Cruising the 2021 Critical Care Literature…A Year in Review

Cardiac Arrest

Haywood KL, et al. Long term outcomes of participants in the PARAMEDIC2 randomized trial of adrenaline in out-of-hospital cardiac arrest. Resuscitation 2021; 160:84-93.

- **Objective**
  - Report on long-term survival, quality of life, and neurocognitive outcome in survivors of OHCA enrolled in the PARAMEDIC2 Trial
    - PARAMEDIC2 Trial
      - Randomized, double-blind, controlled trial
      - 5 EMS agencies in the UK
      - OHCA patients where ACLS was initiated
      - Randomized to epinephrine or placebo
      - Primary Outcome: 30-day survival
- **Study**
  - Evaluated both 6- and 12-month survival using various validated surveys (mRS, MMSE, TSQ, and IQCODE-CA)
- **Results**
  - 6-month survival
    - Epinephrine Group: 2.9%
    - Placebo Group: 2.1%
  - 6-month survival with favorable neurologic outcome
    - Epinephrine Group: 2.0%
    - Placebo Group: 1.5%
    - Severe neurologic impairment more common in those who got epinephrine (22.8% vs. 13.4%)
  - 12-month survival
    - Epinephrine Group: 2.7%
    - Placebo Group: 2.0%
    - No difference in favorable neurologic survival
- **Take Home Point**
  - Epinephrine improved both 6- and 12-month survival but did not demonstrate improvement in favorable neurologic outcome

Vallentin MF, et al. Effect of intravenous or intraosseous calcium vs saline on return of spontaneous circulation in adults with out-of-hospital cardiac arrest. JAMA. 2021; published online Nov.

- **Objective**
  - Does the administration of calcium during OHCA improve ROSC.
- **Study**
  - Randomized, placebo-controlled, parallel group, double-blind, superiority trial
  - Took place in Denmark
  - Patients – Included

        - Adults 18 years of age or greater
        - OHCA
        - Received at least 1 dose of epinephrine
    - Intervention – Randomized 1:1
        - Calcium Group
            - 5 mmol of calcium chloride
            - IV or IO
            - Immediately after first dose of epinephrine
            - Second dose could be given after 2nd epinephrine dose
        - Placebo Group
            - 9 mg/mL of sodium chloride
    - Primary Outcome
        - Sustained ROSC for at least 20 minutes
    - Secondary Outcomes
        - Survival at 30 days
        - Survival at 30 days with favorable neurologic outcome
- **Results**
    - Trial stopped early after 383 patients enrolled (planned for 674 patients)
        - Calcium Group: 193 patients
        - Placebo Group: 198 patients
    - Patient characteristics well balanced
        - 29% female
        - 82% had OHCA
        - 75% had a shockable rhythm
        - Median time from OHCA to study drug: 18 min
    - Primary Outcome – Sustained ROSC
        - Calcium Group: 19%
        - Placebo Group: 27%
        - Not statistically different
    - Secondary Outcome – Survival at 30-days
        - Calcium Group: 5.2%
        - Placebo Group: 9.1%
        - Not statistically different
    - Secondary Outcome – Survival at 30-days with favorable neurologic outcome
        - Calcium Group: 3.6%
        - Placebo Group: 7.6%
        - Not statistically different
- **Limitations**
    - Trial stopped early
    - OHCA
    - Excluded tox cases (calcium channel blocker OD) and hyperkalemia
- **Take Home Point**
    - Administration of calcium did not improve sustained ROSC rates in OHCA patients

Andersen LW, et al. Effect of vasopressin and methylprednisolone vs placebo on return of spontaneous circulation in patients with in-hospital cardiac arrest: A randomized clinical trial. JAMA. 2021; 326:1586-1594.

- **Objective**

- To determine whether the combination of vasopressin and methylprednisolone administered during in-hospital cardiac arrest improve return of spontaneous circulation.

- **Study**
  - Randomized, placebo-controlled, parallel group, double-blind, superiority trial
  - 10 hospitals in Denmark
  - Patients - Included
    - 18 years of age or older
    - IHCA
    - Received at least 1 dose of epinephrine during cardiac arrest
  - Patients randomized in a 1:1 ratio
    - Vasopressin / Methylprednisolone Group
      - 20 IU vasopressin
      - 40 mg of methylprednisolone
      - Given as soon as possible after the first dose of epinephrine
      - Additional doses could be administered after each epi dose for a max of 4 doses
    - Placebo Group
      - Ampules of sodium chloride
  - Primary Outcome
    - Return of spontaneous circulation for at least 20 minutes
  - Secondary Outcomes
    - Survival at 30 days
    - Favorable neurologic outcome at 30 days
- **Results**
  - A total of 501 patients were included in the analysis
    - Vasopressin / Methylprednisolone Group: 237 patients
    - Placebo Group: 264 patients
    - Baseline characteristics were similar between the groups
  - Primary Outcome - ROSC
    - Vasopressin / Methylprednisolone Group: 42%
    - Placebo Group: 33%
    - Risk Ratio of 1.30 (95% CI 1.03-1.63; p=0.03)
    - Fragility Index = 3
  - Secondary Outcomes
    - 30-day Survival
      - Vasopressin / Methylprednisolone Group: 9.7%
      - Placebo Group: 12%
      - Not statistically significant
    - Favorable neurologic outcome
      - Vasopressin / Methylprednisolone Group: 7.6%
      - Placebo Group: 7.6%
      - Not statistically significant
    - Favorable neurologic outcome at 30 days
      - Vasopressin / Methylprednisolone Group: 4.6%
      - Placebo Group: 7.2%
      - Not statistically significant
  - **Limitations**
    - Large number of patients screened, but only 501 patients ultimately included
    - Though multicenter, took place only in Denmark
    - Primary outcome was ROSC, not favorable neurologic survival at discharge

        - Some differences occurred between patients in the post-resuscitation period.
        - 90% of patients had an initial nonshockable rhythm
    - **Take Home Points**
        - Among IHCA patients, the administration of vasopressin and methylprednisolone resulted in a significant increase in ROSC, however did NOT improve survival at 30 days and survival with favorable neurologic outcome.
        - The use of vasopressin and steroid for patients with IHCA, and OHCA, requires further study and is not ready for standard care.

Post-Arrest Care

Desch S, et al. Angiography after Out-of-Hospital Cardiac Arrest without ST-segment Elevation. N Engl J Med. 2021. Published online August 29, 2021.

- **Objective**
    - To determine whether OHCA patients with ROSC but without ST-segment elevation benefit from immediate coronary angiography for treating or ruling out acute coronary events.
- **Study**
    - Investigator-initiated, randomized, multicenter, open-label trial
    - Conducted in 31 centers in Germany and Denmark
    - Patients - Included
        - At least 30 years of age
        - Resuscitated from OHCA of possible cardiac origin
        - Shockable or nonshockable rhythm
        - No ST-segment elevation on ECG
    - Interventions
        - Immediate Coronary Angiography
            - Transferred to the cath lab as soon as possible after hospital admission
        - Delayed Coronary Angiography
            - First transferred to the ICU for further treatment and evaluation of the etiology of OHCA
            - Could proceed to cath after a minimum delay of 24 hours depending on the results of further testing and treatment
            - Cath within 24 hours in this group was permitted for:
                - Substantial increase in troponin
                - Electrical instability
                - Cardiogenic shock
                - New ST-segment elevation
    - Primary Outcome
        - 30-day all-cause mortality
    - Secondary Outcomes
        - MI at 30 days
        - Severe neurologic deficit (CPC 3 to 5) at 30 days
        - ICU LOS
        - Rehospitalization within 30 days for CHF
        - Moderate or severe bleeding
        - Stroke
        - AKI leading to RRT
- **Results**
    - Total of 558 patients eligible for randomization; 554 ultimately included in the trial
        - Immediate Coronary Angiography: 281 patients

        - Delayed Coronary Angiography: 273 patients
        - Patient characteristics well balanced
    - Interventions
        - Immediate Coronary Angiography
            - Performed in 96% of patients
            - Median time from arrest to cath: 2.9 hrs
            - Prevalence of CAD was 61%
            - Revascularization occurred in 40%
        - Delayed Coronary Angiography
            - Performed in 62% of patients
            - Median time from arrest to cath: 46.9 hours
            - Prevalence of CAD was 72%
            - One or more coronary lesions considered responsible in 40%
            - Revascularization occurred in 43%
    - Primary Outcome (30-day all-cause mortality)
        - Immediate Coronary Angiography: 54%
        - Delayed Coronary Angiography: 46%
        - p=0.06
    - Secondary Outcomes
        - No difference in MI at 30-days, severe neurologic deficit at 30-days, ICU LOS, rehospitalization for CHF at 30-days, need for RRT, CVA, or bleeding.
        - A composite outcome of all-cause mortality or severe neurologic deficit favored delayed coronary angiography
- **Limitations**
    - Open-label: physicians/ICU staff were aware of treatment allocation which may have influenced further treatment
    - Excluded in-hospital cardiac arrest and those with ST-segment elevation, electrical, or hemodynamic instability
    - 22 patients randomized to delayed coronary angiography got a cath under 24 hours despite no protocol indication
- **Take Home Points**
    - Among OHCA patients with ROSC and no evidence of ST-segment elevation on ECG there was no benefit to immediate coronary angiography compared with delayed angiography after ICU admission.

Dankiewicz J, et al. Hypothermia versus normothermia after out—of-hospital cardiac arrest. N Engl J Med. 2021; 384:2283-94.

- **Objective**
    - To assess the beneficial and harmful effects of hypothermia as compared with normothermia and early treatment of fever in patients after cardiac arrest.
- **Study**
    - International, investigator-initiated, superiority trial
    - Performed in 61 centers in 14 countries
    - Patients - Included
        - Adults ≥ 18 years of age
        - Admitted to the hospital after OHCA of a presumed cardiac or unknown cause
        - Any initial rhythm
        - More than 20 consecutive minutes of ROSC
        - Remained unconscious and unable to follow verbal commands
    - Hypothermia

        - Immediately cooled to 33 C (cold IVFs, surface device, or intravascular device)
        - Maintained for 28 hours
        - Rewarmed to 37 C in hourly increments
    - Normothermia
        - Maintain temperature of 37.5 C or less
        - If temperature reached > 37.8 C, cooling with surface or intravascular devices was initiated to target a temperature of 37.5 C
        - No active warming or cooling was initiated for patients who had a spontaneous temperature < 37.8 C
    - Neuroprognostication
        - Performed at 96 hours after randomization or later
    - Primary Outcome
        - All-cause mortality at 6 months
    - Secondary Outcomes
        - Poor functional outcome at 6 months (mRS of 4 to 6)
        - Number of days alive and out of the hospital until 180 days
        - Health-related quality of life
    - Adverse Events
        - Pneumonia
        - Sepsis
        - Bleeding
        - Arrhythmia resulting in hemodynamic compromise
- **Results**
    - 1861 patients included in the intention-to-treat population
        - Hypothermia Group: 930 patients
        - Normothermia Group: 931 patients
    - Primary Outcome – All-cause mortality at 6 months
        - Hypothermia Group: 50%
        - Normothermia Group: 48%
        - RR with hypothermia 1.04 (95% CI 0.94 to 1.14; p=0.37)
        - Consistent across subgroups (gender, age, initial rhythm, shock present on admission)
    - Secondary Outcome – Poor functional outcome at 6 months
        - Hypothermia Group: 55%
        - Normothermia Group: 55%
        - RR with hypothermia 1.00 (95% CI 0.92 to 1.09)
    - Adverse Events
        - Arrhythmias
        - Hypothermia Group: 24%
        - Normothermia Group: 17%
        - No difference in pneumonia, sepsis, or bleeding were observed
- **Limitations**
    - Elements of ICU care (sedation, paralysis, mechanical ventilation) included in the trial protocol many not be representative of common clinical practice
    - Non-blinded
    - No control group without TTM was included (almost 50% in the Normothermia Group had TTM applied to keep temp below target)
- **Take Home Point**
    - TTM to target a temperature of 33 C did not lower 6-month all-cause mortality in patients with OHCA compared to those treated with TTM to target normothermia.

RSI

Driver BE, et al. Effect of use of a bougie vs endotracheal tube with stylet on successful intubation on the first attempt among critically ill patients undergoing tracheal intubation. JAMA. 2021. Published online December 8, 2021.

- **Objective**
  - To compare the effect of using a bougie vs an endotracheal tube with stylet on outcomes of tracheal intubation in EDs and ICUs across multiple health systems.
- **Study**
  - Randomized, pragmatic, parallel-group, unblinded trial
  - 15 sites: 7 EDs and 8 ICUs in 11 US hospital
  - Patients - Included
    - Undergoing tracheal intubation
    - Planned use of sedation and a nonhyperangulated blade
  - Intervention
    - Bougie Group
      - Operators instructed to use a bougie for the first attempt at intubation
    - Stylet Group
      - Use an ETT with a malleable stylet for first attempt at intubation
      - Shape stylet with a distal bend of 25-35 degrees
  - Primary Outcome
    - Successful intubation on the first attempt
  - Secondary Outcomes
    - Incidence of severe hypoxemia between induction and 2 min after intubation
    - Defined as SpO2 < 80%
- **Results**
  - **1102 patients** for the primary analysis
    - Bougie Group: 556 patients
    - Stylet Group: 546 patients
  - Baseline characteristics were similar between the groups
    - Most common reasons for intubation: altered mental status and acute respiratory failure
    - Most common operator was EM (63%)
    - Most operators were resident physicians (62%)
    - Operators had performed a median of 60 total intubations
  - Primary Outcome – First pass success
    - Bougie Group: 80.4%
    - Stylet Group: 83%
    - No significant difference
    - No significant difference in the adjusted analysis or between any prespecified subgroups
  - Secondary Outcome – Severe hypoxemia
    - Bougie Group: 11%
    - Stylet Group: 8.8%
  - Airway complications – post-intubation pneumothorax
    - Bougie Group: 2.5%
    - Stylet Group: 2.7%
  - Cardiovascular collapse
    - Bougie Group: 12.2%
    - Stylet Group: 16.7%

- **Limitations**
  - Excluded patients for whom urgency of intubation precluded randomization
  - Excluded use of hyperangulated laryngoscope
  - Excluded patients for whom use of a bougie was indicated
  - Most operators in the trial had limited experience using a bougie
  - Unblinded trial
  - Did not evaluate the use of bougie as a rescue device after failed first attempt
- **Take Home Points**
  - Among critically ill adults undergoing tracheal intubation, use of a bougie did not significantly increase the incidence of successful intubation on the first attempt compared with ETT with stylet.

Post-Intubation Sedation

Pappal RD, et al. The ED-AWARENESS Study: A prospective, observational cohort study of awareness with paralysis in mechanically ventilated patients admitted from the emergency department. Ann Emerg Med. 2021; 77:532-544

- **Objective**
  - Estimate the prevalence of awareness with paralysis in ED patients receiving mechanical ventilation
- **Study**
  - Prospective, cohort study
  - Single-center, academic, residency-affiliated, tertiary care center in St. Louis, MO
  - Patients - included
    - Adults aged 18 years or older
    - Underwent mechanical ventilation through an ETT in the ED
    - Intubation could have been performed either in the ED, prehospital setting, or at a transferring facility
  - Methods of Measurement
    - All measurements and clinical data were gathered from chart review – all variables extracted from the EMR
  - Primary Outcome
    - Awareness with paralysis
    - Investigators used a combination of questions from the Brice questionnaire, and the ICU Memory Tool.
    - Brice questionnaire is the preferred method for evaluating awareness with paralysis
  - Secondary Outcome
    - Perceived threat (identified as a mediator or causal pathway to PTSD symptoms)
    - Assessed using a validated measurement tool
- **Results**
  - 383 patients included in the study
  - 27 patients reported memories of wakeful paralysis and were evaluated for the primary outcome
  - After adjudication, the **prevalence of possible or definite awareness with paralysis was 2.6%** (95% CI 1.3% to 4.7%)
  - Exposure to rocuronium at any time in the ED (RSI and postintubation) was significantly different between patients who experienced awareness with paralysis (70%) versus the rest of the cohort (31%) (OR 5.1; 95% CI 1.3 to 20.1)
- **Limitations**
  - Overall sample size was small

- Single-center
- Subjective assessment of awareness with paralysis
- Authors excluded a large number of neurologically injured patients
- Assessed patients before hospital DC – did not assess them later (i.e., 30 days)

- **Take Home Points**
  - WATCH OUT for prolonged paralysis and no sedation!
  - Awareness with paralysis occurred in 2.6% of this single center cohort of ED patients receiving mechanical ventilation and was associated with rocuronium exposure.
  - Given the volume of patients intubated in the ED annually in the US, this could suggest that thousands of patients may have awareness with paralysis.

Cardiogenic Shock

Mathew R, et al. Milrinone as compared with dobutamine in the treatment of cardiogenic shock. N Engl J Med. 2021. 385:516-25.

- **Objective**
  - To compare the efficacy and safety of milrinone and dobutamine in patients with cardiogenic shock in a pragmatic randomized clinical trial.
- **Study**
  - Randomized, double-blind clinical trial
  - Single quaternary cardiac care unit at the University of Ottawa
  - Patients – Included
    - 18 years of age or older
    - Admitted to the cardiac ICU
    - Had cardiogenic shock, as defined by the Society for Cardiovascular Angiography and Interventions definition
  - Trial Procedures
    - Assigned in a 1:1 fashion to receive either milrinone or dobutamine
    - Once randomized, patients received the medication in a concealed bag at a dose from "stage 1 to stage 5".
      - For milrinone, this corresponded to a dose range of 0.125, 0.250, 0.375, 0.500 and > 0.500 mcg/kg/min
      - For dobutamine, this corresponded to a dose range of 2.5, 50., 7.5, 10.0, and > 10.0 mcg/kg/min
  - Primary Outcome - composite outcome of:
    - In-hospital death from any cause
    - Resuscitated cardiac arrest
    - Receipt of cardiac transplant or mechanical circulatory support
    - Nonfatal MI
    - TIA or CVA
    - Initiation of RRT
  - Secondary Outcomes
    - LOS in the cardiac ICU
    - Arrhythmia requiring intervention
    - Total duration of inotropic duration
    - Total hospital LOS
- **Results**
  - Total of 192 were ultimately enrolled
  - Primary Outcome
    - Dobutamine group: 54%
    - Milrinone group: 49%

        - RR 0.90
        - 95% CI 0.69 to 1.19; p=0.47
        - No effect on prespecified subgroups including affected ventricle or concomitant use of vasopressors
    - Secondary Outcomes
        - No difference in the individual components of the composite primary outcome
        - No difference in total duration of inotropic support, hospital and ICU LOS
        - No difference in arrhythmias that required intervention
        - No differences in heart rate, MAP, serum lactate/creatinine, or urine output
- **Limitations**
    - Single center study – limiting generalizability
    - Dose adjustments based on physician judgment and not a standard study protocol
    - Only in-hospital outcomes were evaluated
    - Time from ICU admission to randomization up to 24 hours in some patients (is this too long?)
    - Power calculations based on a fairly large difference between milrinone and dobutamine (20% difference)
- **Take Home Points**
    - The DOREMI trial did not find a significant difference between milrinone and dobutamine for patients with cardiogenic shock.

Fluid Resuscitation

Zampieri FG, Machado FR, Bioni RS, et al. Effect of intravenous fluid treatment with a balanced solution vs 0.9% saline solution on mortality in critically ill patients. The BaSICS randomized trial. JAMA. 2021. Published online August 10, 2021.

- **Objective**
    - To assess whether the administration of a balanced solution (Plasma-Lyte 148) during the ICU stay compared with NS would improve 90-day mortality in critically ill patients.
- **Study**
    - Investigator-initiated, randomized clinical trial
    - Conducted in 75 ICUs in Brazil
        - Patients - Included
            - Admitted to an ICU
            - Needed at least 1 fluid expansion at the discretion of the attending physician
            - Were not expected to be discharged the next day
            - Met at least 1 of the following:
                - Older than 65 years of age
                - Had hypotension (MAP < 65 mm Hg or SBP <90 mm Hg) or pressors
                - Sepsis
                - Required NIV or MV for at least 12 hours
                - Early signs of kidney dysfunction
                - Cirrhosis or acute liver failure
    - Randomization – patients randomized to receive either 0.9% NS or balanced solution
    - Interventions
        - Fluids supplied in identical 500 ml bags
        - Physicians, patients, and those who assessed outcomes blinded to assigned treatment
        - Overall patient management left to the discretion of the attending physician

- Primary Outcome
  - 90-day survival
- Secondary Outcomes
  - Need for RRT up to 90-days after enrollment
  - Occurrence of AKI
  - SOFA score assessed at a continuous value and individual components at days 3 and 7
  - Number of days not requiring MV within 28 days

- **Results**
  - Ultimately, 10,520 patients included in the analysis (5,230 randomized to balanced solutions; 5,290 randomized to saline solution)
  - Interventions
    - Patients in both groups received a median of 1.5 L of fluid during the first day of enrollment
    - Accumulated median fluid during the first 3 days was 4.1 L
  - Primary Outcome: 90-day mortality
    - Balanced solution group: 26.4%
    - 0.9% NS group: 27.2%
    - HR 0.97 (95% CI 0.90 to 1.05) p=0.47
  - Secondary Outcomes
    - Only 2 were found to be statistically significant
    - SOFA Score at 7 days different for the balanced solution group (median difference 0.27) mostly due to a higher neurologic SOFA score
- **Limitations**
  - High number of elective surgical admissions to the ICU
  - Overall lower mortality for study patients than initially planned/designed. Patients had lower illness severity scores
  - Patients received a relatively small amount of IVFs
    - 1.2 L on the first ICU day
    - 2.9 L during the first 3 days
  - Almost 70% received IVFs before enrollment, of which 45% had > 1 L
  - Only evaluated Plasma-Lyte 148
- **Take Home Points**
  - "Among critically ill patients requiring fluid challenges, the use of a Plasma-Lyte 148 compared with 0.9% NS did not significantly reduce 90-day mortality".