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# Post Cardiac Arrest Care in the Cardiac Intensive Care Unit

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## Abstract

**Purpose of Review** Cardiac arrests constitute a leading cause of mortality in the adult population and cardiologists are often tasked with the management of patients following cardiac arrest either as a consultant or primary provider in the cardiac intensive care unit. Familiarity with evidence-based practice for post-cardiac arrest care is a requisite for optimizing outcomes in this highly morbid group. This review will highlight important concepts necessary to managing these patients.

**Recent Findings** Emerging evidence has further elucidated optimal care of post-arrest patients including timing for routine coronary angiography, utility of therapeutic hypothermia, permissive hypercapnia, and empiric aspiration pneumonia treatment.

**Summary** The complicated state of multi-organ failure following cardiac arrest needs to be carefully optimized by the clinician to prevent further neurologic injury and promote systemic recovery. Future studies should be aimed at understanding if these findings extend to specific patient populations, especially those at the highest risk for poor outcomes.

**Keywords** Cardiac arrest · Intensive care unit · Targeted temperature management · Neuro-prognostication · Post arrest care · Outcomes

## Introduction

The rising incidence of cardiac arrest (CA) contributes substantially to cardiovascular mortality and reduced quality of life [1, 2]. The American Heart Association (AHA) 2022 Annual Update and Cardiac Arrest Registry to Enhance Survival (CARES) data report a surge in the annual incidence of CA with reduced survival for out-of-hospital cardiac arrests (OHCA) compared to pre-pandemic statistics [1, 3]. Understanding the pathophysiologic, metabolic, and reperfusion-injury cascades post-arrest is imperative to provide optimal care and improve survival. Cardiologists with or without critical care training are often engaged in the care of these complex patients as consultants or the primary care team. Early in-hospital care requires a knowledge of when and in whom revascularization and circulatory support strategies should be used, ventilation techniques, and therapies for multi-system organ dysfunction. Additionally, the post-resuscitation

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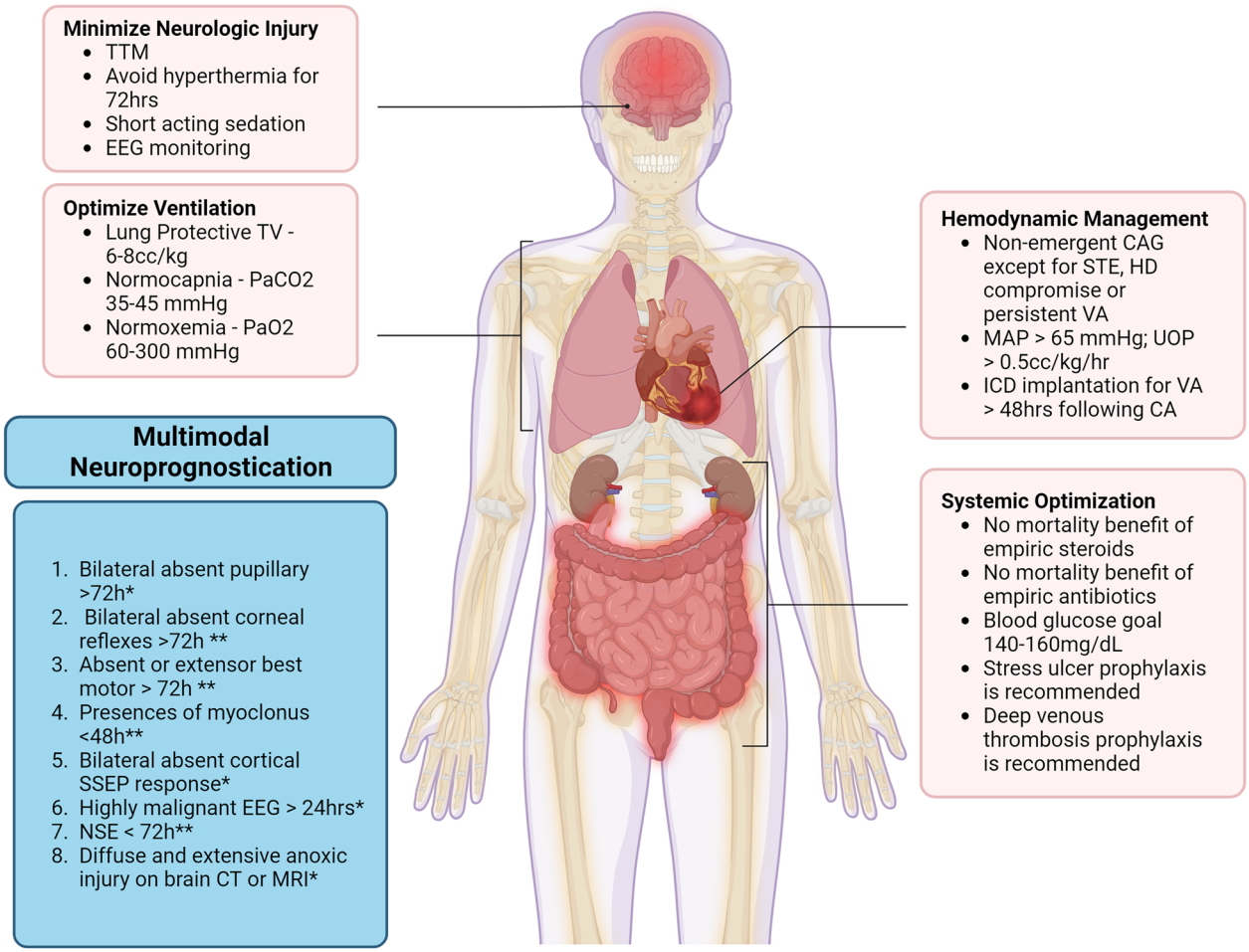
care continuum requires close neurological monitoring, targeted temperature management, supportive care, and neuroprognostication (Fig. 1). In this review, we explore evidence-based practices and multimodal perspectives in post-arrest cares in the intensive care unit (ICU).

## Cardiovascular Specific Interventions

### Timing of Coronary Angiography

Acute coronary syndrome (ACS) is a common etiology of CA, accounting for 59–71% of OHCA cases presenting with a shockable rhythm [3–7], and 30–35% of in-hospital cardiac arrest (IHCA) cases [8, 9]. The current guidelines recommend emergent coronary angiography (CAG) for OHCA with suspected cardiac etiology and ST-elevation myocardial infarction (STEMI), cardiogenic shock (CS), or recurrent arrhythmias. There is no delineation on timing of CAG among patients with non-ST segment elevation myocardial infarction (NSTEMI) [10••, 11••, 12]. The likelihood of coronary artery disease (CAD) increases up to 73% in patients with shockable refractory CA [13] potentially increasing the benefit of CAG regardless of EKG findings in this subgroup. Because serologic and echocardiographic markers of coronary ischemia may not be reliable immediately post-arrest [14, 15] and outcomes are heavily reliant on neurologic recovery [16•], predicting who will benefit from early CAG can be difficult. Several trials have compared a delayed (24–96 h or following neurologic recovery) versus an immediate (< 2 h) strategy for timing of CAG in patients without STEMI after OHCA with shockable [17–20] and non-shockable [18–20] rhythms. Neither these trials nor meta-analyses have shown a difference in outcomes with




TTM: Targeted temperature management, EEG: Electroencephalogram, TV: Tidal Volume, CAG: Coronary angiogram, STE: ST elevation, HD: hemodynamic, VA: Ventricular arrhythmia, MAP: Mean arterial pressure, UOP: Urine Output, ICD: Implantable cardioverter defibrillator, CA: Cardiac arrest, NSE: Neuron Specific Enolase, SSEP: Somatosensory evoked potential, * reliable or modestly reliable, **unreliable

**Fig. 1** Post Cardiac Arrest Care in the Cardiac ICU. Created with BioRender.com

either strategy [17–22]. These findings can be reconciled with a non-emergent CAG strategy among OHCA survivors without STEMI, evidence of post-arrest CS, or refractory/recurrent arrhythmias following resuscitation. A more nuanced assessment of ACS risk in conjunction with the use of early neuroprognostication scores may better identify those patients most likely to have neurologic recovery that would allow them to benefit from an early intervention approach (Table 1) [23].

## Hemodynamic Management

Post-arrest hypotension and shock occurs in 50–70% of patients [24–26]. Hypotension and malperfusion are multifactorial, owing to a combination of acute myocardial injury, myocardial stunning, vascular dysfunction due to systemic inflammatory response, reperfusion injury, metabolic perturbations related to poor perfusion peri-arrest, trauma from cardiopulmonary resuscitation (CPR), and relative adrenal insufficiency. Laurent et al. described the hemodynamics associated with this combination of early myocardial stunning paired with vasoplegia in great detail [27].

Post-arrest myocardial dysfunction or myocardial stunning can occur in addition to or in the absence of myocardial ischemia and may be considered a form of stress-induced cardiomyopathy occurring in up to 69% of survivors of CA [28, 29]. Risk factors include the history of hypertension, prior myocardial infarction (MI), cardiac etiology of arrest, duration of resuscitation, repeated defibrillations, and higher cumulative epinephrine dose [30]. Post-arrest myocardial stunning and associated reduction in cardiac output (CO) may be completely reversible within 48–72 h following ROSC [27, 30]. Vasoplegia following global ischemia–reperfusion injury can compound myocardial stunning. Elevation in cytokines including TNF-α and IL-6 [31], neutrophil activation, coagulation cascade activation, and translocation of endotoxins [32] leads to endothelial cell dysfunction, activation of inducible nitric oxide-synthase, and resultant vascular smooth muscle relaxation [33]. Lactic acidosis from poor end-organ perfusion and respiratory acidosis from hypoventilation during CA may result in reduced responsiveness to endogenous and exogenous catecholamines [34]. This sepsis-like state results in micro-circulatory failure and contributes to post-arrest hypotension [31]. In addition to cardiogenic and vasodilatory shock, Hékimian et al. reported that 42% of post-arrest patients have relative adrenal insufficiency [35] due to direct ischemic adrenal injury and/or inhibitory effects of circulating cytokines [36]. Despite relative adrenal insufficiency among these patients, there is conflicting data regarding the benefit of exogenous steroids [37–40] and current guidelines do not recommend their routine use [10••].

Initial management of post-arrest shock begins with identifying the presence of cardiogenic and/or vasoplegic components. As with traditional septic shock, post-arrest vasoplegia is treated with fluid resuscitation and vasopressors. There is little evidence comparing vasopressor agents for post-arrest patients; however, guidelines recommend norepinephrine as a first-line agent [10••]. A recent observational comparing epinephrine and norepinephrine in patients with post-arrest shock found epinephrine administration was associated with higher all-cause mortality [41•]. When CS contributes to hemodynamic compromise, either in isolation or with vasoplegia, the addition of inotropes and temporary mechanical circulatory support (tMCS) may be warranted. Dobutamine's inotropic properties mitigate left ventricular systolic and diastolic dysfunction that occurs as part of post-arrest myocardial stunning [42] while milrinone has not been well studied in this population. Dobutamine having a shorter half-life is better suited for post-arrest management of CS where rapid uptitration is necessary, and as discussed later, renal failure is highly prevalent in this population making milrinone a less ideal agent as its excretion is highly dependent on renal function [43, 44]. As a more established treatment, dobutamine is the inotrope of choice per the European Resuscitation Council guidelines [10••].

### Invasive Hemodynamic Monitoring Devices

The approach to hemodynamic monitoring varies based on institutional expertise. Given fluctuations in hemodynamics during the post-resuscitation period, patients often necessitate invasive hemodynamic monitoring including peripheral arterial catheterization, central venous catheterization, arterial pulse waveform analysis, and pulmonary artery catheterization (PAC).

While PAC use has not specifically been studied following CA, its use in the management of undifferentiated shock in ICUs and decompensated heart failure has not shown significant differences in outcomes [45–47]. However, more recent data offers a nuanced view of the utility of the PAC in a modern cardiac ICU (CICU) [48, 49]. The use of PAC in patients following CA may provide nuanced hemodynamic profiling in mixed shock states as vasoplegia and myocardial dysfunction are often concomitant [29]; however, more data in this population is necessary.

### Temporary Mechanical Circulatory Support

In patients where fluid resuscitation, vasopressor agents, and inotropes are not sufficient to maintain adequate perfusion, and treatable syndromes such as cardiac tamponade and pulmonary embolus have been addressed, the addition of tMCS, including intra-aortic balloon pump (IABP), percutaneous ventricular assist device (VAD) (Impella©), or veno-arterial

**Table 1** Validated severity scores predictive of poor prognosis following cardiac arrest

| Risk Score | Population | Location of arrest | Score variables/grades | Outcomes | Risk of unfavorable outcomes |
|---|---|---|---|---|---|
| MIRACLE$_2$ score [16•] | King's Out of Hospital Cardiac Arrest Registry (KOCAR) | OHCA | Missed (unwitnessed arrest)<br>Initial non-shockable rhythm<br>Non-reactivity of pupils<br>Age > 60 or > 80<br>Changing rhythms<br>Low pH < 7.20<br>Epinephrine given | Primary end-point: Poor neurological outcome at 6-month follow-up (Cerebral Performance Category 3–5) | Low risk: 0–2<br>Medium risk: 3–4<br>High risk: 5–10 |
| Pittsburgh Cardiac Arrest Category (PCAC) [130] | Two tertiary care centers; University of Pittsburgh Medical Center | IHCA and OHCA | Grade 1: Awake<br>Grade 2: Comatose, no cardiopulmonary failure<br>Grade 3: Comatose with cardiopulmonary failure<br>Grade 4: Deep coma + loss of some brainstem reflexes | Primary outcome: Survival to hospital discharge<br>Secondary outcome: CPC and modified Rankin Scale (mRS) at discharge | 4-level illness severity score as described |
| Cardiac Arrest Hospital Prognosis (CAHP) [128] | Sudden Death Expertise Center registry, France | OHCA | Age<br>Location of cardiac arrest<br>Initial rhythm<br>Duration from collapse to basic life support<br>Duration from CPR to ROSC<br>Total Epinephrine dose<br>Arterial pH | Primary outcome: Poor neurological outcome defined as CPC 3–5 at hospital discharge | Low risk: < 150<br>Moderate risk: 150–200<br>High risk > 200 |
| Out-of-Hospital Cardiac Arrest Score [129] | Four Tertiary Care Centers, France | OHCA | Initial rhythm<br>Estimated no-flow and low-flow intervals<br>Serum lactate at ICU admission<br>Creatinine at ICU admission | Primary outcome: Survival with poor neurological outcomes (CPC 3–5) | Prognostic categories<br>> 2.0<br>> 17.4<br>> 32.5 |
| Target temperature management risk score [175] | TTM Trial Patients | OHCA | Age<br>Location of cardiac arrest (home or not)<br>First monitored rhythm<br>No flow and low flow time<br>Treatment with Epinephrine<br>Pupillary or corneal reflex<br>pH and pCO2<br>GCS motor score | Neurologically poor outcome, CPC 3–5 at 6 months | Low risk > 10<br>Intermediate > 13<br>High risk > 16 |

extracorporeal membranous oxygenation (VA-ECMO), may effectively augment CO to reach hemodynamic goals [50••]. Device use and selection are based largely on the amount of cardiovascular support needed as well as provider and institutional access and expertise. In addition, device selection is patient specific, and patient characteristics may present contraindications to certain devices. For example, a prior mechanical aortic valve replacement or LV thrombus would preclude Impella© or significant aortic insufficiency will preclude the use of IABP and VA ECMO. More general recommendations regarding the decision to initiate tMCS, device selection, and how to escalate tMCS are available [50••]; however, few studies have evaluated the superiority of one circulatory support device over another in the post-arrest setting. A retrospective study of patients from the PROCAT (Parisian Region Out of Hospital Cardiac Arrest) registry with post-arrest shock compared the use of IABP with Impella© and showed no difference in survival; however, patients supported with the Impella© trended towards higher rates of serious bleeding (26% versus 9%), albeit in the setting of therapeutic hypothermia (TH) [49].

VA-ECMO provides the highest level of cardiovascular and pulmonary support [51, 52]. There is conflicting data regarding the efficacy of VA-ECMO as a salvage therapy in the setting of ongoing refractory CA. With the promise of saving 40–45% of patients with refractory shockable OHCA [53], there has been an increased use of VA-ECMO for extracorporeal cardiopulmonary resuscitation (ECPR) [54]. The successful implementation of ECPR depends on appropriate patient selection and dedicated centers with high levels of expertise [13, 55, 56]. Generally, patients who are placed on ECMO during CA remain supported through the aforementioned cardiac stunning period until cardiac function improves.

### Implantable Cardioverter Defibrillator

ICD implantation is recommended in patients following successful resuscitation from VF or hemodynamically unstable VT without any completely reversible causes [57, 58]. Approximately, 55% of OHCA patients will have a reversible cause; most commonly MI (55–58%) or electrolyte abnormalities (10–20%) [59, 60], and do not necessarily require an ICD. Despite addressing reversible causes, some patients continue to have ventricular arrhythmias. If these tachyarrhythmias continue > 48 h following an MI in the absence of ongoing ischemia [61] patients are at an increased risk of death compared to those with ventricular tachyarrhythmia < 48 h following MI (HR 20.7 versus 7.45) [62] requiring consideration of ICDs. Current guidelines do not address ICD implantation in post-arrest survivors with reversible causes but persistent arrhythmia after > 48 h [10••, 11••].

## Ventilatory Management

Pulmonary complications are common after CA and have a variety of etiologies including cardiogenic pulmonary edema, aspiration pneumonitis, ischemia–reperfusion injury, acute respiratory distress syndrome (ARDS), atelectasis, pneumonia, pulmonary contusion from cardiac compressions, and ventilator-associated lung injuries [63]. In this setting, lung protective mechanical ventilation is necessary for the optimization of lung mechanics, while simultaneously avoiding hyperoxemic free radical production and ameliorating acid–base disturbances to improve the homeostatic milieu for neurologically favorable survival [64].

### Tidal Volume

Mechanical ventilation strategies are particularly important post-arrest due to the complex interplay between positive pressure ventilation and intra-thoracic hemodynamics as well as right and left ventricular preload and afterload [65]. The majority of CA patients are supported with lung protective ventilation settings, including low tidal volumes ($V_T$), and minimizing driving and plateau pressures ($P_{PLAT}$) [66]. Current evidence in post-arrest patients without ARDS is limited with variable findings. The Protective Ventilation in Patients without ARDS (PReVENT) trial randomized patients who received invasive ventilation for indications other than ARDS and comprised nearly 25% of CA patients ($N = 230$). Low $V_T$ strategy, 4–6 mL/kg predicted body weight (PBW), did not result in a difference in number of ventilator-free days or mortality at 28 days compared to an intermediate $V_T$ strategy, 10 mL/kg PBW, decreasing by 1 mL/kg PBW per hour if $P_{PLAT} > 25$ $cmH_2O$ [67]. However, observational studies and retrospective reviews have shown that lower $V_T$ ($\leq 8$ mL/kg PBW) is associated with favorable neurological outcomes and more ventilator-free days among OHCA patients [68, 69]. Current expert consensus for post-arrest patients suggests $V_T$ between 6 and 8 mL/kg PBW is reasonable [10••] with a primary $CO_2$ goal of normocarbia ($PaCO_2$ 35–45 mmHg) and avoidance of hypo or hypercarbia [64].

### Positive End-expiratory Pressure (PEEP)

PEEP is the positive pressure that remains in the airway at the end of the respiratory cycle and has important therapeutic implications following CA. Inadequate PEEP increases the risk of atelectasis [70] while excessive PEEP increases intrathoracic pressure causing an unwanted decrease in right ventricular venous return. In addition, PEEP has a complicated relationship with RV afterload and LV hemodynamics that can result in a dramatic reduction in CO and hemodynamic collapse. The net effect of PEEP on ventricular

function and CO is unique to each patient and their pathology. Alviar et al. illustrate the principles governing these interactions well in their article published in JACC in 2018 [65]. In a recent sub-analysis of the TTM2 trial comprising 1848 post-arrest patients, PEEP alone was not an independent predictor of mortality in OHCA [71].

### Plateau and Driving Pressure

$P_{PLAT}$ and driving pressure (ΔP) reflect end-inspiratory small airway pressure when there is no air movement and distending pressure of the lungs as measured as the difference between $P_{PLAT}$ or and PEEP. Excessive $P_{PLAT}$ or ΔP has been correlated with barotrauma and ventilator-associated lung injuries [72•, 73]. Changes in VT directly affect $P_{PLAT}$ and ΔP, where direction and magnitude are dependent on underlying static compliance of the lung [74]. High ΔP has been independently associated with 6-month mortality among patients after CA [71]. Mechanical power (MP) is a measure of energy transferred from the ventilator to the respiratory system per unit time, computed by minute ventilation, inspiratory flow, peak airway pressure, and PEEP [75, 76]. High MP has independently been associated with higher ICU and hospital mortality, fewer ventilator-free days, and longer ICU and hospital length of stay [77]. Additionally, high MP has shown to be an independent predictor of 6-month mortality in patients following CA [71].

## Neurologic Support: Preventing Secondary Brain Injury

Neurologic injury is the largest contributor to mortality and poor neurologic outcomes in patients after CA [25]. As care for patients who have suffered CA has improved, our understanding of primary and secondary brain injury has increased.

Primary brain injury occurs following cessation of cerebral blood flow (CBF) due to depletion of neuronal glucose and oxygen delivery. Anaerobic respiration causes mitochondrial dysfunction, reactive oxygen species (ROS) formation, ATP depletion, and intracellular $Ca^{2+}$ accumulation. These processes lead to widespread cellular damage, loss of cell polarity integrity, cytotoxic edema, and programmed cell death. $Ca^{2+}$ release causes the release of the glutamate resulting in neuronal excitotoxicity and further injury [78–80] Secondary brain injury occurs after restoration of CBF with return of spontaneous circulation (ROSC). Immediately after ROSC, CBF is characterized by early relative hyperemia followed by hypoperfusion resulting in endothelial dysfunction and microcirculatory abnormalities [78, 80, 81]. Additionally, cerebral autoregulation becomes significantly impaired post-arrest, leading to instability in CBF susceptible to fluctuations in MAP and $CO_2$ [82, 83]. Compounding the ischemic injury, endothelial dysfunction caused by cytotoxic damage leads to microthombi and increased cellular permeability worsening cerebral edema [78]. The goal of post-arrest neurologic care is to minimize secondary brain injury.

### Mean Arterial Pressure Goals

Optimal blood pressure targets in this population are unknown; however, they may be of particular importance to ensure adequate CBF in the setting of abnormal cerebral autoregulation and cerebral edema that occurs after anoxic brain injury [84••]. Guidelines recommend avoiding hypotension, SBP < 90 mmHg, or mean arterial pressures (MAP) < 65 mmHg, but lack specific MAP targets. Some have hypothesized MAP targets > 80 mmHg may improve cerebral perfusion [85]; however, the Neuroprotect trial randomized 112 OHCA patients to "early goal-directed hemodynamic optimization" (EGDO) defined as MAP 85–100 mmHg and SvO2 65–75% versus MAP of 65 mmHg. The EGDO group showed improved estimates of cerebral perfusion and oxygenation but failed to reduce anoxic brain injury on MRI or improve neurologic outcomes when compared to the standard-of-care group [86]. Similarly, the BOX trial evaluated MAP targets of 63 mmHg versus 77 mmHg in comatose adults after OHCA and noted no difference between the groups for all-cause death, severe neurological disability, or coma [84••]. This suggests that at a population level, elevated MAP goals do not improve outcomes; however, there are ongoing studies to identify patients who may benefit from higher MAP goals [87]. Generally, hemodynamics should be maintained to optimize end-organ perfusion as demonstrated by urine output > 0.5 mL/kg/h and normal or decreasing lactate [10••, 11••].

### Therapeutic Hypothermia and Targeted Temperature Management

TH has been theorized to mitigate secondary brain injury with several experimental models and early human studies suggesting improved neurologic outcomes [88–92]. However, these results have not translated to large randomized human studies. The Targeted Temperature Management (TTM) and TTM2 trials showed no difference in all-cause mortality when comparing TH (32-34°C) versus normothermia (36–37.5°C) for 28 h following ROSC [93, 94••] (Table 2). Hyperthermia is associated with worse neurologic injury following CA [95, 96]. As such, avoidance of hyperthermia has been considered a standard of practice; however, the optimal duration of strict fever avoidance is unknown [97–100]. Hassanger et al. investigated the role of device-based hyperthermia prevention for 24 h versus 72 h. Their randomized control trial (RCT) of 393 patients showed no

**Table 2** Selected trials evaluating various therapeutic hypothermia protocols

| Trial | Journal year | Population | Control | Intervention | *N* (total) | CPR time (ctrl/intv) (min) | Duration of cooling (h) | Median time from arrest to target temp (h) | Favorable neurologic outcome (ctrl/intv) | Mortality (ctrl/intv) | Adverse events and safety outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| HACA [92] | NEJM 2002 | OHCA VT/VF | Normothermia | 32–34 °C | 275 | 22 /21 | 24 | 8.5 | 55%/39% | 55%/41% | No difference |
| Bernard [90] | NEJM 2002 | OHCA VF | Normothermia | 33 °C | 77 | 25 /26 | 12 | 2.25 | 49%/26% | NA | No difference |
| TTM [93] | NEJM 2013 | OHCA all rhythms | 36 °C | 33 °C | 950 | 25 /25 | 28 | 12 | No difference | No difference | Hypokalemia with hypothermia |
| TTH48 [173] | JAMA 2017 | OHCA "presumed cardiac," all rhythms | 33 °C × 24 h | 33 °C × 48 h | 355 | 20/21 | 24 vs 48 | 5.6 vs 5.0 | No difference | No difference | Hypotension with 48 h |
| Hyperion [91] | NEJM 2019 | IHCA/OHCA nonshockable | 36.5–37.5 °C | 33 °C | 581 | 18 /15 | 24 | 9–12 | 10.2%/5.7% | No difference | No difference |
| TTM2 [94••] | NEJM 2021 | OHCA all rhythms | ≤ 37.5 °C | 33 °C | 1861 | 25 /25 | 28 | 5.5 | No difference | No difference | Arrhythmia with HD compromise with hypothermia |
| Capital Chill [174] | JAMA 2021 | OHCA all rhythms | 34 °C | 31 °C | 389 | 18/20 | 24 | 6.9 vs 5.8 | No difference | No difference | No difference |

*OHCA* out−of−hospital cardiac arrest, *IHCA* in−hospital cardiac arrest, *VT* ventricular tachycardia, *VF* ventricular fibrillation

difference in mortality or severe disability/coma between the groups (33.6% versus 32.3%) [101]. The guidelines synthesize this data by advocating for TTM with a target temperature of 32 to 36 °C for at least 24 h followed by fever prevention for at least 72 h though adjudication with TTM trial data is expected in future iterations [10••, 11••].

## Oxygenation and Ventilation Targets

Post-arrest oxygen targets balance the deleterious effects of tissue hypoxia and reperfusion-related oxygen-derived free radicals. Observational evidence demonstrates higher in-hospital mortality among OHCA patients with hypoxemia (partial pressure of arterial oxygen; PaO2 < 60 mmHg) related to organ tissue hypoxia and hyperoxemia (PaO2 > 300 mmHg) within 24 h following ROSC [102, 103]. In the BOX trial, Schmidt et al. observed similar composite outcomes of death and severe disability/coma, among patients who were treated with restrictive oxygen target (PaO2 68–75 mmHg) after ROSC versus liberal oxygen targets (PaO2 98–105 mmHg) [104••]. Current guidelines recommend a 100% fraction of inspired oxygen (FiO2) initially followed by titration to SpO2 94–98% or a PaO2 75–100 mmHg after reliable pulse oximetry or blood gas values are available [10••, 11••].

Partial pressure of arterial carbon dioxide ($PaCO_2$) is a key determinant of cerebral hemodynamics [105]. Acute hypocapnia induces cerebral vasoconstriction, a rise in cerebral vascular resistance, and a fall in cerebral perfusion [105]. In contrast, an acute rise in $PaCO_2$ induces the opposite effect with increased blood flow to the brain increasing the total intracranial volume potentially exacerbating cerebral edema's compressive effects [106, 107]. The TAME trial, a large RCT, showed that targeted mild hypercapnia (PaCO2 50–55 mmHg) did not lead to better neurologic outcomes compared to targeted normocapnia in OHCA patients [108••]. A meta-analysis by McKenzie et al. suggested both hyper and hypocarbia were associated with an increased mortality compared to normocarbia in post-arrest patients [109].

## Sedation

Sedation selection post-arrest has not been well studied. Guidelines recommend short-acting sedatives and analgesics to not interfere with neuroprognostication [10••, 64]. Ketamine has been described as neuroprotective through its action as an NMDA receptor antagonist [110–113]. It may be useful in preventing secondary brain injury driven by the upregulation of NMDA receptors, increased intracellular $Ca^{2+}$, ROS production, and activation of programmed cell death. Several small preclinical studies have shown promise [110, 114]; however, no human trials have investigated this potential mechanism.

## Neuroprognostication

Neuroprognostication is a challenge for clinicians and a dynamic process requiring frequent evaluation and multiple testing modalities. Prognostication should be delayed at least 72 h post ROSC and rewarming if TH is used and residual sedation and metabolic abnormalities should have resolved [115••]. Persistent coma 72 h post-arrest does not necessarily equate with poor neurologic prognosis. About 10–22% of patients will awaken after 72 h post-arrest [116–121]; with case reports of awakenings after 2 and even 4 weeks [121–127]. While survival with neurologically favorable outcomes remains modest in the post-arrest population [1, 3], a meticulous understanding of neuroprognostication may help prevent premature withdrawal of life-sustaining treatment in patients who may go on to have a favorable recovery.

Many factors determine the extent of brain injury including time without CPR, time to first responder, length and quality of CPR, comorbid conditions, baseline neurologic function, and post-arrest care during the vulnerable period for secondary brain injury. Many scores have been developed to quantify initial risk which include the CAHP, OHCA, MIRACLE2, and PCAC scores (Table 1) [23, 128–130]. Patients with catastrophic brain injury or signs of neurologic recovery may declare themselves early with catastrophic findings on head imaging such as herniation and/or wakefulness respectively. Thus, the goal of neuroprognostic tools focuses on those indeterminate comatose patients without a clear neurologic trajectory.

## Neurologic Examination

The neurologic exam remains one of the most useful tools for patients following resuscitation and a daily exam is recommended [10••]. The level of consciousness, pupillary and ocular findings, best motor response, and myoclonus are clinical exam features used in prognostication post-arrest.

Bilaterally absent pupillary light response at least 72 h following ROSC and rewarming, if applicable, portends poor neurologic outcomes. Bilateral absence of the corneal reflex at 72 h is less specific and should not be considered a reliable predictor of outcome due to the high false positive rate [115••]. Similarly, 72 h after ROSC, an absence of the ability to follow commands or extension response should not be considered a reliable predictor of poor outcome [115••].

Myoclonus is the sudden and involuntary contraction of muscle frequently seen in ICU patients [131]. In post-arrest patients, it was once thought to be a sign of extremely poor neurologic outcomes [132, 133]. However, it is now clear this is not the case [134], and myoclonus is not a reliable predictor of poor outcomes [115••]. Status myoclonus, a similar but sustained entity, is defined as spontaneous repetitive generalized multifocal myoclonus in comatose patients lasting ≥ 30 min within 72 h of CA involving the face, limbs,

and axial musculature and has traditionally been associated with a poor prognosis [133]. Electroencephalography (EEG) may be able to help identify salvageable subgroups with early or status myoclonus [135].

### Neuroimaging

Shortly (< 2 h) after ROSC, a computer tomography (CT) may be obtained to assess for a neurologic etiology of the arrest and signs of catastrophic neurologic injury [11••]; however, early scans are often too soon to see ischemic changes from anoxic injury. Guidelines recommend imaging within 72 h to assess for brain edema which can be quantified with the ratio of the density of the grey matter and the white matter at pre-specified locations [136, 137]. A diffuse pattern of loss of grey-white differentiation with sulcal effacement at least 48 h from ROSC is a moderately reliable predictor of poor outcome [115••].

Similarly, MRI studies can detect neuronal cytotoxic edema. Hyperintensities on diffusion-weighted images (DWI) days 2–7 after ROSC are a moderately reliable predictor of poor outcomes [115••]; however, this modality is limited by conditions such as hyperammonemia, seizures, and status epilepticus as these can also cause cytotoxic edema and DWI hyperintensity [115••].

### Electroencephalography

EEG is recommended in all post-arrest patients [10••, 11••, 138]. EEG suppression (background voltage < 10 μV [139]) and burst suppression pattern have been classified as "highly malignant" at 72 h following CA with high specificity (100%) for poor neurologic outcomes but lacked sensitivity (50%) [115••, 140]. The presence of status epilepticus and status myoclonus are no longer invariably associated with poor outcomes [115••]. EEG tracings must be interpreted in the absence of confounders such as hypothermia, ongoing sedation, and metabolic derangements.

Seizures are common in survivors of CA occurring in 10–35% of this population [64, 78, 141]. Aggressive treatment of seizures based on current practice guidelines [142] is recommended [10••]. The TELSTAR trial showed that suppressing rhythmic and periodic EEG activity (non-seizure activity) with the use of anti-seizure medication in survivors of CA showed no benefit [143].

### Somatosensory Evoked Potential (SSEP)

SSEP testing is a recommended neurophysiologic study used to neuroprognosticate following CA [10••, 11••, 113]. SSEPs assess the afferent functionality of thalamocortical connections in comatose patients. At least 48 h after ROSC bilateral absence of the cortical response with preservation of the cervical spine response is associated with poor outcome with high specificity and variable sensitivities [115••].

### Serum Biomarkers of Neurologic Injury

Several biomarkers have been shown to be markers for severe neuronal injury and poor neurologic outcomes [144]. Neuron-specific enolase (NSE), from neurons and glial cells, and s-100B, from astrocytes, are the only serum biomarkers given a recommendation in published guidelines [10••]. Both are structural proteins released in the setting of hypoxic brain injury. NSE has delayed release following injury thus presenting levels can be normal despite severe injury. Levels at 24 h have the highest specificity for poor neurologic outcomes [145]. Several studies have shown that serial measurements at 48 h and 72 h can be even better predictors and an increase of NSE between any two time points being associated with poor outcomes. On the contrary, patients with decreasing levels of NSE at 48 h are more likely to have a good neurologic recovery [144–146]. The ERC/ESICM 2021 guidelines state an NSE > 60 μg/L at 48 h may be associated with poor neurologic outcomes [10••]; while the other guidelines caution against the use of NSE alone, describing it as an unreliable predictor of functional outcome owing to the inconsistency of its predictive value related to various and unclear thresholds [11••, 113].

### Multimodal Approach

Neuroprognostication is challenging for clinicians and requires a pragmatic approach. Guidelines strongly recommend a multimodal approach as no single test has sufficient positive predictive value [10••]. This approach includes a combination of clinical exams, neuroimaging, neurophysiological (EEG and SSEP), and biomarker data. This data should be interpreted with assistance from experienced providers familiar with recommended testing modalities.

## Other Supportive Measures

### Empiric Antibiotic Use

While bacteremia may be common (13–38%) [147, 148], empiric antibiotic use in this setting is not well understood. Pneumonia is even more common occurring in up to 61% of patients [148, 149]. Several RCTs and meta-analyses indicate that the use of prophylactic antibiotics in post-arrest patients does not significantly reduce the length of ICU stay or overall mortality rate [150–152]. However, an empiric 2-day course of amoxicillin-clavulanate decreases

the incidence of early-onset pneumonia in OHCA patients treated with TH, presumably related to aspiration events during the CA [150, 151]. While the 2015 AHA guidelines do not comment on prophylactic antibiotic use, the ERC/ESICM 2021 guidelines advise against them [10••].

### Nutrition

There is scarce data regarding the optimal timing of nutrition initiation in post-arrest patients. Post-resuscitation care including the use of vasopressors and TH if applicable may lead to hypo-perfusion and ischemia of the gastrointestinal system [153, 154]. Furthermore, TH can result in decreased absorption and peristalsis leading to increased gastric residuals and aspiration [155]. On the other hand, early initiation of feeding (within 24 h to 72 h) in general critically ill patients is associated with decreased mortality, decreased infection, and favorable outcomes [156–159]. In the post-arrest population specifically, studies have shown conflicting results regarding the superiority of early (< 48 h after admission to the ICU) versus delayed (> 48 h after admission to the ICU) feeding in patients treated with TH [160, 161]. The guidelines recommend starting enteral trophic feeding during TH and increasing the rate after rewarming if TH is implemented [10••].

### Renal Replacement Therapy (RRT)

Acute kidney injury (AKI) occurs in more than 45% of patients after CA and at least a third of these patients require RRT [162, 163]. AKI has been associated with an increased risk of mortality; however, the relationship between RRT and mortality post-arrest is not as clear [164–168]. Risk factors for AKI post-arrest include increased age, poor baseline renal function, increased resuscitation time, OHCA outside the public setting, initial non-shockable rhythm, and post-resuscitation shock. Currently, there are no specific guidelines regarding the timing of RRT post-arrest and general indications apply. Notably, renal recovery occurs in most survivors [166].

### Usual ICU Care

Best practices in general intensive care management should be used, including deep venous thrombosis and stress ulcer prophylaxis [10••, 169, 170]. Optimum blood glucose concentration is unknown in the post-arrest period, but strict glucose control (72–108 mg/dL) has no survival benefit and may be harmful secondary to hypoglycemia [171]. Guidelines have recommended a target glucose level of 140–180 mg/dL [10••, 11••, 172].

## Conclusion

Research in post-arrest care and our understanding of ideal management to promote neurologic recovery continues to grow yet much work remains. As our understanding of these complex patients continues to deepen, it is imperative that cardiologists engage in multidisciplinary team approaches to patient care and remain vigilant to their commitment to evidence-based practices and contributing to research endeavors that advance the field.

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare no competing interests.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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