# Post-ROSC Cares in 2015

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## Outline

- Disclosure
  - No disclosures
  - No off label use.
- Raising of Lazarus. Rembrandt.
- Chain of Life
- Persistent precipitating disease
  - In order to improve hemodynamics after cardiac arrest, it is mandatory to identify and treat all the possible reversible causes of cardiovascular impairment, including cardiac tamponade, pulmonary embolism, tension pneumothorax, and distributive shock (anaphylactic or septic)
  - Also, in the case of suspected myocardial infarction, coronary angiography should be rapidly performed to treat any critical stenosis, especially in the case of shockable rhythms
- Post-Cardiac Arrest Syndrome
  - Systemic ischemia/reperfusion response
  - Persistent physiologic derangements
  - Inflammatory Reposnse
  - Brain injury
  - Myocardial dysfunction
    - Cardiac dysfunction is part of the post- cardiac arrest syndrome, a sepsis-like syndrome that includes myocardial stunning, impaired vasoregulation and systemic hypotension
    - Hemodynamic instability is related to acute myocardial dysfunction characterized by impaired contractile function, decreased work capacity, and variable diastolic dysfunction, which resolve within hours or days after the return to spontaneous circulation
    - Myocardial stunning due to hypoperfusion during ventricular fibrillation or the effects of transthoracic electrical shocks may result in profound but reversible myocardial depression.
  - Coaguloapthy

**Outline**

- Coagulation/anticoagulation and fibrinolysis/antifibrinolysis systems are activated in patients undergoing cardiopulmonary resuscitation,
- Thrombolytics don't work either
- Adrenal dysfunction

▼ Hemodynamics

- Post-ROSC hypotension and/or vasopressor/ inotrope therapy are associated with worse outcomes following resuscitation from cardiac arrest.
- ▼ In the study by Kilgannon et al. [8&] correlating TWA-MAP with outcomes, the TWA-MAP thresholds greater than 70mmHg were not associated with improved outcomes.
  - Attaining TWA-MAP more than 70 mmHg without vasopressors was associated with a better neurologic outcome than attaining it with vasopressors (48 vs. 24%, P 1⁄4 0.01).
  - Nevertheless, attaining adequate TWA-MAP with vasopressors may improve outcomes among patients who cannot attain adequate TWA-MAP without vasopressors.
- More cardiac dysfunction at 33
- However, accurate assessment of the cause of hypotension, including myocardial function, relative fluid status and vascular tone should inform optimal therapy.

▼ Oxygen

- ▼ During CPR
  - High FiO2 during CPR does not appear to expose brain tissue to hyperoxic injury.
  - No available data exist indicating oxygen administration during CPR is harmful.
  - ▼ NIRS
    - Uses an algorithm to display a value (rSO2) which appears to correspond to cerebral venous saturation
    - Normal range of 60–80%
    - 30% universally fatal
    - When oxygen demand exceeds supply, cerebral venous oxygen saturation falls.

**Outline**

- In this study, during CPR rSO2 was significantly higher in survivors than nonsurvivors.

- Prehospital
  - Exposure to high FiO2 during the prehospital resuscitation period was associated with greater histological evidence of brain injury.
  - It remains unclear whether it is possible to deliver titrated oxygen in the prehospital period in a manner that avoids arterial hyperoxaemia, and if oxygen controlled can be achieved, whether or not this influences clinical outcomes
- Inhospital
  - Limited available evidence, based on a series of retrospective studies, exists to support avoidance of hyperoxia in the hospital setting, though animal data suggestive of potential harm associated with hyperoxia.
  - Although inhospital increased PaO2 may be marker of illness severity after ROSC
  - Emerging data suggest that increasing maximum PaO2 measured during the first 24 h is associated with increasing hospital mortality and poor neurological status at hospital discharge.
- Goals
  - Confounder of measuring O2 because of shock
  - PaO2 100-150
  - If using Alpha-Stat, you must correct the PaO2 by Subtracting 5 for every degree below 37 of
    patients actual core temp

- Carbon Dioxide
  - EtCO2 invaluable to predict outcome of resuscitation
  - Hypercapnia (hypovent) increaes CBF/increases ICP
  - Hypocapnia (hypervent) vasoconstricts and decreases CBF and oxygen delivery
    - The ILCOR extrapolated from studies of patients with traumatic brain injury that hyperventilation could result in further ischemic injury in patients after cardiac arrest.
  - Hypo is probably worse than Hyper

**Outline**

- Goal 40-45 mmHg
- alpha-stat vs ph-stat
- ICP Management
  - The issue of cerebral perfusion is rendered more complicated by changes in ICP.
  - Global cerebral anoxia may result in diffuse cerebral edema, which in turn causes raised ICP
  - Maintaining the patient in Fowler's position (with the head of bed raised to 308 and the head held in midline) reduces ICP by encouraging venous drainage.
  - Precautions against agitation, fever, and seizures avoid episodes of high metabolic demand resulting in increased ICP.
- Ventilator Management
  - Lungs may be damaged from trauma due to chest compressions, aspiration of blood/gastric content or development of pneumonia
  - Post-ROSC ventilator-induced lung injury may also occur.
    - In experimental studies, mechanical ventilation can also directly injure the brain through aberrant vagal nerve inputs, which activate dopamine D2 receptors in the hippocampus and induce local apoptosis without causing hypoxia, oxidative or inflammatory stress.
    - Use of high tidal volume (VT) can be harmful to the brain because it is associated with cerebral blood flow (CBF) instability, white matter injury and vascular leakage with edema formation
  - 6 ml/kg or less
- Glycemic Control
  - Hyperglycemia is common after cardiac arrest
  - Post-arrest phase of secondary cerebral injury constitutes a hypermetabolic state in which hypoglycemia rapidly leads to harm.
  - Third, when studied in the context of therapeutic hypothermia, tight glucose control leads to an increased incidence of hypoglycemia without a corresponding reduction in mortality
  - Target level of less than 144 mg/dl may be acceptable

**Outline**

- Seizures
  - When studied using electroencephalogram (EEG), up to 36% of comatose survivors of cardiac arrest are found to have seizure activity and most of these are suffering SE
  - EEG is commonly used to detect seizures and postanoxic status epilepticus (PSE), which occur in 10 – 40% of patients and are associated with a poor outcome.
  - Status epilepticus itself is a strong predictor of mortality after cardiac arrest
  - Reflects not only the initial insult of global ischemia but also the fact that seizures represent the state of most intense metabolic activity possible for the brain.
  - Status epilepticus can double or triple the rate of whole brain metabolism and promotes release of excitotoxins
  - The ILCOR does not recommend prophylactic use of antiepileptics, citing the lack of benefit of the Brain Resuscitation Clinical Trial 1 (BRCT 1)
  - 12% of patients had NCSE; it was associated with poor outcome (Neurocrit Care 2012;16:114)
  - Yield of intermittent versus continuous EEG in comatose survivors of cardiac arrest treated with hypothermia. Critical Care 2013, 17:R190
  - Nevertheless, good neurological outcome has been reported following aggressive antiepileptic therapy for seizures
- Revascularization
  - Coronary plaque rupture or erosion, fragmentation, and embolization of thrombus can trigger cardiac arrest
  - If ACS, there is a clear benefit, but should it be routine
    - Among 896 patients admitted after OHCA during a 10-year period, an early coronary angiography (performed within the first hours after hospital admission) revealed a culprit coronary lesion in 524 patients (50%).
    - 40% of NSTEMI had culprit lesion
  - Diagnostic benefit
  - Does intervention help?

**Outline**

- The pioneering study that investigated the potential benefit of early PCI in post-OHCA and comatose patients was published by Spaulding. This study reported the beneficial effect of a successful invasive strategy after OHCA in multivariate analysis with an odds ratio of 5.2 [95% CI (confidence interval) 1.1, 24.5; P 1⁄4 0.04].
- In the same manner, Dumas reported successful PCI as an independent factor of survival, regardless of the postresuscitation ECG findings [odds ratio 2.1 (95% CI 1.2, 3.7)] in a large Parisian cohort of 435 OHCA patients without obvious extracardiac cause.
- Clinical benefit of early revascularization is probably not restricted to crude survival but could also be associated with an improved quality of life.
  - cognitive function, participation in social activities and instrumental daily activities

- How do you know who to take?
  - No symptoms or incomplete history to go by
  - Those with obvious noncardiac etiology.
    - Sepsis, trauma, metabolic disorder, hemorrhage
  - Eliminating the diagnosis of ACS after OHCA remains difficult.
  - ECG and clinical data lack sensitivity and specificity to predict an acute coronary artery occlusion as the cause of OHCA.
  - Consensus
    - Conventional STEMI criteria (Anatomically-Sequential ST elevations, Sgarbossa LBBB)
      - You may want to make sure the pattern persists on a repeat EKG
    - Clear Ischemic EKG that persists 20-30 minutes into resuscitation
    - As Dr. Smith’s post explains, immediate EKGs post-arrest may look ischemic, but resolve during the ED course)
    - Electrical Storm/Persistent Ventricular Dysrhythmia
    - Severe Cardiac Stunning (To look for a lesion and to place IABP)
    - Cardiogenic shock

**Outline**

- Substantial cTn
- Echocardiographic evidence of RWMA

- Early or late?

- Temperature
  - History
    - Early attempts
    - Cold incompatible with life
    - Temple Fey
  - Two landmark papers 2002
    - HACA-study-group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002; 346:549–556.
    - Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002; 346:557 – 563.
    - Both trials had exclusion criteria
    - Shockable rhythms
  - Widespread adoption
    - Use expanded beyond original studies
  - Timing of hypothermia
    - Seattle
      - Well known EMS system and arrest care
    - 1364 pts
    - 2 L 4deg saline, sedation, paralysis
    - 1 deg separation at admission
    - No difference in survival or neurologic outcome
    - Higher rearrests and pulmonary edema
    - Is it better for longer transport times?

## Outline

- Intra-arrest cooling vs post-rosc cooling
  - alternate cooling not saline
    - transseptal
- Depth
  - TTM Trial
    - 36 was chosen because registry data showed that was median arrival temperature
      - And if control devices were use, temp would not stray into febrile range
    - TTM trial sought to be pragmatic, reflecting current clinical practice of applying mild induced hypothermia to the entire out-of-hospital cardiac arrest population.
    - The trial protocol and analysis plan were published in advance and attempted to address possible deficiencies of previous trials. These included the following: a sample size twice as large as all previous RCTs combined (939 versus 478) adequately powered to detect or reject differences in survival, documentation of coma level at randomization, avoidance of hyperthermia both during and after completion of target temperature management in unconscious patients, standardized neurological assessment/prognostication, and guidance for withdrawal of treatment (adverse events, including infections, bleeding, electrolyte disturbances, seizures, and arrhythmias, were also recorded); a blinded neurological follow-up extending beyond crude scales (Cerebral Perform- ance Category and modified Rankin Scale), including tests on quality of life and cognitive function assessing both sur- vivors and relatives in a face-to-face visit in the majority; and a bio-bank of approximately 20,000 blood samples to investigate the role of biomarkers.
    - Prognostication was de- layed for 108 hours (unless specific withdrawal criteria were met) and performed by a clinician who was blinded to the intervention and who then recommended with- drawal, continuation, or no further escalation of care.
    - Several IRBs turned down the study for being unethical
  - Results
    - Neutral — no benefit of either temperature in any outcome including adverse events

**Outline**

- Cannot say that cooling is unnecessary
- Does not add to literature of benefit of cooling

▼ Criticism

- Precision of temperature control
- ▼ Time to reach target temperature
  - 4 hours for randomization, another 4 hours to get to temperature
  - ▼ Admission temp?
    - No difference in outcomes from LA days to northern michigan ambient temperatures (room vs outside?)
- Less ill cohort
- ▼ Large portion of bystander CPR
  - 70%
- ▼ To generalizable
  - Miss subgroups
- Sedation and shivering not protocolized
- ▼ Short time to BLS
  - <1min
- ▼ Higher deaths in 33 group before prognostication
  - 33 vs 36
  - Poor heart and multiorgan failure
- Midazolam and propofol are neuroprotective and doses weren't recorded
- ▼ Rate of rewarming
  - Was done at 0.5 deg/hr per current guidelines

▼ Response

- Probably was tightly controlled
- ▼ Shock reanalayis

**Outline**

- Still no benefit
- Faster to cool the HACA

▼ So what

▼ Avoid paralytics

- Prognosticaina harder
- Risk of pneumonia, neuromyopathy, delayed extuabtion
- What I think also is that many sites that have done 33 and are very confident that this is the thing to do, they will also change to do milder hypothermia when they have problems and they will feel safe. But I also think that the main take-home from the TTM trial is that we should not be so sure about dogma, what is the right thing to do

- Costs

▼ Rebound Hyperthermia

- postulated that rebound hyperthermia etiology may be related to either a physiolog- ical response to the cooling process or the post-cardiac arrest development of systemic inflammatory response syndrome.

▼ Prognostication

▼ AAN 2006

- List of clinical and laboratory criteria that were felt to define an iron-clad “no-hope” situation.
- Before hypothermia
- The studies used to support these findings were conducted before therapeutic hypothermia came into widespread use.

▼ Since 2006, a series of isolated reports of good neurological recovery have challenged the foundation of evidence supporting various no-hope criteria after cardiac arrest in patients who have been cooled.

- First absent motor responses on day 3 or later
- Then peak NSE >33
- Bilateral absent N20 SSEP response

**Outline**

- Myoclonic status epilepticus (MSE) has long been considered a catastrophic finding among victims of cardiac arrest.
- We now know that exceptions to these conventional no-hope criteria can occur.

▼ Move away from dichotomous assessments

- CPC or modified Rankin
- CPC 1-2 vs 3-5

- Four main categories of tests are used to predict poor outcome in comatose resuscitated patients.

▼ Clinical Exam

▼ Pupils

- Absence of pupillary light reflex at ROSC is associated with false prediction of poor outcome in about one-third of patients.
- Reliability of these signs increases during the first 72 h after arrest in patients not treated with controlled temperature, and it reaches a maximum at 3 days from ROSC
- TTM prognostic 118h
- In both TH and non-TH, the most accurate clinical-based predictor at 72h or more from ROSC is the absence of pupillary reflex to light [false positive rate (FPR) 0%.

▼ In accurate exam

- Pupilometer — quantitative

- Corneal Reflex
- Absent corneal reflex is also usually associated with a poor outcome, but is slightly less specific than the pupillary reflex (FPR up to 5%)

▼ Motor Exam

- Sensitive, but not specific (FPR10-40%)
- Like ocular reflexes affected by drugs

▼ Myoclonus

**Outline**

- Clinical sign of central nervous system injury
- Sudden, brief, involuntary jerks caused by muscular contractions or inhibitions.
- Postarrest myoclonus is a clinical phenomenon, which may be associated or not with epileptiform activity on EEG
- Should not be confused with Lance-Adams syndrome, a chronic form of postanoxic myoclonus, which occurs in conscious patients, is triggered by voluntary movements and is often limited to the limb being moved (action myoclonus).
- Generalized myoclonus (including face, trunk and limbs) and continuing for more than 30min can be regarded as a status myoclonus.
- 9% had good outcomes

▼ Electrophysiology

▼ Short-latency somatosensory evoked potentials (SSEPs)

- In non-TH-treated patients, bilateral absence of the N20 SSEP wave predicts an invariably poor outcome as early as 24 h from ROSC
- In therapeutic hypothermia-treated patients, SSEPs also perform well when recorded after rewarming.
- SSEPs are less affected by sedative drugs or hypothermia
- SSEPs are particularly prone to the bias of ‘self-fulfilling prophecy.’

▼ EEG

- Malignant EEG patterns
- Low voltage or burst-suppression
- Usually associated to poor neurological outcome, both in TH and non-TH
- Inconsistent definition

▼ Biomarkers

- Neuron-specific enolase (NSE) from neurons
- S-100 protein, from Schwann cells

**Outline**

- Cell death vs function
- Neuroimaging
  - CT
    - Early postanoxic injury after cardiac arrest appears as a diffuse brain edema
    - Quantified as the ratio between the densities of the grey matter and the white matter
  - MRI
    - Neuronal cytotoxic edema on MRI is optimally detected using DWI sequences, especially at basal ganglia level and on posterior cortical area
  - Imaging studies are not affected by sedation and paralysis
  - Imaging only gives structural information
- Summary
  - Nothing immediate
  - Almost nothing early
  - Wait, then wait, then wait some more
  - Multimodal
- Summary
- References
- Closing