



Should We Target Mild Hypercapnia in the Post Arrest Patient?

Key Article

- Eastwood G, Nichol AD, Hodgson C, et al. Mild hypercapnia or normocapnia after out-of-hospital cardiac arrest. *N Engl J Med.* 2023; published online June 15, 2023.

Background

- Hypoxic-ischemic encephalopathy is the leading cause of death among adults with coma after ROSC from OHCA.
- Cerebral hypoperfusion may contribute to cerebral hypoxia, exacerbate cerebral damage, and result in poor neurologic outcomes.
- PaCO₂ is a major physiologic regulator of cerebrovascular tone and hypercapnia is known to increase cerebral blood flow.
- Cerebral vascular reactivity to PaCO₂ is maintained in the post-arrest state.
- Current guidelines recommend normocapnia in comatose adults with ROSC from OHCA. However, normocapnia may not be sufficient to maintain adequate cerebral blood flow/perfusion.
- Observational studies and an inadequately powered RCT have suggested that mild hypercapnia may result in better outcomes post-arrest.
- At present, the most effective PaCO₂ in comatose adults with ROSC after OHCA remains uncertain.

Objective

- To test the hypothesis that targeted mild hypercapnia improves neurologic outcomes at 6 months compared with targeted normocapnia in adults with coma following ROSC from OHCA.

Methods

- International, investigator-initiated, open-label, randomized trial
- Patients
 - Inclusion criteria
 - Adults aged ≥ 18 years old
 - Sustained ROSC (≥ 20 min) following OHCA
 - Presumed cardiac or unknown cause
 - Exclusion criteria
 - Interval from ROSC to screening > 180 minutes
 - Unwitnessed arrest with initial rhythm of asystole
 - Limitations of care
- Intervention
 - Randomized 1:1 to targeted mild hypercapnia or targeted normocapnia
 - Attending clinicians aware of intervention assignment
 - Targeted mild hypercapnia: 50-55 mm Hg
 - Targeted normocapnia: 35-45 mm Hg

- RASS target of -4 for sedation
- Used ABGs and ETCO2 to guide ventilation during intervention period
- Neurologic Prognosis
 - Assessed 96 hrs after randomization or later
 - Protocol-guided neurologic assessment by clinician unaware of assignment
- Primary outcome
 - Favorable neurologic outcome (Glasgow Outcome Scale – Extended score of 5-8 at 6 months)
- Secondary Outcomes
 - Death within 6 months
 - Poor functional outcome at 6 months (mRS of 4-6)
- Statistical Analysis
 - Calculated that 1624 patients needed to reject a difference of 8% between the groups.
 - All analyses performed with ITT population
- Subgroups
 - Age: < or > 65 years of age
 - Time from arrest to ROSC
 - Initial cardiac rhythm
 - Presence or absence of circulatory shock at hospital admission

Results

- 1700 patients from 63 ICUs in 17 countries
 - Targeted mild hypercapnia: 847 patients
 - Targeted normocapnia: 853 patients
- CO2 Intervention
 - Values similar in both groups at hospital arrival
 - Separation of values between the groups at 4 hours and continued through 24 hr intervention period
 - PaCO2 target was abandoned in 8.2% of mild hypercapnia group and in 3% of the normocapnia group
- **Primary Outcome – Favorable Neurologic Outcome at 6 months**
 - Targeted mild hypercapnia: 43.5%
 - Targeted normocapnia: 44.6%
- Secondary Outcomes
 - Death at 6 months
 - Targeted mild hypercapnia: 48.2%
 - Targeted normocapnia: 45.9%
 - Poor functional outcome at 6 months
 - Targeted mild hypercapnia: 53.4%
 - Targeted normocapnia: 51.3%
- Adverse Events
 - No difference in pneumonia, arrhythmias, sepsis, bleeding, death due to cerebral causes

Limitations Identified by the Authors

- ED and ICU staff not blinded to interventions
- Mechanical ventilation, concomitant care not specified in protocol

- Hypercapnia common at randomization and may have attenuated the difference between groups
- Trial only included OHCA patients
- ICP not routinely monitored – number of patients with elevated ICP or cerebral edema unknown
- Data on primary outcome missing in 7.6% of patients
- Patients – most with witnessed arrest, bystander CPR, shockable rhythm, large % STEMI

Author conclusions

- In comatose adult patients with ROSC after OHCA, targeted mild hypercapnia did not improve 6 month neurologic outcome compared with normocapnia.