title: "Optimizing Post-Cardiac Arrest Outcomes: The Role of Sedation and Neuroprotection"
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date: "2024-05-10"
subtitle: "RWJBaranbas/HCCC Paramedic Program - Class 25"
subject: "Ketamine and Cardiac Arrest"
keywords: [Cardiac Arrest, ROSC, Ketamine]
lang: "en"
header-left: "\thetitle"
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Abstract

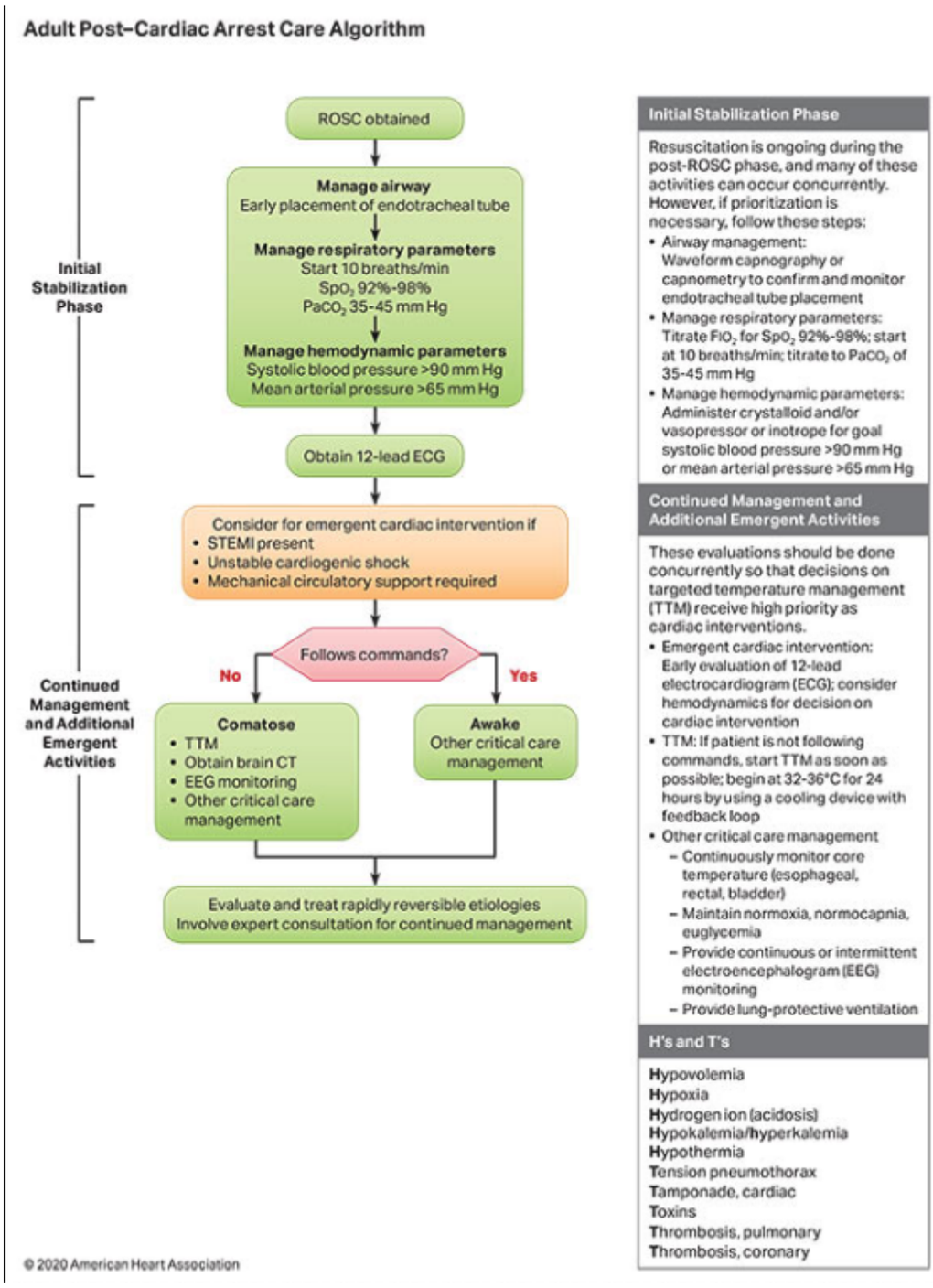
Post-cardiac arrest (**PCAC**) care remains a critical area in need of comprehensive clinical research to improve outcomes for patients experiencing return of spontaneous circulation (**ROSC**). The American Heart Association Emergency Cardiovascular Care Committee and the Neurocritical Care Society convened a panel of experts to identify and address gaps in knowledge across multiple organ systems affected PCA, with consensus statements developed for targeted management strategies. This paper reviews the physiological challenges post-ROSC, including ischemia/reperfusion injury, hemodynamic instability, and systemic inflammatory responses, as well as key elements of the PCAC algorithm, such as targeted temperature management (**TTM**), neurological recovery, and sedation protocols.

Special focus is given to sedation agents, particularly ketamine, and their dual roles in patient comfort and neuroprotection. While ketamine has historically raised concerns regarding its impact on intracranial pressure (**ICP**) and cardiovascular stability, emerging evidence suggests its potential to mitigate excitotoxicity, reduce cerebral edema, and improve neurological outcomes in ischemic brain injury. Recent studies in PCA brain injury (**PCABI**), traumatic brain injury (**TBI**), and hypothermic circulatory arrest (**HCA**) models underscore ketamine's anti-inflammatory and anti-apoptotic effects, making it a promising candidate for further investigation. This paper synthesizes current evidence to highlight the need for additional research into sedation strategies that optimize both hemodynamic and neuroprotective outcomes in PCAC. By addressing these gaps, the medical community can better refine protocols to improve survival rates and long-term neurological recovery in PCA patients.

Post Cardiac Arrest Care

To address the lack of clinical studies on the overall management of CA patients the American Heart Association Emergency Cardiovascular Care Committee and the Neurocritical Care Society cosponsored an expert panel - Hirsch et al., (2024) - on PCAC topics. The authors make clear that some topics like TTM have a lot of research to refer to but others have little or none. The focus of this panel was to generate topic statements and come to a consensus as to their relevance. "Topics were identified and prioritized by the panel and arranged by organ system to facilitate discussion, debate, and consensus building. Statements related to PCA management were generated, and 80% agreement was required to approve a statement." The topic breakdowns are: neurological, cardiac, pulmonary, hematological, infectious, gastrointestinal, endocrine, and general critical care management (Hirsch et al., (2024).

Figure 1
Algorithm for post-cardiac arrest care. Adapted from the American Heart Association (*n.d.*). *Part 3: Adult Basic and Advanced Life Support - Algorithm ACLS PCAC*. CPR Guidelines Images.



Multisystem Challenges and the ACLS Algorithm for Post-Cardiac Arrest Care

The range of topics shows how varied the PCA patient can be. The "Hs and Ts" very possibly still need to be addressed so CA does not recur. Recirculation brings with it ischemia/reperfusion toxicity. Hemodynamics are unstable, and endogenous catecholamines are depleted. A general inflammatory response constricts vessels and slows perfusion. Pulmonary aspiration and seizures are common post-ROSC. And (though most folks are unresponsive after ROSC) if the person is somewhat conscious they are dealing with significant pain and trauma. Multiple systems under attack all at the same time.

ACLS Algorithm in Neurological Recovery

The ACLS PCAC algorithm checks whether or not the patient can follow commands. If not then the critical care includes targeted temperature management, MRIs of the brain, and EEGs as neurological recovery is primary. In general, the outcomes are not good one study of OHCA neurological outcomes after PEA (Stead et al., (2022) showed that with 235 patients, 26% made it to "sustained ROSC" and 7% left the hospital. However, only 3% overall had good neuro outcomes (measured by a Cerebral Performance Categories (CPC) score of 1).

Neurological Focus: Seizures, Sedation, and Analgesia

(Hirsch et al., (2024) breakdown the following neurological subtopics:

- brain oxygenation
  - perfusion
  - edema and ICP

- seizures
- sedation and analgesia

When discussing seizures the authors reveal a problem related to sedation - barbiturates are effective for treatment of seizures but "can confound neurological examination for several days, given their long half-lives and sedative effects" (Hirsch et al., (2024). Ketamine is identified as a "third line treatment" for seizures and might have less of a confounding impact on a neuro assessment.

Sedation and analgesia are commonly used for mechanically ventilated patients as well as ones undergoing TTM. More generally sedation medications "provide comfort, prevent recall, and reduce the metabolic demands of shivering and other motor activity" (Hirsch et al., (2024). The potential negative effects include vasodilation and a drop in blood pressure; disruption of normal ventilation; changes in pH and muscular weakness - in addition to the confounding effect already mentioned. It is important to consider that sedation under TTM can be prolonged due to reduced metabolism of the drug due to hypothermia.

Hirsch et al., (2024) show the consensus in the group (note the percentages).

- **Sedation and Analgesia Statements**

    i. The goals of analgesia and sedation during temperature control after CA are to provide comfort, reduce shivering, and prevent recall during NMB (100%, 21/21).
    ii. Short-acting sedative and analgesic agents are preferred for patients in post-CA coma undergoing temperature control to reduce the duration of mechanical ventilation, time to awakening, and confounding of delayed prognostication (100%, 21/21).
    iii. Propofol, remifentanil, and fentanyl are favored over midazolam and morphine infusions (85.7%, 18/21).
    iv. Use NMB as needed during temperature control rather than as a continuous infusion. In addition, it is important to note that NMB may mask seizures in unmonitored patients (95.3%, 20/21).

Ketamine is not mentioned here except in a paragraph on "short-acting sedative and analgesic agents". However, the expert panel discussion gives a framework to understand what to consider when needing to use sedation in PCAC.

Prehospital and Emergency Department Sedation Strategies

Common use cases for sedation in the ER and pre-hospital include: rapid sequence intubation; agitation/delirium; procedural sedation; trauma. Engstrom et al., (2023) assert that in the case of RSI, the choice of induction agent is critical when dealing with patients in shock or more specifically sepsis (etomidate performed slightly better than ketamine in this context). The recommendation is to exercise "caution when using ketamine in patients that may be catecholamine depleted on presentation and subject to hypotension and myocardial depression with ketamine use". The authors note: "One reason for the unexpected increase in hypotension found with ketamine in these two studies could be from its increased use in patients who were already hypotensive or at high risk of hypotension compared to the etomidate cohort." Engstrom et al., (2023)

Engstrom et al., (2023) indicate uncertainty for this hypotensive effect - "The mechanism of hypotension in septic patients receiving ketamine remains to be elucidated" - but there are several studies that point to this phenomenon.

Sharif et al., (2024) in their meta-analysis of procedural sedation and analgesia in ER and ICU considered over 8,000 patients looking at recovery time, adverse effects, and patient success. The study considered several combinations of midazolam, opiates, ketamine, propofol, etomidate, and dexmedetomidine. In the conclusion "Compared with midazolam-opioids for procedural sedation and analgesia in the acute care setting, ketamine was associated with fewer respiratory adverse events, sedation recovery time is shortest with propofol, and patient satisfaction is highest using a combination of ketamine-propofol. Compared with ketamine-propofol, propofol-opioids may be associated with higher rates of respiratory and cardiac adverse events, and probably fewer gastrointestinal adverse events." (Sharif et al., (2024)

McKinley et al., (2021) in a large study at a tertiary-care, academic ED, where ketamine was used for "indications of agitation, procedural sedation, rapid sequence intubation, pain, sedation, seizure, status asthmaticus, and unknown" it was found to be versatile, safe and effective with less than 5% adverse effects reported.

Ketamine has a similar profile in prehospital studies - in one case over 11,000 patients in pre and in-hospital care (roughly 50% for pain and trauma; 34% for agitation/AMS; 13% for cardiopulmonary issues and the rest for seizures). Adverse effects were tracked specifically hypoxia (8.4%) and hypercapnia (17.2%). There were 8 deaths where ketamine could not be ruled out as a cause (0.07%). Fernandez et al., (2021)

The 2020 position paper by The American College of Surgeons Committee on Trauma (ACS-COT), the American College of Emergency Physicians (ACEP), the National Association of State EMS Officials (NASEMSO), the National Association of EMS Physicians (NAEMSP) and the National Association of EMTs (NAEMT) similarly characterized ketamine as safe:

"This consensus document outlines the role of ketamine in the management of trauma patients in both the prehospital and hospital setting. Low-dose or sub-dissociative dose ketamine is a safe and effective analgesic that can be used for adult and pediatric trauma patients as an alternative to opioids, with opioids for synergistic effect, or for patients taking buprenorphine products with minimal effects on hemodynamic stability. Ketamine dissociative doses are safe and effective in adult and pediatric trauma patients and are an excellent agent for induction of RSI, post-intubation sedation/analgesia, and procedural sedation in the hypotensive trauma patient. Ketamine has a wide therapeutic window and thus can also be used for acute agitation and excited delirium." Morgan et al., (2021)

Ketamine and Neuroprotection

The research around CPR and PCA recovery focuses on positive outcomes beyond survival. Several recent studies look at the possibility that ketamine might have a "neuroprotective" effect in cases of TBI, ischemic stroke, or the ischemia/reperfusion assault on the brain. The term neuroprotection covers the strategies aimed at protecting the nervous system—particularly neurons—from injury or degeneration caused by conditions such as ischemia, trauma, or neurodegenerative diseases. There are not a lot of clinical trials in this area as Ornowska et al. (2022) detail in their "scoping review" of 181 studies. The authors further show that "PCABI (post-CA brain injury) is the primary cause of death in 68% of out-of-hospital CA patients, regardless of the etiology of the arrest."

The mechanism of injury is twofold. The "first hit" is the initial hypoxia from the CA which causes ischemia. The cerebrum requires around 20% of cardiac output and is quickly damaged during CA. An "excitotoxic cascade" begins quickly during cerebral ischemia, sodium/potassium pumps fail and the cells get flooded with calcium.

The "second hit" comes with reperfusion. "Increase in intracellular calcium levels during the primary ischemic event results in glutamate exocytosis onto the post-synaptic cell and subsequent upregulated expression of calcium-permeable NMDA receptors." Ornowska et al. (2022) The incoming oxygen cannot be properly used and reactive oxygen species (**ROS**) are formed. At the same time the general immune system response post CA causes cerebral edema and vasoconstriction. It is a stagnant mess and cell apoptosis cascades spread the damage.

Electrical conduction is affected, not only by seizures but also by Cortical spreading depolarization (CSD). CSD is a spreading loss of "ion homeostasis, altered vascular response, change in synaptic architecture, and subsequent depression in electrical activity following an inciting neurological injury." Kramer et al., (2016)

The consequences for recovery are severe. "PCABI results in apoptosis of neurons, particularly in the highly metabolically active hippocampal and neocortical areas." Results of this damage include "impairments in memory, executive functioning, and visual-motor skills" as well as "psychiatric comorbidities including depression, anxiety, and post-traumatic stress disorder." Ornowska et al. (2022)

As an NMDA antagonist, ketamine can ameliorate the damage caused by excitotoxicity. Ketamine blocks the glutamate-containing vesicles' ability to bind to the presynaptic membrane. "By preventing glutamate exocytosis and blocking calcium entry into the post-synaptic cell, intracellular calcium buildup may be diminished. If ketamine is administered following CA upon hospital admission for sedation, it may be effective in inhibiting the above-mentioned apoptotic cascades, thus resulting in improved neurologic outcomes." Ornowska et al. (2022)

Research in the related areas of TBI and circulatory arrest for cardiac surgery finds a similar effect. Giuliano et al., (2023) studied the effect of pre-dosing canine subjects with ketamine before the procedure (hypothermic circulatory arrest (HCA)). "In ketamine-treated animals (n = 5), a total of 2.85 mg/kg of ketamine was administered IV half (1.425 mg/kg) of this dose was administered IV prior to initiation of cardiopulmonary bypass (CPB), and the other half was administered on re-initiation of CPB following HCA" The randomized control group was given normal saline.

The timing of the 2 doses was meant to cover the "2 hits" - both the initial ischemic injury and the reperfusion one. The researchers discovered that "In our canine model of hypothermic circulatory arrest, treatment with ketamine led to significantly decreased neurobehavioral deficit scores (ie, fewer deficits) and reduced levels of CSF pNF-H, a marker of axonal and dendritic injury, and NSE, a marker of neuronal damage" additionally there were no "hemodynamic disturbances".

With TBI the biggest historical concern with ketamine involved ICP. Ketamine was thought to increase ICP thus making it a dangerous option for traumatic brain injury. 3 studies indicated that ketamine did not increase and may decrease ICP - Godoy et al., (2021); Gregers et al., (2020); Madsen et al., (2021). Sedation has many applications in the treatment of brain injury. The patient is conscious but is likely in much pain, anxiety, and perhaps agitated. They might have seizures. If unconscious, they are likely intubated. In both cases, sedation should not increase cerebral metabolism or ICP. TTM requires sedation as well.

The profile for ketamine as sedation under a TBI is similar to the characterization above for PCA. "Ketamine appears to inhibit cortical spreading depolarisations in both animal and human studies [1–3, 5], has been suggested to attenuate excitotoxicity, and has anti-inflammatory and anti-apoptotic effects. Ketamine administration could therefore be advantageous in critically ill patients with severe acute brain injury." Madsen et al., (2021)

Challenges of Ketamine in PCAC

Ketamine is not a 'magic bullet,' as Augoustides (2023) suggests. In a similar vein, Sharif et al., (2024) indicate that "there is no perfect pharmacological agent for procedural sedation and analgesia". Concerns about hypotension occurring when ketamine is given in a catecholamine-depleted patient remain. Emergence phenomenon can cause psychological trauma. Adverse effects of alcohol (and other substances) have been reported.

The possibility that it can have "neuroprotective" properties after CA or TBI (or possibly stroke and other cerebral insults) makes it a very intriguing choice for sedation when the brain is facing severe threats from ischemia or reperfusion '2nd hit'. This is a key piece in the overall PCAC algorithm and clinical research in this area is needed.

Conclusion

The management of PCAC remains a complex challenge requiring a multidisciplinary approach and targeted interventions to address the cascading physiological insults post-ROSC. This review highlights the critical need for further research into sedation agents, particularly ketamine, as both a sedative and potential neuroprotective agent in mitigating ischemia/reperfusion injury and its aftermath. While preliminary evidence underscores ketamine's promise in reducing excitotoxicity, cerebral edema, and apoptotic cascades, significant gaps remain regarding its optimal use in PCA patients.

Moving forward, robust clinical trials are essential to validate ketamine's role in improving neurological outcomes and to refine its integration into PCA care algorithms. Additionally, a broader exploration of sedation strategies in relation to TTM, hemodynamic stability, and long-term recovery is warranted. Addressing these gaps will not only advance our understanding of PCA brain injury but also improve survival rates and quality of life for patients.

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