Targeted Temperature Management and Post-Cardiac Arrest Care

Key Article

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Introduction

- Over 500,000 patient suffer sudden cardiac arrest in the US each year
- Survival is gradually improving, but varies greatly by region
- Numerous advances in post-resuscitation care have been associated with improved outcome, but implementation has been challenging, and best practices are not clearly defined
- Key elements of post-arrest care include targeted temperature management (TTM), coronary angiography (CAG), ventilator management, and prognostication
- TTM is particularly controversial, as data are confusing and implementation has been challenging in some settings

Targeted Temperature Management Updates

- Hypothermia is thought to confer neuroprotection via over 20 different mechanisms derived from animal, OR, and other clinical studies dating back to the 1950s.
- In 2002, two landmark studies (ref: HACA and Bernard) demonstrated improved survival and neurological outcome when patients with return of spontaneous circulation (ROSC) after out-of-hospital cardiac arrest (OHCA) due to ventricular fibrillation or tachycardia (VF/VT) were cooled to a range of 32-34 degrees Celsius for 12-24 hours after their arrest event.
- A subsequent large randomized trial, known as the TTM trial, found no difference between goal temperatures of 33 and 36 degrees in over 900 patients with OHCA.
- Subsequent observational studies have been mixed.
    - Several have demonstrated that the 36-degree goal was widely and rapidly adopted after publication of the TTM trial (Salter et al 2018, Bradley et al 2019)
    - Several studies have demonstrated changes in care processes, including lower utilization of TTM and more fever, since publication of the TTM trial. (Salter, Bray et al 2016)
    - Two trials demonstrated that mortality for OHCA, which had been improving over time, abruptly increased after publication of the TTM trial, though it's unknown whether this was caused by a change in TTM practices. (Salter et al 2018, Bradley et al 2019)
- The optimal method of cooling is also unknown.
- Several important trials related to TTM are pending
    - TTM2 (33vs 37, RCT)
    - ICECAP (adaptive design RCT looking at 3 different TTM durations – 12, 24, 48 hours)
- Prehospital cooling is not currently recommended.
    - Kim et al 2016 and Bernard et al 2013, 2 RCTs evaluating pre-hospital cooling failed to show benefit.
    - PRINCESS trial – RCT of 677 evaluating effect of pre-hospital cooling on neurologic outcome at 90 days using transnasal evaporative cooling device. Found that 16.6% of

patients in the prehospital hypothermia group achieved CPC 1-2 at 90 days compared with 13.5% in the control group, which did not reach statistical significance.

Coronary Angiography Updates

- Imperative to obtain post-arrest EKG
- Immediate coronary angiography recommended for all patients with post-ROSC STEMI
- In those without STEMI, the data has been less clear. A meta-analysis of 7 observational studies and 1 RCT found associations between urgent CAG and both improved survival and favorable neurologic outcome among post-arrest patients without STEMI. (Ref: Khan et al. 2017)
- COACT trial (Ref: Lemkes et al, April 2019)- RCT 552 pts in the Netherlands comparing early vs late CAG in VF/VT patients' post-ROSC without STEMI on ECG.
    - No difference in primary outcome of survival at 90 days (64vs67%)
    - No diff in secondary endpoints *(survival at 90 days with good cerebral performance or mild or moderate disability, myocardial injury, duration of catecholamine support, markers of shock, recurrence of ventricular tachycardia, duration of mechanical ventilation, major bleeding, occurrence of acute kidney injury, need for renal-replacement therapy, time to target temperature, and neurologic status at discharge from the intensive care unit.)*
    - Of note, overall, very few patients in their population had CAD (14% unstable lesion in immediate group, 17% in delayed group). 32-39% underwent any revascularization procedure. Unclear if this data applies to the US population.
- At this time, we would still recommend consideration of early CAG in VF/VT patients without another clear non-cardiac cause of arrest identified.

Hemodynamic Management Updates

- Patients often suffer significant hemodynamic compromise after cardiac arrest which may be due to myocardial stunning and systemic inflammatory response.
- Hypotension has been found to be an independent predictor of mortality, and observationally, higher maps have been associated with improved outcomes (Chu et al 2018, Kilgannon et al 2008, Trzeciak et al 2009) however it is unclear if artificially elevating MAP to a higher target (e.g., 85mmHg vs 65mmHg) is beneficial or neuroprotective.
- Neuroprotect Trial published after submission of our paper (June 2019) by Ameloot et al. is a phase 2 trial that sought to address this question of whether targeting higher MAPs could lead to improved brain perfusion and improved neurologic outcome compared standard therapy (goal 65mmHg).
    - The study compared 112 randomly assigned patients to goal directed therapy (map 85-100mmHg and mixed venous O2 sat 65-755 during first 36 h of ICU stay) vs standard MAP 65mmHg. This intervention was found to be safe and feasible, and led to increased perfusion and oxygenation, but did not show any difference in anoxic brain injury on DW MRI or functional outcome at 180days.
- We still recommend careful hemodynamic monitoring after cardiac arrest with consideration of invasive arterial BP monitoring, obtaining baseline echocardiogram, and trending measures of end organ function such as: lactate, urine output, central venous O2 saturation.

- At this time, it is still recommended to target normotension, however it may be reasonable to target higher MAPs (at the discretion of the clinician).

Updates in Ventilator Management

- Ventilator management in the post-cardiac arrest period should focus on prevention of secondary lung injury and targeting normocarbia and normoxemia.
- Both hyperoxemia and hypoxemia have been associated with poor clinical outcomes. We recommend targeting SpO2 94-97% as soon as feasible.
- Arterial hypocarbia has been associated with poor neurologic outcome. We recommend early blood gas analysis immediately after ROSC is achieved, as arterial CO2 is poorly correlated with prescribed minute ventilation and end-tidal CO2 in this setting.
- Several pilot trials have tested mild permissive hypercarbia as an experimental strategy, postulated to improve cerebral perfusion in the setting of impaired cerebrovascular autoregulation. The TAME trial is currently enrolling. This trial is an RCT that aims to evaluate whether mild hypercarbia in the first 24h post-arrest may improve neurologic outcomes at 6 months.
- This patient population is at increased risk of pulmonary infection and ARDS.
- Patients who suffer cardiac arrest are at increased risk of pulmonary infection and acute respiratory distress syndrome (ARDS). The authors recommend vigilance for signs of infection and consideration of early sampling of the lower respiratory tract and empiric antimicrobial therapy
- Several studies have demonstrated that nearly two-thirds of cardiac arrest patients meet criteria for ARDS. (Johnson et al. Resuscitation 2019)
- Data are mixed as to whether empiric low tidal volume ventilation is beneficial in post-cardiac arrest patients. A propensity-matched cohort study demonstrated an association between lower-tidal volumes and favorable neurologic status in 256 patients who suffered OHCA, (Beitler et al 2017). A similar study in IHCA showed no difference (Moskowitz et al 2018) however a recent randomized trial, in which 25% of patients of the 961 patients experienced cardiac arrest, demonstrated no benefit to low-tidal volume ventilation among patients without ARDS. (Simonis et al 2018)
- We recommend that clinicians apply a low-tidal volume strategy to post-arrest patients who do meet criteria for ARDS and consider such a strategy even in those who do not.

Prognostication

- In the setting of therapeutic hypothermia, it is recommended to delay neuroprognostication until 72h after rewarming (72h post-arrest if they did not undergo TH)
- Although certain physical exam features have been associated with poor outcome (absent pupillary reflex, absent corneal reflex, absent motor response or extensor posturing, status myoclonus), these findings are unreliable for determining prognosis, particularly in first 24h.
- We recommend multimodal approach including clinical exam, biomarkers (NSE, S-100), SSEP, EEG, imaging and delayed prognostication to avoid premature withdrawal of life sustaining treatment in patients who may have otherwise had a meaningful neurologic recovery.

Take home points

- Patients who suffer cardiac arrest represent the extreme of critical illness.

- Meticulous attention to temperature management, identifying and reversing precipitating pathologic condition, mechanical ventilation, and hemodynamics are key components of post-arrest critical care.
- Most patients who suffer OHCA should undergo TTM, but the ideal target temperature and duration are still being defined.
- Coronary angiography should be performed emergently for patients with post-arrest STEMI and urgently for patients in whom clinical or historical features suggest a primary cardiac cause. It should be considered in patients with an unknown cause of their arrest.
- Hyperoxemia (PaO_2 > 300 mmHg) should be avoided, as it may contribute to secondary injury. Oxygen saturation of 94-97% should be targeted. Mild therapeutic hypercarbia ($PaCO_2$ 40-50 mmHg) may be beneficial, but more data are needed. Patients should be ventilated with low tidal volumes (6-8 ml/kg using predicted body weight).
- Prognostication should generally be deferred until 72 hours after rewarming and should use a multimodal approach.