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Emergency Neurological Life Support: Resuscitation Following Cardiac Arrest

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Abstract Cardiac arrest is the most common cause of death in North America. An organized bundle of neurocritical care interventions can improve chances of survival and neurological recovery in patients who are successfully resuscitated from cardiac arrest. Therefore, resuscitation following cardiac arrest was chosen as an Emergency Neurological Life Support protocol. Key aspects of successful early post-arrest management include: prevention of secondary brain injury; identification of treatable causes of arrest in need of emergent intervention; and, delayed neurological prognostication. Secondary brain injury can be attenuated through targeted temperature management (TTM), avoidance of hypoxia and hypotension, avoidance of hyperoxia, hyperventilation or hypoventilation, and treatment of seizures. Most patients remaining comatose after resuscitation from cardiac arrest should undergo TTM. Treatable precipitants of arrest that require emergent intervention include, but are not limited to, acute coronary syndrome, intracranial hemorrhage, pulmonary embolism and major trauma. Accurate neurological prognostication is generally not appropriate for several days after cardiac arrest, so early aggressive care should never be limited based on perceived poor neurological prognosis.

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Introduction

Cardiac arrest (CA) is the most common cause of death in both North America and throughout the developed world [1]. In the United States (US), more than 500,000 patients suffer a cardiac arrest each year [2]. With advances in prehospital care, rates of return of spontaneous circulation (ROSC) are improving, and more than 60,000 patients are treated in US hospitals each year after resuscitation from cardiac arrest [2]. This has resulted in significant improvements in the rates of long-term survival with good neurological outcomes. Many studies now report survival rates of $>50\%$ in patients with witnessed CA and an initial rhythm of pulseless ventricular tachycardia/ventricular fibrillation (VT/VF) [3]. Among those who survive to hospital treatment after cardiac arrest, withdrawal of life-sustaining therapy, based on perceived neurological prognosis, is the most common proximate cause of death [4].

The Emergency Neurological Life Support (ENLS) algorithm for the initial management of resuscitation following cardiac arrest is shown in Fig. 1. Suggested items to complete within the first hour of resuscitation following cardiac arrest are shown in Table 1.

Immediate Stabilization and Triage

Rearrest is common in the first minutes after resuscitation from cardiac arrest, occurring in about 1 in 5 cases [5, 6]. Hypotension and hypoxia are also common, and associated

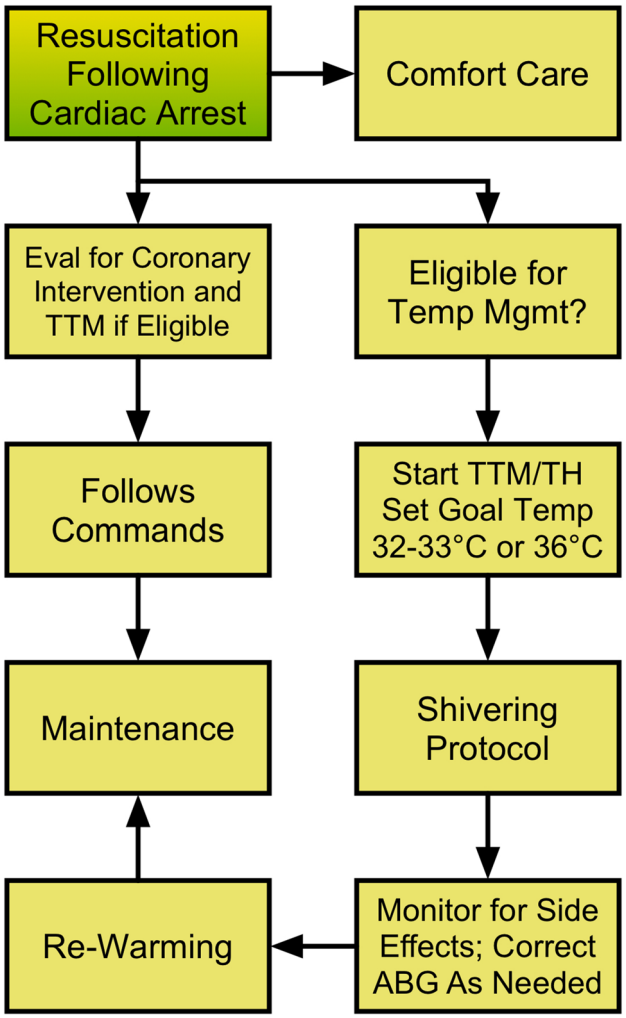

Fig. 1 ENLS resuscitation following cardiac arrest protocol

with worse outcomes [7]. Patients resuscitated from cardiac arrest require intubation, mechanical ventilation, close cardiac and hemodynamic monitoring, and attentive general critical care. Post-arrest patients cared for at high-volume centers have improved short- and long-term outcomes. After initial stabilization, transfer to a specialty center may be reasonable [8–10].

Prevention of Secondary Brain Injury

Active Temperature Management and Induction of Hypothermia

Targeted temperature management (TTM) results in substantially improved outcomes after cardiac arrest when implemented with a well-defined post-arrest bundle of car [11–14]. Reducing core body temperature decreases cerebral oxygen demand and attenuates multiple cellular pathways involved in ongoing brain injury in the hours and days after cardiac arrest [15, 16]. Clinical trials first demonstrated improved survival and neurological outcomes with induced hypothermia to a core temperature of 32–34 °C in selected patients resuscitated from out-of-hospital cardiac arrest (OHCA) due to ventricular tachycardia or fibrillation (VT/VF) [11, 12]. Subsequent work has shown that overall outcomes are equivalent when mild hypothermia actively targeting a core temperature of 36 °C rather than 33 °C is chosen [17]. These findings and their implications for current practice continue to be hotly debated [3, 18, 19]. A recently published study reported a trend to worsening outcomes after switching target temperature from 33 to 36 °C, possibly due to more difficulties in maintaining a target temperature of 36 °C as a result of a more pronounced shivering response in this temperature range [80].

An in-depth discussion of the pros and cons of each target temperature is beyond the scope of this article, and the reader is referred elsewhere for a more detailed discussion of these issues [3, 18–20]. Patients with asystolic and pulseless electrical activity (PEA) arrest may also derive some benefit from TTM, although the level of evidence for these populations is much lower [21]. It is important to note that 36 °C is *not* normothermia and that in the absence of active TTM, most post-arrest patients will develop fevers early after resuscitation [12]. Regardless of whether 36 °C or a lower target temperature is selected, TTM requires active temperature management, shivering prevention, and a comprehensive bundle of care. Developing systems to safely and effectively deliver TTM

Table 1 Resuscitation following cardiac arrest checklist for the first hour

Checklist
☐ Initiate hemodynamic and ventilator support
☐ Perform electrocardiogram, consider common treatable causes of arrest
☐ Assess eligibility for targeted temperature management
☐ Begin induction to target temperature
☐ Start anti-shivering regimen

requires significant institutional support, particularly to ensure that intervention is continuously available [13, 22].

Considerations: When TTM is Not Required

There are few absolute contraindications to TTM. Patients that rapidly awaken after cardiac arrest (e.g., they able to follow verbal commands such as "wiggle your toes," and "squeeze my fingers") are unlikely to derive benefit (Fig. 1). Similarly, patients with do not resuscitate (DNR) orders, contra-indications for intensive care unit (ICU) admission, or preexisting illnesses that preclude meaningful recovery should have discussions with family or proxies regarding goals of care early in the hospital course. Some of these patients will move directly to comfort care. Finally, patients who are more than 12 h after cardiac arrest are less likely to benefit from TTM [21, 23, 24].

Eligibility: When is Targeting 36 °C Preferable to 33 °C?

Because significant hypothermia may potentiate coagulopathy and surgical bleeding, findings of intracranial bleeding, a traumatic etiology of cardiac arrest, or anticipated hemorrhagic diathesis should prompt a multidisciplinary risk-benefit discussion. Since ultra-mild hypothermia targeting 36 °C does not affect coagulation ability, TTM to 36 °C is probably advisable in these patients.

Patients with known cold agglutinins have a potential contra-indication to TH. The key considerations are that these proteins generally aggregate below 31 °C and temperature in the distal extremities may reach this level with surface cooling. It may be preferable to use intravascular devices to maintain temperature in these patients. Warming the extremities during TTM should also be considered. The need for acute coronary revascularization is not a contraindication for TTM and TTM can be initiated prior to or during percutaneous coronary intervention. There is some evidence that having a lower core temperature at the moment of coronary reperfusion can mitigate myocardial reperfusion injury [81, 82].

Induction of TTM

After reviewing the contraindications discussed above, eligible patients should undergo immediate TTM. All patients should be intubated at this point. Core temperature monitoring is also required. The route of temperature monitoring in approximate order of preference is endovascular, esophageal, and bladder or rectal. Axillary, oral, tympanic, and temporal temperature monitoring are unreliable during TTM [25–27].

In patients with a goal core temperature of 32–33 °C, rapid induction of TTM is best accomplished by combining several cooling induction methods. In patients without significant left ventricular heart failure, pressure bag infusion of up to 40 mL/kg of cold (4 °C) saline or Ringers lactate decreases the core body temperature by approximately 1 °C for each liter of fluid administered [26, 28–30]. Some facilities keep saline in refrigerators for this purpose [13, 22]. Fluid should be infused as rapidly as possible. This can be achieved by using a pressure bag to ensure that the fluid does not re-warm during infusion. Of note, two recently published trials have found that prehospital administration of cold fluids may be associated with increased risk of pulmonary edema and re-arrest in the field [31, 83]. Such complications may be better managed when the patient is in the emergency department or ICU, and administration of cold fluids may be held until the airway is secure and the patient is in the hospital.

If TTM to 36 °C is the goal, additional efforts may not be required to achieve this temperature. Many patients are mildly hypothermic following resuscitation from cardiac arrest, thus maintaining this temperature may be all that is required [20, 28, 32]. Regardless of target temperature, sedation and management of shivering are required for successful induction (see below). In fact, the shivering response is likely to be more pronounced because the patients' thermoregulatory defenses, which are partly suppressed at 32–33 °C, will be much more active at 36 °C [15, 26].

Targeted temperature management can be achieved using surface or intravascular cooling. For patients requiring extracorporeal membrane oxygenation therapy, body temperature may be strategically managed through this process. Automated surface or intravascular cooling should be started concurrently with IV fluid administration or as soon as possible thereafter. Multiple commercially available devices are available. Important features of any device are good contact to ensure adequate heat exchange (a simple cooling blanket is seldom sufficient) and continuous input of the patient's core temperature to ensure temperature remains within range. Limited information is available regarding comparison of surface and intravascular cooling methods. One randomized clinical trial found better temperature control and a trend to improved outcome in patients treated with endovascular cooling compared with surface cooling. However, the surface cooling methods in the study were comparatively primitive [84]. Two retrospective studies found similar trends but no significant differences in outcome [33, 85]. It may be the precision and efficacy of temperature control rather than the precise cooling method that affects outcome [85]. Some surface cooling and intravascular devices permit a choice of the goal temperature and the speed of cooling. During

induction, the device should be set for the goal temperature and maximal rate of cooling. Rapid induction to goal temperature is the current practice, but there are no studies that have investigated the potential survival benefit with earlier achievement of goal temperature.

Many patients shiver vigorously during cooling induction because the shivering response is maximal at temperatures of approximately 35 °C [15]. This problem is pronounced with lack of inadequate sedation (see below). Skin counter warming using an air warming blanket should be applied in all patients treated with TTM, even if surface cooling methods are used to induce hypothermia [15, 26, 85]. Bolus doses of fentanyl (50–100 mcg), meperidine (12.5–25 mg), magnesium (4–6 g), midazolam (2–5 mg IV), or diazepam (10–20 mg IV) will decrease shivering during induction [15, 26, 34]. A single dose of short-acting neuromuscular blockade can be helpful in cases of refractory shivering occurring in patients who are already maximally sedated. More details on drug dosing to prevent shivering can be found in the ENLS manuscript on pharmacology.

Sedation and Shivering

Sedation is a requirement for the induction and maintenance of goal temperature in post-cardiac arrest patients. Inadequate sedation that allows the breakthrough of shivering is the most common cause of failure to achieve or maintain goal temperature. Thus, the possibility of inadequate sedation should be a primary consideration if the goal temperature is not achieved or maintained. One potential method for suppressing shivering is outlined in Fig. 1 of the Pharmacology ENLS chapter, but each clinician and facility may have individual preferences for sedative and analgesic agents. The properties of the most commonly employed medications used during TTM are outlined in Table 11 of that article.

While adequate sedation may be provided by buspirone, meperidine, dexmedetomidine, or fentanyl, the primary purpose of these agents is to prevent shivering. If the patient is hemodynamically stable, propofol is effective for insuring adequate sedation, and allows for meaningful serial neurologic examinations due to its short half-life [35]. In patients without significant bradycardia, dexmedetominidine is an alternative, and directly lowers the shivering threshold via central alpha-2 agonism [36]. In hemodynamically unstable patients, a midazolam infusion may be used. However, the half-life of midazolam is prolonged by hypothermia and residual sedation may reduce the accuracy of the neurologic examination [37]. Therefore, during TTM, low continuous infusions of midazolam supplemented with bolus doses are preferred. Morphine should not be used because of prolonged time to onset and risk of hypotension [26].

Neuromuscular blockade may be used to abate otherwise refractory shivering. However, this results in a number of drawbacks, such as obscuration of convulsive activity that is typically detected by the neurological evaluation. The incidence of non-convulsive status epilepticus in the comatose post-arrest patient has been found to range from 12–24% [38–40], and even higher incidence has been reported in pediatric cardiac arrest [41]. Of note, seizures following cardiac arrest are linked to increased mortality [38–40]. Therefore, continuous EEG should be utilized in comatose post-arrest patients, especially if paralysis is used [42].

Skin counter-warming (i.e., warming of the non-cooled areas of the skin with a warm air blanket) markedly reduces the shivering response and should be considered, even when surface cooling methods are used [26, 43, 44].

Key Physiological Changes Induced by Hypothermia

Hypothermia produces a number of predictable, dose-dependent physiological changes. A detailed discussion of these effects is outside the scope of this manuscript, and has been well reviewed elsewhere [15]. Instead, we focus briefly on selected physiological changes particularly relevant to the first hours of neurocritical care.

One expected physiologic change that occurs during hypothermia is bradycardia. A heart rate of 34–40 beats per minute is common at goal temperature and generally does not warrant therapy unless associated with hypotension [15]. Indeed, hypothermia-induced bradycardia may be associated with improved outcomes [86]. Hypothermia-induced bradycardia is generally accompanied by an increase in stroke volume, so cardiac output is maintained. Atropine is generally ineffective in hypothermia-induced bradycardia. Instead, symptomatic bradycardia may be treated with beta agonists [15].

Arrhythmias may develop if the core temperature decreases below 28 °C (30 °C if electrolyte disorders are present). Should significant arrhythmia develop with a core temperature less than 30 °C, the patient should be re-warmed rapidly to a core temperature greater than 30 °C, followed by gradual warming to goal temperature. Arrhythmias should not be viewed as a reason to discontinue treatment, as mild hypothermia (greater than 30 °C) does not cause or worsen arrhythmias. QT prolongation is common during TH, and concomitant QT prolonging drugs should be used with caution [15].

During induction of hypothermia, an initial cold diuresis may result in hypokalemia, hypomagnesaemia, and

hypophosphatemia. Moreover, hypothermia shifts potassium from the extracellular to intracellular space. Frequent assessment of electrolytes and repletion are indicated. However, overly aggressive repletion of potassium should be avoided since serum potassium levels will predictably rise when rewarming is initiated. A goal potassium level of 4.0 mmol/L is reasonable, and magnesium and phosphorus should be maintained in the high—normal range.

Seizure Prevention

EEG monitoring is indicated in the comatose post-arrest patient [40]. The incidence of non-convulsive status epilepticus (SE) ranges from 12–24% in adults and up to 47% in pediatric cardiac arrest [38–41]. Other abnormal EEG patterns are found in up to 40% of patients and may be amenable to early, aggressive therapy [38]. Seizures may directly worsen brain injury, and should be treated. More details can be found in the ENLS chapter on SE.

Hemodynamic Management

After return of spontaneous circulation, protracted cerebral hypoperfusion develops within hours and lasts hours to days [45–48]. During this time, cerebral vascular resistance is increased and pressure autoregulation is right-shifted or absent, resulting in decreased blood flow oxygen delivery, and increased perfusion pressure needed to sustain microvascular flow [48–51]. Observational studies show a consistent association between lower post-arrest blood pressure and mortality [7, 52]. Moreover, augmenting systemic blood pressure to a goal mean arterial pressure (MAP) >80 mmHg is associated with improved outcomes, even if achieved at the expense of vasopressor dependence [14, 52–54]. Transient left ventricular systolic and diastolic dysfunction early after ROSC is also common, but may be less clinically significant and can usually be managed conservatively [55–57].

Pulmonary Management

Comatose post-arrest patients should be intubated and mechanically ventilated. Although cerebral pressure autoregulation may be impaired after resuscitation, response to carbon dioxide (CO_2) usually remains intact. Hyperventilation may result in cerebral vasoconstriction and inadequate blood flow, and a Phase II randomized controlled trial showed better outcomes when a $PaCO_2$ of 50–55 mmHg was targeted [58]. Although there is insufficient evidence to recommend routine use of mild hypercapnea after cardiac arrest, hyperventilation should be avoided. Targeting a temperature-corrected PaCO2 $\geq$40 mmHg is reasonable.

Both hypoxia and hyperoxia have been independently linked to adverse outcome after cardiac arrest, presumably because of inadequate cerebral oxygen delivery and oxidative stress, respectively [7, 59, 60]. Both should be avoided, and a temperature-corrected PaO2 of 80–120 mmHg is reasonable.

Blood gas measurements are affected by body temperature so the clinician needs to correct for these changes to properly interpret the values. Some blood gas labs ask for patient temperature and make this correction automatically, but many do not. If the lab does not correct for patient temperature, approximate correction is as follows (alpha-stat method) [15, 26, 61]:

- For every degree below 37 °C, subtract 5 mmHg from the PaO2 lab value
- For every degree below 37 °C, subtract 2 mmHg from the PaCO2 lab value
- For every degree below 37 °C, add 0.012 units to the pH lab value

Identification of Treatable Causes of Cardiac Arrest

Acute Coronary Syndrome

Acute coronary syndrome resulting in myocardial infarction and subsequent malignant dysrhythmias is a common cause of cardiac arrest. Electrocardiography (EKG) should be performed immediately following the return of spontaneous circulation to evaluate for acute myocardial ischemia, regardless of the primary rhythm associated with the arrest. Significant coronary disease is found in the majority of patients following resuscitation from cardiac arrest, and percutaneous coronary intervention is associated with improved neurological outcome [62–64].

Intracranial Hemorrhage

CT imaging of the brain is warranted in the comatose post-arrest patient. Up to 5–10% of post-arrest patients demonstrate intracranial hemorrhage, potentially changing the therapeutic approach [65–67]. In addition to identifying potential causes of arrest, early brain imaging has important prognostic value. Early cerebral edema after cardiac arrest strongly predicts poor outcomes [65–67]. If hypothermia is used in patients for the treatment of brain edema, longer cooling periods (until brain edema resolves) should be considered, as warming a patient in the setting of brain edema can worsen outcome [15, 21, 68].

Other Causes

Pulmonary embolism (PE) is a common cause of cardiac arrest, and hemodynamic instability defines a "PE" as high risk. If there is clinical suspicion for possible PE, it should be promptly evaluated or empirically treated. If there is rapid hemodynamic improvement, heparinization alone may be reasonable. Otherwise, thrombolysis should be strongly considered [69]. Trauma, gastrointestinal hemorrhage, overdose, septic shock and anaphylaxis are less common etiologies of cardiac arrest. However, each requires disease-specific management. If the clinical history and initial presentation are suggestive of one of these etiologies, they should be evaluated and managed appropriately.

Delayed Neurological Prognostication

As in many neurocritical care conditions, accurate neurological prognostication after cardiac arrest is challenging. A detailed discussion of post-arrest prognostication is beyond the scope of this manuscript. Critical to the initial evaluation and management of the post-arrest patient is an understanding that in the first 72 h after cardiac arrest, no sign, symptom or combination of findings short of brain death precludes favorable recovery [70, 71]. Even clinical findings compatible with brain death are not definitive for at least 24 h following resuscitation or rewarming, whichever comes later [72]. Premature withdrawal of life-sustaining therapy based on perceived neurological prognosis has been linked to thousands of preventable deaths after cardiac arrest annually [4]. Early limitations in care may be appropriate in some patients, for example those with preexisting advanced directives or severe concomitant medical comorbidities. However, early aggressive care should not be limited or withheld based only on perceived poor neurological prognosis.

Pediatric Considerations

Cardiac arrests occur in 0.7–3% of pediatric hospital admissions and 1.8–5.5% of pediatric intensive care unit admissions, and CPR duration is independently associated with survival to hospital discharge and neurological outcome [73].

Differences in the etiology and pathophysiology of cardiac arrest in children compared to adults should caution extrapolation of adult evidence for TTM and other aspects of post cardiac arrest care of children. Therapeutic hypothermia for neuroprotection in selected neonates with perinatal encephalopathy has demonstrated efficacy, but it is important to also note that the pathophysiology of brain injury due to perinatal asphyxia is quite different from that of pediatric cardiac arrest –for example, very few if any patients in the neonatal hypothermia studies received chest compressions [74, 75] .

Furthermore, the etiology and outcomes of in-hospital and out-of-hospital cardiac arrest in pediatric patients vary, and there has been very little high-quality data to guide the optimal TTM approach in each group. Similar to adults, pediatric cardiac arrest patients with a Glasgow motor score >4 or who do not require intubation and mechanical ventilation are unlikely to benefit from aggressive TTM. Consideration is also given to the fact that certain approaches such as endovascular cooling are not available for induction and maintenance of TTM in children. However, with greater body surface area to mass ratio in pediatric patients, surface cooling has been quite effective for TTM in pediatric cardiac arrest [76] . A recently published multicenter randomized controlled trial, Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA) was designed to determine if a target temperature of 33 °C was superior to one of 37 °C post pediatric cardiac arrest [77, 78]. This trial had two separate study arms for in-hospital and out-of-hospital cardiac arrest comparing TTM to 33° versus 37° for 48 h with slow rewarming. The results did not demonstrate a statistically significant difference in survival with good neurologic outcome between the two target temperature groups. This held true for both in hospital and out of hospital pediatric cardiac arrest.

While data is limited, extracorporeal CPR is generally considered for selected patients refractory to conventional CPR. In a multicenter study, 44% of pediatric patients who failed conventional CPR for in-hospital cardiopulmonary arrest and who were reported to the National Registry of CardioPulmonary Resuscitation as treated with extracorporeal CPR survived to hospital discharge [79]. The majority of survivors with recorded neurologic outcomes experienced favorable recovery.

Finally, although limited by lack of data on age appropriate neurophysiological targets, initial care of children post-cardiac arrest aims at avoiding secondary insults such

Table 2 Resuscitation following cardiac arrest communication regarding assessment and referral

Communication
☐ Duration of cardiac arrest
☐ Most likely etiology of arrest, if known
☐ Neurological examination on first assessment
☐ Time hypothermia started
☐ Current core temperature
☐ Current drug infusions (especially sedative and vasoactive agents)

as hypotension, seizures, fever and electrolyte abnormalities. There is no clinical evidence on the safety and efficacy of glucose control after pediatric cardiac arrest but, in general, significant hyperglycemia is avoided if ongoing brain ischemia is suspected (serum glucose >180 mg/dL).

Communication

When communicating to an accepting or referring physician about this patient, consider including the key elements listed in Table 2.

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