Critical Care Management Focused on Optimizing Brain Function After Cardiac Arrest

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The discussion of neurocritical care management in post-cardiac arrest syndrome (PCAS) has generally focused on target values used for targeted temperature management (TTM). There has been less attention paid to target values for systemic and cerebral parameters to minimize secondary brain damage in PCAS. And the neurologic indications for TTM to produce a favorable neurologic outcome remain to be determined. Critical care management of PCAS patients is fundamental and essential for both cardiologists and general intensivists to improve neurologic outcome, because definitive therapy of PCAS includes both special management of the cause of cardiac arrest, such as coronary intervention to ischemic heart disease, and intensive management of the results of cardiac arrest, such as ventilation strategies to avoid brain ischemia. We reviewed the literature and the latest research about the following issues and propose practical care recommendations. Issues are (1) prediction of TTM candidate on admission, (2) cerebral blood flow and metabolism and target value of them, (3) seizure management using continuous electroencephalography, (4) target value of hemodynamic stabilization and its method, (5) management and analysis of respiration, (6) sedation and its monitoring, (7) shivering control and its monitoring, and (8) glucose management. We hope to establish standards of neurocritical care to optimize brain function and produce a favorable neurologic outcome.

Key Words: Critical care management; Neurologic indications; Post-cardiac arrest syndrome; Secondary brain damage; Targeted temperature management

Post-cardiac arrest syndrome (PCAS) is defined as a complex syndrome consisting of brain injury, myocardial dysfunction, and systemic ischemia/reperfusion response after cardiac arrest. Definitive therapy includes the management of pathologies that result from cardiac arrest in addition to those causing the cardiac arrest. Representative therapy of the former is neurocritical care, including targeted temperature management (TTM), and the latter is coronary intervention.

PCAS is a major cause of death or disability after cardiac arrest, therefore its definitive treatment needs to be established. Following landmark studies of therapeutic hypothermia in 2002\(^1\) and TTM in 2013,\(^3\) the focus of neurocritical care management in PCAS has been on targeted values for TTM, including body temperature targets and duration of temperature management.\(^5,6\) By contrast, there has been little discussion on the monitoring and targeting values for cerebral and systemic parameters. In addition, little research has been done to clarify the neurologic indications for TTM to produce a favorable neurologic outcome. Lack of standards of care and poor adherence to recommended management for PCAS may be associated with poor outcomes.\(^7\)

The purpose of post-cardiac arrest care is to improve the patient’s neurologic outcome. We present a scheme of post-cardiac arrest care focusing on brain function in Figure 1. Post-arrest care comprises care of brain parameters, including prediction of outcome, cerebral blood flow (CBF) and metabolism, and seizures. Post-arrest care also comprises care of systemic parameters, including hemodynamics, respiration, sedation, shivering, and glucose levels, as well as TTM. Cooperation between cardiologists performing special treatment, such as coronary intervention, and general intensivists performing intensive care, such as respiratory care, is necessary.

We reviewed the literature about out-of-hospital cardiac arrest (OHCA)/in-hospital cardiac arrest (IHCA) up to August 2016 in PubMed, in English, to assess these topics and propose practical management goals. We aimed to review the literature for cardiologists and general intensiv-
with OHCA treated with therapeutic hypothermia. A single test, even patients with a GCS motor score of 1 had a 52.2% probability of good neurologic outcome after TTM. There was a significantly better outcome in patients with pupil diameters ≤4 mm compared with those with pupils ≥4 mm.

EEG monitoring has also been used to estimate neurologic outcome. Recent studies noted that time to continuous normal voltage (CNV) on amplitude-integrated EEG (aEEG) within 24 h after return of spontaneous circulation (ROSC) was associated with a good outcome. Researchers reported that a cutoff value of 1.17 for the gray matter to white matter attenuation ratio (GWR), comparing the putamen and corpus callosum, predicts a poor neurologic outcome with a specificity of 100% on a CT obtained immediately after ROSC (median, 69.5 min). Another report on GWR, averaging the basal ganglia and cerebrum, found that a cutoff value of 1.14 also predicted a poor neurologic outcome with a specificity of 100%. In both studies, sensitivity was low. Thus, lower normal values of GWR on brain CT obtained immediately after resuscitation can predict a poor neurologic outcome in patients with OHCA.

Other researchers reported that regional saturation of oxygen (rSO2) ≥40% on arrival at the hospital predicted
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on aEEG within 24 h of ROSC represents a good outcome. We emphasize the use of multiple modalities or predictive models (e.g., pupil diameter, GCS, aEEG, GWR on CT, rSO2, 5-R score etc.) to evaluate brain damage and inform decision making regarding the initiation of TTM at the time of admission.

**CBF and Metabolism**

Jugular vein oxygen saturation (SjO2) and cerebral oxygen saturation (ScO2), such as rSO2, indicate the intracranial balance of CBF and metabolism. However, no studies have investigated tissue oxygen saturation as a guide to managing systemic circulation, respiration, or oxygen balance.

We consider ScO2 measured by near-infrared spectroscopy to represent the sum total of systemic function (e.g., airway, breathing, circulation, time course after arrest, and clinical conditions such as fever, shivering etc.). We therefore think it is important to understand the factors contributing to oxygen balance. In this section, we first explore the relationship between various cerebral oxygen parameters to offer a basis for discussion in the following section on the management of systemic parameters, and then discuss about the validity of using SjO2 or ScO2 for neuromonitoring PCAS.

**Changes in CBF and Metabolism After Cardiac Arrest**

Factors affecting the relationship between CBF and metabolism are shown in Figure 2. For example, decreased blood viscosity is associated with an increase of SjO2. Blood transfusion may decline SjO2 or ScO2 by increasing viscosity, though generally it is believed that blood transfusion brings SjO2 higher. Similarly, a decrease in ScO2 may be caused by fever, shivering and insufficient sedation. Decreases in cardiac output (CO) because of cardiogenic shock, hypovolemia, low systemic vascular resistance (SVR), or with excess sedatives may also influence ScO2. In addition, hypocapnia may reduce SjO2 because of cerebral vasosstriction. On the other hand, it may increase SjO2 because...
NAKASHIMA R et al. have a similar vector to $S_j O_2$, instead of a difference of measurable brain area ($S_c O_2$ measures the frontal area of brain; $S_j O_2$ reflects the whole hemisphere).

In a study comparing $S_c O_2$ measured by the INVOS® near-infrared system and $S_j O_2$ measured by jugular bulb oximetry, INVOS indicated significantly higher values at low $S_j O_2$ ($\leq 60\%$) and significantly lower values at high $S_j O_2$ ($\geq 60\%$) in patients after cardiac arrest.

Another study indicated the feasibility of monitoring intracranial oxygen saturation during the post-resuscitation period.

However, no studies have investigated tissue oxygen saturation as a guide to managing systemic circulation, respiration, or oxygen balance. In addition, the algorithm of calculating $S_c O_2$ is undocumented. Therefore, it is difficult to analyze $S_c O_2$, but it has the possibility of becoming a monitoring method that contributes to better neurologic outcome.

Summary $S_j O_2$ and $S_c O_2$ may reflect systemic or cerebral conditions such as mean arterial pressure (MAP), partial pressures of oxygen and carbon dioxide in arterial blood ($P_a O_2, P_a CO_2$, respectively), body temperature, etc. It is difficult, however, to analyze the $S_j O_2$ or $S_c O_2$ value in patients undergoing TTM because knowing only the target value for $S_c O_2$ is inadequate without understanding other factors influencing $S_j O_2$ or $S_c O_2$. $S_c O_2$ must therefore be assessed very carefully.

Figure 3. aEEG (Upper) and cEEG (Lower) of CNV, ESE, BS, and low voltage during TTM after cardiac arrest. ESE evolving from CNV reflects a less injured brain, although ESE evolving from BS is resistant to treatment and reflects poor outcome. Initial low voltage has no prognostic value. BS, burst-and-suppression; ESE, electrographic status epilepticus. Other abbreviations as in Figure 1.
Detection, Treatment, and Prevention of Seizures
Seizures are not only the result of brain injury caused by cardiac arrest but also a risk for secondary brain injury. Seizures are caused by abnormal excessive or synchronous neuronal activity in the brain. They are classified as generalized convulsive seizures or non-convulsive seizures. Muscle contraction and relaxation are absent in the case of non-convulsive seizures. The incidence of non-convulsive seizures after cardiac arrest is from 12% to 24% in adults and up to 47% in pediatric cardiac arrest cases. Some studies indicate that seizures occur most often within the first 8 h after ROSC according to continuous EEG (cEEG) records. Seizures are masked by neuromuscular blockage (NMB) in between 3% and 44% of cases. For these reasons, it is recommended to use cEEG for patients with PCAS.

Prognostication of Outcome by EEG aEEG monitoring is a well-developed type of quantitative EEG. One study reported the possibility of predicting outcome after cardiac arrest by using aEEG. An initial low-voltage aEEG had no prognostic value, but a burst-and-suppression (BS) pattern was strongly associated with a poor neurologic outcome at any time. Electrographic status epilepticus (ESE) had 2 patterns: ESE evolving from BS had an earlier start and was resistant to treatment, whereas ESE evolving from a continuous pattern evolved later. ESE evolving from a continuous pattern reflected a less injured brain that was potentially salvageable (Figure 3). Recent studies suggest that the appearance of CNV within 24 h of ROSC is associated with a good outcome.

Prophylactic and Therapeutic Use of Antiepileptic Drugs Although seizures may be the result of brain injury caused by the cardiac arrest, they may themselves also cause secondary brain injury. Some investigations have revealed that antiepileptic drugs (AEDs) do not decrease the incidence of convulsive seizures or improve neurologic outcome. As there is no standard method to diagnose seizures with cEEG and the drugs may cause adverse effects, the prophylactic use of AEDs is not recommended.

There is no high-grade evidence showing a relationship between AEDs and survival or neurologic outcome. But as seizures may lead to secondary brain injury, treatment of recurrent seizures could be considered as standard therapy in comatose patients with PCAS.

Summary The prognostic utility of aEEG has been validated. A continuous pattern or ESE with a continuous pattern is associated with good outcomes. However, there is a lack of evidence informing decisions on when or how to intervene with AEDs following the results of cEEG because of a lack of knowledge regarding the relationship between AEDs and PCAS.

Management of Systemic Parameters
Stabilization of Hemodynamics Myocardial systolic or diastolic dysfunction and a decline in SVR have been observed transiently in PCAS. In this section, we discuss the management of hemodynamics after ROSC.

MAP Target Value The question is how MAP should be managed to improve outcome in patients who have suffered a cardiac arrest. This has been investigated from various viewpoints. One study showed the best survival in patients with a MAP of 76–86 mmHg and mixed venous oxygen saturation (SvO2) of 67–72%. Another observational study assessed the relationship between MAP and outcome after ROSC, finding a time-weighted average MAP ≥70 mmHg was associated with a better neurologic outcome than lower levels. In a retrospective study, MAP ≥100 mmHg during the 2 h after ROSC was associated with better neurologic recovery at hospital discharge.

On the other hand, a study by Young and colleagues found no relationship between higher MAP during therapeutic hypothermia and neurologically intact survival. Similar to early goal-directed therapy in sepsis, some investigators looked not only at MAP but also at other hemodynamic factors (e.g., central venous oxygen saturation and hemoglobin). Bundled care with goals of MAP of 80–100 mmHg, CVP ≥8 mmHg, and central venous oxygen saturation ≥65% led to better neurologic outcomes and less mortality than in historic controls. A similar bundle requiring MAP ≥65–70 mmHg, CVP ≥8–12 mmHg, and hemoglobin ≥9–10 g/dL showed a better survival rate to hospital discharge and neurologic outcome at 1 year. Those studies suggest that MAP should be kept higher than a defined threshold during the post-arrest period. Although the cerebral perfusion pressure (CPP)-CBF relationship or autoregulation of CBF is theoretically impaired, there is no evidence that a higher MAP causes increased ICP and worsening of outcome. Therefore, it is reasonable to aim for MAP ≥65 mmHg at all times during TTM.

How to Achieve Hemodynamic Goals One study reported that the amount of fluid required to maintain MAP after arrest was 3.5–6 L. However, the relationship between fluid or blood products and outcome after ROSC is unclear, in contrast to what is known about albumin in sepsis.

If fluid resuscitation alone is ineffective, it is reasonable to use vasoactive drugs. There is, however, some concern about higher MAP achieved with vasoactive agents and poor outcomes.

The importance of heart rate control, another factor regulating CO, is controversial. In hypothermia, bradycardia occurs normally and is associated with reduced systolic dysfunction in animal models. Acute coronary syndrome is a common cause of cardiac arrest. In patients with ST-segment elevation or left bundle branch block on initial ECG after ROSC, the prevalence of an acute coronary lesion is more than 80%. Many observational studies indicate that percutaneous coronary intervention (PCI) improves survival or neurologic outcome. Some observational studies have also demonstrated better survival and functional outcome after ROSC achieved with a combination of TTM and PCI for ST-elevation myocardial infarction (STEMI). In one randomized controlled trial and pooled analysis without cardiac arrest, this combination reduced the size of the ischemic lesion of cardiac muscle in a case of hypothermia having been achieved when the coronary artery was reperfused. Studies of survival or neurologic outcome of emergency coronary intervention for non-STEMI are inconsistent, with some investigators finding it not helpful but others reaching the opposite conclusion.

By the way, cardiologists can participate in CPR or in intensive care after ROSC within their speciality. One study revealed that intra-aortic balloon pumping (IABP) with PCI contributed to improved neurologic outcome under cardiogenic shock after ROSC. Another study revealed that cardiopulmonary bypass (CPB) in addition to PCI improved neurologic outcome in patients who failed to respond to conventional CPR if the collapse-to-
bypass interval was within 55.5 min. It may be considered to institute IABP or CPB in a patient in whom it is suspected that the cause of cardiac arrest is reversible. And cardiogenic shock should not be a reason to avoid TTM.

**Summary** Recent studies indicate MAP should be maintained higher than a defined threshold during the post-arrest period. Although there is no evidence that a higher MAP causes harm, many studies indicate the MAP should be maintained above a certain threshold, the value of which has yet to be definitively determined. Therefore, we aim for MAP ≥ 65 mmHg at all times during TTM. To achieve this, we suggest the use of fluids, vasoactive agents, and immediate coronary interventions, particularly in cases of STEMI.

**Respiratory Support**

In this section, we discuss oxygenation and ventilation management after ROSC.

**Oxygenation** Hyperoxemia after ROSC promotes the formation of reactive oxygen species, which can induce secondary injury in brain tissue already damaged by cardiac arrest. Both observational studies and meta-analyses show that hyperoxemia is associated with poor survival and neurologic outcome in PCAS. Although the conclusions of other studies have differed, it may be necessary to avoid hyperoxemia after ROSC.

The etiology of hypoxemia in patients with PCAS includes lung contusion induced by chest compressions, atelectasis, ventilator-associated lung injury, and others. It is no wonder that hypoxemia in PCAS may induce secondary brain damage beyond that during the arrest itself. Some studies have indicated that hypoxemia after ROSC is associated with worse outcome than normoxemia. Both hypoxemia and hyperoxemia may need to be avoided after ROSC.

Positive end-expiratory pressure (PEEP) is another factor associated with oxygenation. Interestingly, according to an observational study, protective mechanical ventilation with a lower tidal volume and higher PEEP is more commonly used after cardiac arrest. This appears to reduce the incidence of pulmonary complications, although other organs are still at risk. A consensus on PEEP settings for patients with PCAS is lacking, although increasing PEEP may elevate ICP. It may therefore be rational to maintain PEEP as low as possible as long as higher concentrations of oxygen can be avoided.

**Ventilation** CO2 reactivity of the cerebral vasculature after ROSC is preserved during mild therapeutic hypothermia. Therefore, CO2 should be controlled during TTM. Hypocapnia following hyperventilation causes cerebral vasoconstriction and, based on some observational studies, it can certainly cause and/or worsen cerebral ischemia, worsen outcome, and cause injury to other organs in PCAS.

On the other hand, increased PaCO2 may cause further worsening of an elevated ICP by increasing the CBF. However, evidence of the effect of hypercapnia on outcome after ROSC is conflicting. Although one study found that S100b concentrations decreased over time in patients with PaCO2 maintained at 50–55 mmHg but not in those with a PaCO2 of 35–45 mmHg, hospital mortality did not differ significantly between the 2 groups.

Considering these studies, the risk of poor outcome appears to differ for hypocapnia and hypercapnia, even if differences in PaCO2 from normal are comparable. Therefore, clinicians should monitor for hypocapnia and avoid this outcome more than hypercapnia.

**pH-Stat and α-Stat** Ventilation strategies during therapeutic hypothermia are based on blood gas analysis using either the pH-stat or α-stat method. In the latter, mechanical ventilation is set to achieve a physiological PaCO2 level measured at 37°C, unadjusted to the patient’s actual temperature, whereas in the pH-stat method, ventilation is set to achieve a physiological PaCO2 measured at the patient’s actual temperature. Compared with pH-stat, the α-stat has less CO2 (Fig. 4).

With the α-stat method, autoregulation of the cerebral vasculature may be preserved and the incidence of cerebral microemboli can be decreased. On the other hand, this method may promote intracellular acidosis and impair cerebral oxygenation.

One study showed that after ROSC, SjO2 was significantly lower with the α-stat method compared with pH-stat method, whereas the arteriojugular oxygen content difference and CEO2 were significantly higher, but no differences were found in CBF measured by Doppler. For patients undergoing TTM after cardiac arrest, it remains unclear which method is best, and either method is probably acceptable, in contrast to recommendations for hypothermic arrest for cardiac surgery. However, we believe hypocapnia should be strictly avoided, measured by α-stat, which is more sensitive to hypocapnia than pH-stat.

**Summary** Both hypoxemia and hyperoxemia may need to be avoided after ROSC. PEEP should be kept as low as possible as long as higher oxygen concentrations can be avoided. Many studies indicate there is a risk of poor outcomes associated with hypoxemia; however, results regarding the association between hypercapnia and outcome have been conflicting. Therefore, clinicians should monitor for hypoxemia and avoid this outcome more than hypercapnia, especially when using α-stat.

**Sedation Management**

Sedation is widely used during critical illness. Light or minimal sedation is associated with shorter duration of mechanical ventilation, a shorter stay in the intensive care unit, and immediate coronary interventions, particularly in cases of STEMI.

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Critical Care Management for Cardiac Arrest

We should consider all the potential advantages and disadvantages of sedative drugs. Propofol, currently used in many ICUs, has a rapid onset and short duration of action. It is associated with a greater risk of hypotension with cerebral hypoperfusion than other drugs, as well as the risk of propofol infusion syndrome. Although intravenous sedative agents other than ketamine decrease the CMRO2 and CBF, propofol significantly decreases CBV by causing vasoconstriction.

Midazolam results in less hemodynamic instability than propofol, but it prolongs the duration of mechanical ventilation and length of ICU stay, and it may prolong the time to awakening and reduce the accuracy of the clinical examination. One study showed that patients undergoing TTM (≤33°C) recovered consciousness in a mean of 3.8 days, with approximately 20% awakening after 5 days post-arrest.

Benefits and Harms of Sedation During TTM Sedation may reduce secondary cerebral ischemia and decrease elevated ICP by reducing the CMRO2, CBF and cerebral blood volume. Sedation and analgesia also help control shivering and seizures, which is required for the induction and maintenance of TTM to reduce the risk of brain damage caused by seizures.

On the other hand, sedation makes it difficult to perform an accurate neurologic examination and clinical assessment. After arrest, residual sedation or paralysis confounds the clinical examination. One study showed that patients undergoing TTM (≤33°C) recovered consciousness in a mean of 3.8 days, with approximately 20% awakening after 5 days post-arrest.

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Dexmedetomidine is short-acting, provides mild to moderate sedation and analgesic effects, allows clinical assessment, and may be neuroprotective.\(^9\) Dexmedetomidine, however, frequently causes hypotension and bradycardia. Volatile anesthetics have been reported as efficacious,\(^8,9\) but there is little data allowing comparison with other sedatives. NMB is commonly administered during TTM, resulting in more rapid achievement and maintenance of target temperature and control of shivering.\(^9\) Some studies suggest that continuous NMB has a beneficial effect and improve outcomes,\(^9,10\) but it masks seizures. EEG monitoring should be considered in comatose patients after cardiac arrest, particularly if NMB is used.\(^8\) We present the drugs commonly used during TTM in Table 1, and sedation and anti-shivering methods in Figure 5.

**Monitoring the Depth of Sedation** The best choice of sedative for PCAS and the depth or dose of sedation is unknown. One review shows that moderate sedation may be effective and safe.\(^10\)

In critical care, conventional sedation scoring tools such as the Richmond Agitation Sedation Scale and the Sedation-Agitation Scale are widely used and may be reasonable tools in some brain-injured patients.\(^10\) However, in patients who are comatose, deeply sedated, or who have muscle flaccidity, these tools cannot be used to measure the depth of sedation. cEEG, quantitative EEG and bispectral index have been studied to monitor depth of sedation. Bispectral index values significantly correlated with Richmond Agitation Sedation Scale and the Sedation-Agitation Scale in brain-injured patients\(^10\) and may be useful for monitoring deeply sedated patients in the ICU.\(^10\) The EEG suppression ratio may also help assess the depth of sedation.\(^10\) However, these monitoring techniques are of questionable use in patients with PCAS because of changes in electrical activity in the brain cortex and the influence of shivering. Therefore, there is no reliable tool to monitor the depth of sedation during TTM.

**Weaning of Sedation** Early interruption of sedation during TTM causes shivering. In brain-injured patients, interruption of sedation causes increased ICP.\(^10\) Therefore, a wake-up test should be avoided during the first 24 h after ROSC.\(^10\) It is suggested that the tapering of sedative infusions should not exceed 25% per day.\(^10\)

In the patient at risk of brain edema or who has an elevated ICP, uncontrolled status epilepticus, and ongoing hypothermia, sedatives should not be abruptly discontinued. When weaning of sedation commences, attention should be paid to these risks with appropriate use of such tools as CT, EEG, and ICP monitoring.

**Summary** Sedation is essential for patients with PCAS during TTM because of the protective effect on the injured brain. As mild sedation is not always beneficial in PCAS, we suggest sufficient sedation while paying attention to seizures, shivering, and complications. The best choice of sedative drugs is unknown, as is the best monitoring method, particularly if NMB is used. However, the amount of sedation should be tapered slowly.

**Shivering Control**

Shivering is a physiologic homeostatic mechanism to maintain body temperature; it is usually initiated at approximately 36°C.\(^10\) Sustained shivering causes an increased metabolic rate and CO, increasing brain oxygen consumption and ICP.\(^10\) and it increases the stress response. Shivering commonly occurs during TTM and may lead to failure to achieve or maintain adequate hypothermia. Therefore, the management of shivering, including its evaluation and treatment, is important during TTM.

**Assessment and Suppression of Shivering** Shivering is often assessed with a subjective, simple, and reliable clinical scale such as the bedside shivering assessment scale (BSAS).\(^10\) Indirect calorimetry and electromyography have also been used.\(^10\)

At initiation of hypothermia, skin counterwarming with non-pharmacologic methods should be considered even when surface cooling methods are used for TTM.\(^11,12\) This involves the warming of non-cooled areas of the skin (i.e., the face, hands, feet) with a warm-air blanket. Pharmacologic methods include acetaminophen, buspiron, magnesium sulfate, meperidine, fentanyl, dexmedetomidine, propofol, midazolam, and NMB. To suppress shivering and prevent prolongation of sedation and paralysis, a stepwise anti-shivering protocol during TTM is suggested.\(^13\) In general, patients with PCAS who are comatose during TTM need tracheal intubation and therefore require sedation and analgesia. To suppress shivering, a combination of methods should be used (Figure 5). The advantages and disadvantages of these drugs (Table 1) should be carefully considered, and shivering should be aggressively controlled.

On the other hand, one recent study reported that patients with the most severe brain injury have less shivering.\(^14\) Other studies have shown that the faster the target temperature is reached, the higher the mortality and the worse the neurologic outcome.\(^11,14\) It is hypothesized that patients with more severe or irreversible neurologic damage are less reactive to low temperatures, so there is less shivering\(^11\) and less requirement for NMB.\(^15\) The relationship between shivering and outcome has yet to be fully elucidated.

**Summary** As shivering is a cause of failure to achieve or maintain TTM, shivering should be monitored using methods such as BSAS and aggressively controlled, including pharmacological or non-pharmacological methods.

**Glycemic Control in PCAS**

Glycemic control is important in the management of critically ill patients. Current concepts of glycemic control are to avoid hypoglycemia and minimize glycemic variability (GV). In this section, we discuss the characteristics of glycemic behavior after cardiac arrest and compare management of glucose in PCAS with that in other critically ill patients.

**Glycemic Behavior After Cardiac Arrest** Stress-induced hyperglycemia is a well-recognized phenomenon.\(^16\) Hyperglycemia has been observed in the early phase after cardiac arrest.\(^12\) During TTM, the incidence of hypoglycemia reportedly increased significantly during the rewarming phase compared with during maintenance.\(^12\) One analysis has reported that insulin sensitivity is significantly lower and more variable during the cooling period, but it increases with warming.\(^12\)

The association between early hyperglycemia after arrest and unfavorable neurologic outcome or death has been described in several studies.\(^12,13,14\) Delayed correction of hyperglycemia at admission was associated with unfavorable neurologic outcome and death.\(^15\) On the other hand, blood glucose levels at 12 h after ROSC had a non-linear association with a favorable neurologic outcome.\(^16\) Hyper-
glycemia after arrest may be a target for intervention, but it may merely reflect disease severity.

The effect of GV has been assessed, and an association between GV and mortality has been reported. One database study in France showed a smaller magnitude of GV was observed in patients with a good neurologic outcome compared with those with a poor outcome. Other studies report that increased GV was associated with increased mortality and unfavorable neurologic outcome. This suggests that attention should be paid to GV.

**Target Glucose Range** An optimal glucose target range is an important issue for patients with PCAS. One study showed that mortality in patients resuscitated from VF significantly increased with increasing mean blood glucose during the first 72 h of treatment. Another study examined a bundle of care that included a target glucose range (90–144 mg/dL). Their protocol improved survival and neurologic outcome at hospital discharge, but how much of this effect was related to glycemic control is unknown. A small randomized controlled trial comparing strict (target of 72–108 mg/dL) with moderate (target of 108–144 mg/dL) glucose control revealed no benefit of strict control on mortality at 30 days, and the trial was stopped.

Based on these studies, it appears that strict glucose control may not be necessary. However, it remains unclear what range of glucose levels is safe.

One analysis by the National Registry of Cardiopulmonary Resuscitation in the USA of patients with IHCA found interesting data suggesting that maximal glucose values above the range of 111–240 mg/dL and minimum values below the range of 71–170 mg/dL decreased survival odds in patients without diabetes.

For patients with diabetes, a similar result was found for minimum glucose values, but they appeared to be more tolerant of higher maximal glucose values.

**Summary** In patients with PCAS, the optimal target range remains unknown. However, insulin sensitivity increases and blood glucose levels decrease as body temperature rises during TTM. Further, patients with diabetes may be tolerant of higher glucose values. Accordingly, blood glucose levels should be checked frequently to avoid hypoglycemia and hyperglycemia.

**Conclusions** We are now in an era of tailoring the temperature target and duration of TTM depending on the degree of brain injury. However, the optimal target range remains unknown. Further studies are needed to determine the optimal target range for patients with PCAS.

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**Table 2. Factor or Parameters Comprising Post-Cardiac Arrest Care and Recommended Practical Method**

<table>
<thead>
<tr>
<th>Factor or parameter comprising of post-cardiac arrest care</th>
<th>Recommended practical use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prediction on admission</td>
<td>GCS, EEG, CT (GWR &lt;1.14), rSO2 (&lt;40%), prediction model recommend multiple modalities. Time to CNV on aEEG within 24 h after ROSC is associated with a good outcome.</td>
</tr>
<tr>
<td>CBF and metabolism</td>
<td>SjO2 or ScO2: N/A assess carefully</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>MAP: Maintain MAP &gt;65 mmHg at all times. HR: N/A. Emergency PCI: STEMI: recommend, non-STEMI: unknown. Other interventions: Massive fluid infusion, vasoactive agents, IABP, CPB.</td>
</tr>
<tr>
<td>Respiration</td>
<td>FIO2: Avoid hyperoxemia and hypoxemia. PEEP: Keep low as long as higher oxygen concentration can be avoided. PaCO2: Avoid hypocapnia, especially with β-stat.</td>
</tr>
<tr>
<td>Glycemic control</td>
<td>Check frequently. Target range: unknown.</td>
</tr>
</tbody>
</table>

BSAS: bedside shivering assessment scale; CBF, cerebral blood flow; CNV, continuous normal voltage; CPB, cardiopulmonary bypass; EEG, electroencephalography; aEEG, amplitude-integrated EEG; cEEG, continuous EEG; GCS, Glasgow Coma Scale; GWR, gray matter to white matter attenuation ratio; IABP, intra-aortic balloon pumping; MAP, mean arterial pressure; PaCO2, partial pressure of carbon dioxide in arterial blood; PEEP, positive end-expiratory pressure; PCI, percutaneous coronary intervention; ROSC, return of spontaneous circulation; rSO2, regional saturation of oxygen; ScO2, cerebral oxygen saturation; SjO2, jugular vein oxygen saturation; STEMI, ST-elevation myocardial infarction.
improves the prognostic performance compared to either alone in comatose cardiac arrest survivors treated with therapeutic hypothermia. Resuscitation 2013; 84: 1387 – 1392.


