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Optimizing the Early Resuscitation After Out-of-Hospital Cardiac Arrest

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Abstract

Resuscitation after out-of-hospital cardiac arrest can be one of the most challenging scenarios in acute-care medicine. The devastating effects of postcardiac arrest syndrome carry a substantial morbidity and mortality that persist long after return of spontaneous circulation. Management of these patients requires the clinician to simultaneously address multiple emergent priorities including the resuscitation of the patient and the efficient diagnosis and management of the underlying etiology. This review provides a concise evidence-based overview of the core concepts involved in the early postcardiac arrest resuscitation. It will highlight the components of an effective management strategy including addressing hemodynamic, oxygenation, and ventilation goals as well as carefully considering cardiac catheterization and targeted temperature management. An organized approach is paramount to providing effective care to patients in this vulnerable time period.

Keywords

cardiopulmonary resuscitation, critical care, return of spontaneous circulation, cardiac arrest

Introduction

The resuscitation of patients following out-of-hospital cardiac arrest (OHCA) is a challenging scenario for any acute-care clinician. There is substantial morbidity and mortality that persists long after the return of spontaneous circulation (ROSC), stemming from both the precipitating pathology and the resultant postcardiac arrest syndrome. In-hospital mortality rates of over 70% can be expected for those patients surviving to intensive care unit (ICU) admission.[1]

An organized approach to the postarrest patient is crucial to ensure rapid determination and treatment of the underlying etiology while concurrently stabilizing and managing their clinical state. This narrative review will focus on the initial resuscitation of patients after obtaining ROSC from OHCA. The discussion goes beyond intra-arrest management and the application of Advanced Cardiac Life Support (ACLS) guidelines and will instead provide an evidence-based review of the essential management priorities in the early postarrest period. The emphasis will be on optimizing the early resuscitation including addressing physiologic goals, the indications for cardiac catheterization, and the initial approach to targeted temperature management (TTM). As the article is focused on the first few minutes to hours postarrest, some of the downstream issues such as delayed organ dysfunction, neurologic prognostication, and duration of cooling will not be addressed.

Postcardiac Arrest Syndrome

Postcardiac arrest syndrome is a complex pathophysiologic process. The patient experiences profound hypoperfusion as they progress from a state of complete circulatory arrest to a period of severe hypoperfusion, which begins from the initiation of cardiopulmonary resuscitation (CPR) and can persist well into the early ROSC period. This process of global

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ischemia–reperfusion causes marked oxidative stress and triggers a cascade of severe cardiocirculatory dysfunction that may lead to multiorgan failure and death.[2,3] The main components of the postarrest syndrome include the persistent precipitating pathology, systemic ischemia–reperfusion response, postarrest myocardial dysfunction, and postarrest brain injury.[3]

Persistent Precipitating Pathology

Persistent precipitating pathology refers to the underlying etiology of the arrest. The efforts undertaken to achieve ROSC necessarily occur without regard for the inciting event, and so the majority of ACLS interventions do not focus on treating the primary pathology. Many conditions causing cardiac arrest will require diagnosis and specific intervention, such as acute coronary syndrome, neurologic events, massive pulmonary embolism, metabolic derangements, or toxicologic overdose.

Systemic Ischemia–Reperfusion Response

Systemic ischemia–reperfusion reflects the profound shock sustained during the arrest, CPR, and subsequent low-flow state. Global deficiency of oxygen and nutrient delivery during this time results in a massive inflammatory cascade leading to vasodilatory shock and dysfunction of many different systems including the microcirculation and the immune and coagulation systems.[3] The cumulative systemic inflammatory response in many ways resembles that of early severe sepsis.

Postarrest Myocardial Dysfunction

Concurrent postarrest myocardial dysfunction is also common and can occur independent of acute coronary syndrome.[3] Observational studies have demonstrated incidence rates of approximately 35% to 50% in OHCA.[4-6] Animal models have shown reduced left ventricular function after induced arrest from 55% to 20%, despite no alterations in coronary blood flow, reinforcing myocardial stunning as a contributing mechanism.[7,8] Although the effect is mainly transient and normalizes within 24 hours,[4] in the interim it can cause profound cardiogenic shock.[3]

Postarrest Brain Injury

Postarrest brain injury is the leading cause of morbidity and mortality in patients who survive the first 48 hours.[2,3,9] The brain has a limited tolerance to ischemia and can develop an impairment of cerebral autoregulation, cerebral edema, and postischemic neurodegeneration following arrest.[3] Development of neuroprotective strategies may represent one of the greatest opportunities to improve outcomes for patients with OHCA.

An understanding of the pathophysiology of postcardiac arrest syndrome is vital to anticipating the challenges that may arise early in the resuscitation. These principles form the foundation for the development of resuscitation goals, and it is helpful to keep these factors in mind when developing a management plan after ROSC.

Resuscitation Goals

Initial Evaluation

The initial evaluation is focused on addressing immediate life threats and then elucidating the underlying pathology. Obtaining an electrocardiogram (ECG) quickly is a critical part of the initial workup as ST-segment elevation (STE) usually necessitates immediate cardiac catheterization.[10,11] Point-of-care ultrasonography can also be extremely helpful in the initial stages to both guide the resuscitation and work through the differential diagnosis.[12,13] Other components of the initial assessment include a more thorough history and physical examination as well as preliminary investigations such as a chest X-ray and blood work.

Aside from determining cause of the arrest, the clinician should also be vigilant for injuries that may have occurred from the resuscitation itself, such as complications from vascular access attempts and chest compressions leading to rib fractures and secondary pneumothorax or solid organ laceration. Similarly, injuries precipitated by the loss of consciousness during arrest, such as motor vehicle collisions and falls, are not uncommon and will need to be diagnosed and triaged appropriately.

Ideally, an initial evaluation will readily determine the cause of arrest and dictate subsequent treatment and disposition. However, in some cases, advanced testing will be necessary in order to either confirm the suspected diagnosis or search for a potential alternate etiology. Concurrent resuscitation must carry on through this time period. The evidence surrounding some of the specific physiologic goals is presented here.

What Are the Optimal Targets for Oxygenation and Ventilation

Although it has long been known that hypoxia is dangerous in the postarrest period, more recent studies have demonstrated the risks associated with hyperoxia as well.[14,15] A meta-analysis by Wang et al demonstrated an increased mortality with hyperoxia in this setting (odds ratio [OR]: 1.4, 95% confidence interval [95% CI]: 1.1%-1.9%).[15] Additionally, Roberts et al conducted a prospective cohort analysis of 280 patients with ROSC and demonstrated an association between hyperoxia and both mortality and poor neurologic outcome.[14] The association with poor neurologic outcome began at levels of partial pressure of oxygen greater than 300 mm Hg. Therefore, it is prudent to target normoxia after ROSC or a saturation of 94% to 98% per the European Resuscitation Council (ERC) guidelines.[16] If an arterial blood gas measurement is available, a partial pressure of oxygen less than 200 mm Hg is advised.[11]

Controlling ventilation helps to optimize cerebral blood flow.[16] Hypocapnia secondary to hyperventilation can lead to cerebral ischemia and has been associated with increased

mortality in the postarrest patient.[17,18] Conversely, hypercapnia can dilate cerebral blood vessels and improve cerebral blood flow.[19] In theory, this would be beneficial in the OHCA patient with postarrest brain injury, but this comes at a cost of increasing cerebral blood volume, potentially leading to raised intracranial pressure and decreased cerebral perfusion.[18] Kilgannon et al conducted a prospective multicenter cohort study examining the association between partial pressure of arterial carbon dioxide ($Paco_2$) and good neurologic outcome in 280 patients resuscitated after cardiac arrest.[20] They found that $Paco_2$ had an inverted "U"-shaped association with good neurologic outcome, with the highest probability centered over a mean $Paco_2$ of 68 mm Hg. Other observational studies have also demonstrated an association between mild hypercapnia and improved neurologic outcome.[21,22] Hopefully, future randomized controlled trials (RCTs) such as the TAME trial (NCT03114033), comparing a target $Paco_2$ of 50 to 55 mm Hg versus 35 to 45 mm Hg, will inform more directed ventilation goals postarrest.

The American Heart Association (AHA), Canadian Cardiovascular Society (CCS), and the ERC all support maintaining normocapnia in the postarrest period with a $Paco_2$ between 35 and 45 mm Hg.[10,11,16] If end-tidal carbon dioxide is used acutely to monitor and titrate ventilation, one needs to consider that this method will underestimate blood gas values by an average of 5 mm Hg, although this difference may be increased in the context of sizeable dead space pathology (eg, pulmonary embolism) or low flow states.[23] Similarly, with low flow states, there may be a gap between $Paco_2$ and venous carbon dioxide levels ($Pvco_2$) with $Pvco_2$ more elevated due to decreased tissue perfusion.[24,25] Arterial blood gas measurements are ideal for careful titration of ventilation targets in the postarrest period.

What Is the Optimal Perfusion Pressure

International guidelines including AHA[10] and CCS[11] recommend a mean arterial pressure (MAP) of at least 65 mm Hg in the postarrest period. Hypotension has been consistently associated with increased mortality and must be avoided.[26-28] Furthermore, some observational studies have demonstrated an association between higher MAP and improved neurological outcomes.[29-32]

In a recent large multicenter prospective cohort study, Roberts et al examined the association between an MAP greater than 90 mm Hg and 70 to 90 mm Hg over the first 6 hours postarrest and good neurologic outcome (ie, modified Rankin Scale $\leq$3).[30] There was an association with improved neurologic outcome for the higher MAP targets (relative risk: 2.5, 95% CI: 2.1%-2.9%) and a dose–response relationship between MAP and probability of good neurologic outcome. Another study by Russo et al found a similar trend, demonstrating higher rates of severe neurologic dysfunction when MAP targets <75 mm Hg were used.[31]

However, owing to their observational design, the current available studies are hypothesis-generating only. Randomized controlled trials are needed to conclusively determine whether elevated MAP targets are warranted in the postarrest period, and if so, which patient populations stand to benefit the most. With the ultimate goal of organ perfusion, the optimal strategy may be to start with an MAP target >65 mm Hg, followed by individualized blood pressure targets that take into account the patient's known baseline blood pressure (or history of hypertension), shock phenotype, and that are titrated to signs of adequate end-organ perfusion.[33-35] Of note, there are ongoing RCTs examining high normal versus low normal MAP in OHCA including the BOX (NCT03141099) and the COMACARE (NCT02698917) studies.

The tools to achieve optimal hemodynamics are also a continual source of debate. Fluid resuscitation will largely depend on the clinical scenario and a volume assessment.[36] As discussed previously, often patients will have components of both distributive and cardiogenic shock, which will influence the choice of further vasopressor and/or inotrope therapy.[37] A Cochrane meta-analysis on the treatment of cardiogenic shock and low-cardiac output syndrome highlighted the need for more randomized trials in this setting.[38]

Recent evidence has shown possible harm with the use of epinephrine in cardiogenic shock.[39,40] Levy et al randomized patients with cardiogenic shock after acute myocardial infarction to either epinephrine or norepinephrine.[40] Although there were similar effects on arterial pressure and cardiac index, the epinephrine group had a higher incidence of refractory shock (37% vs 7%, $P = .008$). Heart rate and double product (heart rate multiplied by systolic blood pressure) were also increased in the epinephrine treatment arm, which may explain the differences between groups, as this measure can be used as a surrogate for myocardial oxygen consumption.[41] The trial was stopped early due to increased harm with epinephrine.

Furthermore, Leopold et al conducted a meta-analysis of studies examining the use of epinephrine in cardiogenic shock.[39] Patient data from 16 cohorts and 2583 patients were combined. After propensity matching for differences between patients, epinephrine was associated with an increase in short-term mortality (OR: 4.2, 95% CI: 3.0%-6.0%) when compared to other vasoactive agents.

The AHA, CCS, and the ERC guidelines do not make any specific recommendations with regard to choice of vasoactive agent to treat hypotension postarrest.[10,11,16] This is likely because of the lack of evidence and also because of the heterogenous patient population where clinical context will direct pressor management. The pharmacological approach should be tailored to the clinical context whenever possible and can then be adjusted as more information becomes available.

Coronary Angiography and Revascularization

Guidelines strongly recommend considering immediate coronary angiography and potential revascularization when criteria are met for STE myocardial infarction on the initial ECG postarrest.[10,11,16] However, the ECG is not always diagnostic in the postarrest period. Early management decisions can become more challenging in the absence of STE, as there are patients

who may still have an underlying coronary occlusion and benefit from percutaneous coronary intervention (PCI). A meta-analysis by Millin et al examined the rates of PCI in 11 observational studies, comparing those with and without STE on initial ECG assessed by coronary angiography postarrest.[42] Although patients with STE were more likely to undergo PCI, almost one-third of the non-STE patients also had a culprit lesion that required intervention (32.2% vs 71.9%). Similarly, another large registry study from the United States demonstrated a sizable rate of PCI (24.7%) among patients without STE and an initial rhythm of pulseless electrical activity (PEA) or asystole.[43] Currently, the AHA suggests a class IIa recommendation for emergent coronary angiography in select patients without STE on the initial ECG who have a suspected cardiac etiology of the arrest (eg, clinical presentation or comorbidities, evidence of ongoing ischemia, or hemodynamic or electrical instability).[10]

Recently, the results of the COACT trial were published, which examined a strategy of immediate versus delayed angiography in patients without STE after OHCA.[44] Patients were included in the study if they had an initial shockable rhythm, were comatose postarrest, and if there was no ongoing hemodynamic or electrical instability. Coronary angiography was performed in 97% of the immediate group versus 64.9% in the delayed group with a median time to angiography of 2.3 hours versus 121 hours. Overall, there was no significant difference in the primary outcome of survival at 90 days (64.5% vs 67.2%) or in any of the secondary outcomes including neurologic status at ICU discharge, markers of shock, or duration of hemodynamic support.

There are important limitations to consider when interpreting this trial. First, this was a highly select population of OHCA patients with sustained ROSC after an initial shockable rhythm. Pulseless electrical activity and asystole were excluded. Additionally, obstructive culprit pathology on angiography was relatively small, limiting any potential benefits of PCI to a select few patients. so opportunity for benefit from PCI was limited to a small number of the included patients. Only 13.6% of patients in the immediate angiography group had an acute unstable lesion (greater than 70% stenosis and the presence of characteristics of plaque disruption) and 3.4% had an acute thrombotic occlusion. Overall, this trial demonstrated no benefit to immediate coronary angiography for OHCA patients if cardiac ischemia is not the suspected etiology.

Alternatively, some have advocated for immediate coronary angiography in all patients without an obvious noncardiac etiology, regardless of the presence of STE.[45,46] Along these lines, Akin et al published the initial results of their novel and aggressive Hannover Cardiac Resuscitation Algorithm (HaCRA).[47] All patients treated according to the HaCRA undergo mandatory therapeutic hypothermia (to 32°C) and cardiac catheterization in the absence of an overt noncardiac etiology of the arrest and, where necessary, additional hemodynamic support such as an intra-aortic balloon pump, extracorporeal membrane oxygenation, or insertion of other ventricular assist devices. They report on 233 consecutive OHCA patients evaluated at their center using this protocol, including 10% with ongoing CPR.[47] Patients with both shockable and nonshockable rhythms (27%) were included. Coronary angiography was performed in 96% of patients. Rates of PCI were much higher than in COACT, with 60% of their cohort receiving intervention. Percutaneous coronary intervention was performed in 62% of patients with STE versus 52% of those without STE. Overall 30-day in-hospital mortality was 37% in their cohort.[48] Although this study is single center and observational, this standardized protocol incorporating early angiography demonstrates encouraging results, and discrepancies may reflect the variation in selection of patients between a refined RCT and an all-comer cohort.

Targeted Temperature Management

Targeted temperature management and prevention of hyperthermia in comatose patients postarrest are purported to have many neuroprotective benefits including decreasing the ischemia–reperfusion response, decreasing the permeability of the blood–brain barrier, and improving cerebral microcirculation.[49] Cerebral metabolism is also reduced by approximately 6% to 10% for every 1°C decrease in core temperature during the cooling period.[49] Conversely, the drawbacks include electrolyte disturbances, hemodynamic changes, hyperglycemia, coagulopathy, and susceptibility to infection from immunosuppression.[49] However, the net benefits of temperature management postarrest have been demonstrated by multiple studies including the landmark Hypothermia After Cardiac Arrest trial and the Bernard et al study, with both demonstrating improved neurologically intact survival among OHCA patients with applied mild hypothermia (either 32°C-34°C or 33°C respectively).[50,51] Temperature management is ubiquitous to guideline recommendations,[10,11,16,52] but to what degree remains in debate.

The TTM trial by Nielsen et al in 2013 was a large international RCT comparing a target temperature of 33°C versus 36°C after OHCA.[48] They found no difference in all-cause mortality or neurologically intact survival. There was also no difference in safety outcomes such as bleeding, infection, or dysrhythmias. In sum, no major differences were found between groups. However, there are important considerations when interpreting the TTM results including an expanded recruitment to include PEA and asystole, the lack of standardization of cooling protocols between centers, and the noninferiority trial design.[53,54]

Given the discrepancy between the TTM trial and prior studies, there is no consensus among guideline recommendations with regard to temperature targets. The AHA and ERC have modified the upper limit of temperature range and recommend a temperature of 32°C to 36°C,[10,16] while the CCS recommends 33°C to 36°C[11] in concert with the TTM trial. The American Academy of Neurology takes a different stance and offers a stronger (Level A evidence) recommendation for a range of 32°C to 34°C for ventricular tachycardia (VT)/ventricular fibrillation (VF) arrest, reflecting the older trials, and a more moderate (Level B evidence) recommendation for a

target of 36°C for PEA/asystole and VT/VF arrests as per the TTM trial.[52] Other groups such as the Canadian Critical Care Society continue to recommend a target temperature range of 32°C to 34°C due to the limitations of the TTM trial.[53] Ongoing RCTs such as the CAPITALCHILL trial (NCT02011568) comparing mild (34°C) to moderate (31°C) hypothermia may lend new perspective to the debate.

Notably, regardless of the actual temperature range chosen, both groups in the TTM trial were actively cooled.[48] The most important principle remains to prevent hyperthermia. A common misconception is to have a goal of 36°C equated with normothermia. A single-center retrospective evaluation of protocol adherence before and after implementation of a temperature change from 33°C to 36°C found that patients spent less time at their target temperature and rates of fever increased significantly.[55] Fever is common in the postarrest period,[56] and the risk of an unfavorable neurologic outcome increases with every degree higher than 37°C.[57]

Although most patients will present relatively hypothermic, the priority in the acute phase of the resuscitation is to obtain a measure of the core temperature and then actively defend against hyperthermia.[58] There is currently insufficient evidence to recommend a specific temperature measurement modality or cooling method, however the initiation of temperature management does not need to be complicated. Insertion of a bladder temperature probe followed by application of a cooling blanket, or ice packs to junctional areas, can be performed quickly, even in resource-poor environments. Cooling should also be started as soon as possible after ROSC, as the beneficial effects are understood to decrease with delayed initiation.[53] Albeit, this must be thoughtfully balanced with logistical considerations such as organizing transfer for diagnostic imaging or definitive intervention and considering the presence of any possible contraindications such as refractory shock, uncontrolled bleeding, or the presence of severe infection.[53]

It should be noted that shivering can be a significant challenge to maintaining temperature goals postarrest, and rates of shivering may increase with lower target temperatures.[55,59] However, it can be managed effectively with both pharmacologic and nonpharmacologic interventions.[60] The Columbia Anti-Shivering Protocol is one example of a step-wise algorithm to manage shivering including acetaminophen, magnesium sulfate, and skin counter-warming as first steps, followed by deep sedation and neuromuscular blockade reserved for the most challenging cases.[60]

Future Directions

Cardiac arrest management will likely change significantly in the coming years. As discussed, there is still ongoing debate regarding many of the management targets. More research is needed to determine best practice for the postarrest patient, and many ongoing studies including the aforementioned RCTs may offer more direction for clinical practice. One key aspect of early resuscitation investigations that requires more attention is identifying which interventions are linked to survival and which interventions demonstrate improved patient-centered outcomes over the long term (eg, preservation of cardiac function, reduced hospital readmissions, and quality of life).

The development and evolution of protocols including early access to the cardiac catheterization laboratory offers an exciting perspective as well.[61] Early coronary angiography can be both informative and therapeutic via PCI. Further, continuing the resuscitation in this setting has the potential to expedite the initiation of mechanical circulatory support such as venoarterial extracorporeal membrane oxygenation (ECMO). The ECMO CPR can be particularly valuable in cases of rearrest, allowing for the continuation of coronary angiography and PCI without ongoing chest compressions. Experience worldwide with ECPR is increasing, and the Extracorporeal Life Support Organization 2017 summary report outlines a total of 3485 cases with an overall survival to hospital discharge of 28%.[62] Although there have been no RCTs to date, some observational studies have demonstrated promising results when compared to conventional methods.[63,64]

Conclusion

Providing effective care in the postarrest period is a challenging endeavor. There are multiple concurrent management priorities including the diagnosis and treatment of the underlying cause, as well as restoring cardiorespiratory stability. Effective management demands an organized approach, which includes addressing specific resuscitation goals, carefully considering cardiac catheterization, and initiating TTM.

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Supplemental Material

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