). The favorable neurologic outcome was noted not only in the glucose range of 67 to 115 mg/dL, but also in those with blood glucose levels from 116 to 143 mg/dL [116]. As more clinical trials are needed to clarify the impact of glucose control, it is important to recognize the detrimental effect of hypoglycemia as we control blood glucose levels in cardiac arrest survivors.

Seizure control

Seizures and myoclonus are common after cardiac arrest [117] and the occurrence of status epilepticus is a strong predictor of death [118]. Seizures can be detrimental to recovering brain because of the increased cerebral metabolic demand and elevated ICP. Seizures also can slow recovery of consciousness after resuscitation. Prophylactic antiepileptic drugs are not used commonly; however, if a patient develops seizure activity, it should be treated with standard antiepileptic medications [117]. An EEG should be performed on any patient who

is suspected of having seizures, and it should be considered if the patient fails to regain consciousness after resuscitation to rule out nonconvulsive status epilepticus.

Summary

Brain injury continues to be the leading cause of disability after cardiac arrest, despite seminal advances in intensive care and cardiovascular therapy over the past several decades. Care of these patients can be challenging, and it requires a great deal of medical resources and expense. In addition, dozens of clinical trials of neuroprotective strategies that showed promise in preclinical studies have yielded disappointing results in clinical trials. The emergence of therapeutic hypothermia as a successful neuroprotective measure in comatose survivors of ventricular fibrillation arrest demonstrating benefit in survival and functional outcome measures has created renewed enthusiasm for the amelioration of brain injury in these patients. Several challenges and uncertainties persist about therapeutic hypothermia, including basic understanding of mechanisms of benefit, the optimal depth of hypothermia, timing of initiation of therapy, treatment duration, the best mechanism for achieving hypothermia (internal or external cooling), and the availability of a bedside indicator of brain response to hypothermia. These questions need to be answered by larger series of clinical trials and registry-reported data. Implementation of the American Heart Association and ILCOR recommendations to initiate hypothermia as soon as possible after resuscitation from out-of-hospital ventricular fibrillation arrest has been slow, even in academic medical centers. With a number needed to treat of around six to achieve survival and functional benefits, hypothermia is proving to be an extremely robust and important therapy for cardiac arrest survivors. Hospitals must prioritize establishing hypothermia protocols and systems to improve compliance with treatment recommendations.

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