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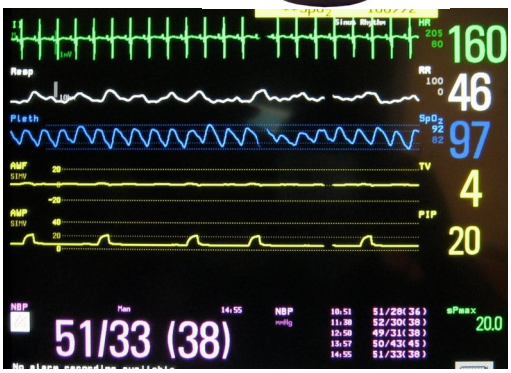
Early Use of Norepinephrine in Septic Shock Resuscitation (the CENSER trial)

Reviewed by Jessica Faiz PGY3, @im_jesssayinn

Bottom Line:

In patients with sepsis with hypotension, the early use of norepinephrine(NE) had increased shock control by 6 hours after diagnosis.



Why it's Important in Emergency Medicine:

Sepsis is a leading cause of death worldwide, with mortality ranging up to 50%. Early recognition and initiation of treatment in sepsis is critical. Fluids and antibiotics have been the mainstay of initial treatment in sepsis. However, some retrospective studies have suggested that early vasopressor administration can also improve hemodynamics and mortality. CENSER is the first prospective randomized trial studying vasopressors in sepsis.

Major Points:

- 76.1% in the early NE group vs. 48.4% of the control group achieved shock control at 6 hours (95% CI 2.09 – 5.53; P<0.001)
- Shock control was defined as sustained MAP>65 (>15 minutes) plus 2 consecutive hours of urine output >0.5ml/kg/hr or decrease in serum lactate >10% from the initial lactate level
- 28d mortality was lower in the early NE group (15.5% vs 21.9%; 95% CI, 0.53-1.11; P=0.15) not statistically significant.
- cardiogenic pulmonary edema (14.4% vs 27.7%; 95% CI 0.56-0.87; P<0.004) and new-onset arrythmia (11% vs 20%; 95% CI 0.56-0.94; P<0.03) occurred less in the early norepinephrine group

Design:

- Single-center, randomized, double-blind, placebo-controlled clinical trial of 310 patients (155 in treatment and 155 in placebo).
- Inclusion criteria: patients ≥18 years old presenting to the ED with hypotension (MAP <65mmHg) and infection as the suspected cause
- Treatment group received norepinephrine 16 µg/ml vs. placebo 250 ml of 5%D/W infused for 24h without titration. All eligible patients received care including crystalloid solution, antibiotics, etc.

Criticisms:

- single-center trial which limits generalizability
- no mortality difference at 28d, but suggestion of benefit
- Due to limited ICU capacity, some patients who still needed adjustment of their norepinephrine infusion dosage were treated in the general medical ward, which is unusual, and leads to varied nursing ratios
- Splanchnic hypoperfusion secondary to vasoconstriction by norepinephrine is an important concern, and no objective measurements of altered perfusion to the gut and kidney were made
- Fluid resuscitation rate varied, which may have affected the treatment outcome

References:

Helman, Anton. "Ep 122 Sepsis and Septic Shock – What Matters from EM Cases Course." *Emergency Medicine Cases.* <https://emergencymedicinecases.com/sepsis-septic-shock/> Accessed 23 December 2019.

Permpikul et al (2018). Early Use of Norepinephrine in Septic Shock Resuscitation. Am J Respir Crit Care Med 199 (9):1097-1105

Rezaie, Salim. "The CENSER Trial: Early Norepinephrine in Septic Shock." *Rebel EM.* <https://rebelem.com/the-censer-trial-early-norepinephrine-in-septic-shock/> Accessed 23 December 2019.

Bag-Mask Ventilation during Tracheal Intubation of Critically Ill Adults (PreVent Trial)

Reviewed by Alejandra Alvarez, PGY3

Bottom Line: Providing bag-mask ventilation from the time of induction medication administration to intubation to critically ill adults results in higher oxygen saturation, lower incidence of severe hypoxemia and no difference in incidence of aspiration.

Why it's Important in Emergency Medicine: Hypoxemia is a common complication of intubation, especially in critically ill patients. Most emergency department intubations fall into the critically ill category, predisposing our patients to higher rates of hypoxemia and associated complications such as cardiac arrest and death.

Major Points:

- Median lowest oxygen saturation was 96% in the bag-mask group and 93% in the no ventilation group (in a post hoc analysis adjusting for preoxygenation and presence of PNA or GI bleed, the mean difference in lowest oxygen saturation was 5.2 percentage points) -- the difference in the lowest oxygen saturation between the groups was greater for patients with lower oxygen saturation at induction
- 10.9% of patients in the bag mask group had an oxygen saturation of less than 80% vs 22.8% in the no ventilation group
- Median decrease in oxygen saturation from induction to the lowest oxygen saturation was 1 percentage point in the bag mask group vs 5 percentage points in the no ventilation group
- No significant difference in incidence of operator reported aspiration (2.5% vs 4.0%) or the presence of a new opacity on CXR (16.4% vs 14.8%) in the bag mask vs no ventilation groups
- No significant difference in in-hospital mortality, number of ventilator free days or days out of the ICU between the groups

Design:

- Seven academic ICUs in the US, inclusion criteria: adults >/= 18 years undergoing intubation in ICU; exclusion criteria: immediate need for intubation (no time for randomizing), if treating physician dubbed ventilation clinically indicated/contra-indicated (ie treating hypoxemia/severe acidemia vs increased risk of aspiration-ongoing emesis/hemoptysis), pregnant, incarcerated
- Multicenter, parallel-group, unblinded, pragmatic, randomized trial comparing rates of hypoxemia between bag mask ventilation to no ventilation during interval from administration of sedative medication to two minutes after intubation

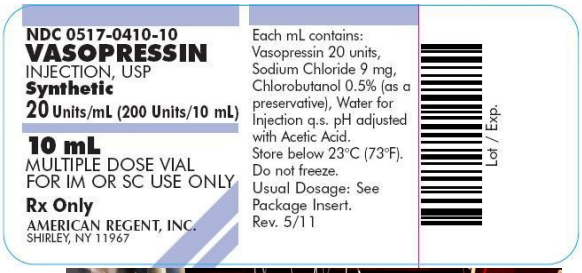
Criticisms:

- Unblinded- knowing which group the patient was assigned to could have led to differences in pre-oxygenation methods
- Pre-oxygenation, apneic oxygenation and induction medications were not standardized (though post hoc analysis accounting for preoxygenation methods did not find a significant difference in oxygen saturation at the time of induction between the groups)
- Patients requiring emergent intubations were excluded, unclear how well you can generalize study ICU population to emergency department population

Reference: Casey et al (2019). Bag Mask Ventilation during Tracheal Intubation of Critically Ill Adults. NEJM 380 (9); 811- 821.

Effects of Low-Dose Supplementation of Arginine Vasopressin on Need for Blood Product Transfusions in Patients With Trauma and Hemorrhagic Shock (AVERT-Shock)

Reviewed by Madeline Brockberg, PGY3 @madpalmberg



Bottom Line:
Trauma patients presenting with hemorrhagic shock who received early low-dose vasopressin had lower blood transfusion requirements and no increase in complications. Larger, multi-center studies are required to further elucidate the effects on mortality.

Why it's Important in Emergency Medicine:
Trauma team to trauma 2……
We see 70% of Boston's penetrating trauma and have an acute understanding of how complex it can be to resuscitate these patients. Historically we have been taught that there is no role for pressors in the management of hemorrhagic shock. While I don't think this study is practice changing, it does pave the way for continued conversation about resuscitation with something other than blood. This study also provides a great model for trauma research, which is notoriously difficult.

Major Points:
Hemorrhagic shock is associated with a state of arginine vasopressin (AVP) deficiency. Animal models have shown that AVP may help with vasomotor tone, improved platelet function, vasoconstriction of injured vessels and shunting blood to vital organs.

- ***In the group that received AVP, there was no increase in complications and there was a decrease in the quantity of blood products required.***
- This group also had a decreased number of DVTs.

Design:
Double-blind placebo-controlled trial. Trauma patients who required at least 6 uPRBCs were randomized into two groups. Intervention group patients received 4U bolus of AVP and 0.04U/min infusion after the bolus. Both groups were resuscitated with 1:1:1 blood products and had MAP goals >/= 65 for 48 hours.

Criticisms:

- Single center study with largely young men who experienced penetrating trauma. Would be interested to see a more diverse population both from a mechanism stand-point and demographic standpoint
- The study found a significant decrease in the amount of blood products used between the two groups. This is certainly an important endpoint given that blood is perishable and limited. However, this study did not find any significant differences in morbidity (including AKI, abdominal compartment syndrome, days on vent, ARDS), ICU length of stay or mortality.

References:
Sims CA et al. Effect of low-dose supplementation of arginine vasopressin on need for blood product transfusions in patients with trauma and hemorrhagic shock: A randomized clinical trial. JAMA Surg 2019 Aug 28

Thrombolysis Guided by Perfusion Imaging up to 9 Hours after Onset of Stroke
Reviewed by Allen Lockhart, PGY3

Bottom Line:

In select patients with acute ischemic stroke, use of alteplase at 4.5 - 9 hours after the onset of symptoms more frequently resulted in no or minor neurological deficits at 90 days and symptomatic ICH than the use of placebo.

Why it's important in Emergency Medicine:

An understanding of the data behind TPA is critical in the ED. Ultimately, we are the doctors who order it, and we need to have a nuanced understanding of its unique risk/benefit profile.

The 'four hour window' for TPA is integral to our current understanding of how to use this much-maligned intervention. This targeted use is based on a meta-analysis of nine large RCTs published in the Lancet in 2014. Subsequent trials involving TPA and thrombectomy have attempted to ascertain exactly who, among our patients with acute ischemic stroke, are the most likely to benefit from intervention. This search has evaluated subgroups within the four hour window, and is now expanding outside the limit of timing altogether.

Major Points:

In EXTEND, the authors examined patients with acute ischemic stroke presenting from 4.5 - 9 hours after symptom onset (and patients who awoke with symptoms of unknown duration) who had hypoperfused but salvageable regions of brain detected on automated perfusion imaging. This is a highly selected subset of patients who should have, based on our current understanding of the therapy, a maximal benefit from reperfusion.

Design and Results:

- Multicenter, randomized, placebo controlled**,** stopped early with **N**=225 of 310 initially planned
- The primary outcome was modified Rankin scale (mRS) score of 0 to 1 at 90 days (indicating an excellent functional outcome with a return to all usual activities)
- Various secondary and tertiary outcomes of questionable utility
- Safety outcomes were death at 90 days and development of symptomatic intracerebral hemorrhage
- The primary outcome of a mRS 0-1 was attained by 35.4% v. 29.5% of the alteplase v. placebo groups
- 6% of patients had symptomatic intracerebral hemorrhage in the alteplase group v. 1% for placebo group
- Mortality within 90 days did not differ significantly between groups

Criticisms:

This trial suffers from two major issues that prevent it from being practice changing. First, methodologically, it was insufficiently powered due to halted enrollment based on the favorable results of a separate, non-comparable trial called WAKE-UP. Secondly, the identification of this subset of patients involves an imaging modality that we do not routinely use at BMC.

TPA remains a hammer in search of nails. More research is required to identify which patients with acute ischemic stroke will benefit the most from pharmacologic reperfusion therapy, and advanced imaging is likely to play an important role.

References:

- H Ma, BCV Campbell, et al. Thrombolysis Guided by Perfusion Imaging Up to 9 Hours After Onset of Stroke. New England Journal of Medicine 2019 May 09;380(19)1795-1803,
- Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet 2014; 384(9958): 1929-35.

ANDROMEDA-SHOCK: Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients With Septic Shock

Reviewed by Morgan Broccoli, PGY4 @MorganBroccoli

Bottom Line:

Capillary refill time (CRT) may be considered as an alternative resuscitation target in septic shock, particularly in low-resourced settings.

Why it's Important:

We take care of patients in septic shock every shift. In the era of Surviving Sepsis we know that there are many issues with using lactate as a resuscitation target, such as delayed lactate normalization after shock resolution, sources of lactate elevation other than tissue hypoperfusion, and (in many parts of the world) resource limitations. CRT is easy to use, resource independent, and may be a more responsive resuscitation sign.

Major Points:

- 74 patients (34.9%) died by day 28 in the peripheral perfusion group, compared to 92 patients (43.4%) in the lactate group (hazard ratio 0.75[95% CI 0.55 to 1.02], p=0.06)
- Peripheral perfusion-targeted resuscitation was associated with less organ dysfunction at 72 hours (mean SOFA score 5.6 [SD 4.3] vs 6.6 [SD 4.7], mean difference -1.00 [95% CI -1.97 to -0.02], p=0.045)
- Patients in the peripheral perfusion group received less IV fluid in the first 8 hours (mean 2359 vs 2767 cc, mean difference -408 cc [95% CI, -705 to -110], p=0.01)

Design:

- Multicenter RCT at 28 ICUs in 5 countries
- Inclusion criteria: consecutive adult patients admitted to the ICU w/ septic shock, defined as suspected or confirmed infection plus lactate ≥2 mmol/L and requiring vasopressors to maintain a MAP ≥65 mmHg after an IV fluid bolus of at least 20 cc/kg.
- Enrolled 424 patients - 212 randomized to peripheral perfusion group, 212 to lactate group
- Lactate level assessed q2h, CRT assessed q30min until normalization (then qh) for 8 hours.
- Fluid responsiveness was assessed q30min (via pulse pressure variation and passive leg raise with VTI), fluid responders then received 500cc bolus of crystalloid until perfusion normalized. Those who were not fluid responsive and had not met perfusion goals received trial of higher MAP goal (80-85 mmHg) if history of chronic hypertension, then trial of inodilator.

Criticisms:

- Authors report this as a negative study (did not reach statistical significance for their primary outcome) but they found an **absolute risk reduction of 8.5%** for 28 day mortality in the peripheral perfusion group.
- The study was likely underpowered, but may show that CRT is reasonable stand-in for lactate for fluid resuscitation in septic shock.

References:

Hernández G, et al. Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock: the ANDROMEDA-SHOCK randomized clinical trial. Jama. 2019 Feb 19;321(7):654-64.

Does Point-of-care Ultrasound Use Impact Resuscitation Length, Rates of Intervention, and Clinical Outcomes During Cardiac Arrest? A Study from the Sonography in Hypotension and Cardiac Arrest in the Emergency Department (SHoC-ED) Investigators

Reviewed by Sean Burns, PGY3

Bottom Line

- Cardiac activity on ultrasound during cardiac arrest was associated with longer resuscitations, more interventions, and increased rates of ROSC, but NOT survival to hospital discharge when compared to control in this observational study
- The authors say it best themselves: "It is difficult to know if the improved outcomes recorded are due to the increased resuscitative effort or if PoCUS simply identifies those patients who are more likely to survive"

Why it's important

We LOVE ultrasound and use it frequently in cardiac arrests. But there's been evidence to show that POCUS delays tried and true resuscitation efforts (longer pauses). This paper DOES NOT demonstrate improvement in the patient-oriented outcome (survival to discharge). POCUS will likely aid in identifying poor prognosis patients (although in this study these patients had less resuscitative efforts so it is a bit of a self fulfilling prophecy)

Major Points

- 11.6% of patient's getting POCUS had cardiac activity, of which 76% had ROSC (vs 16% ROSC in the no cardiac activity group)
- 9% of the cardiac activity group survived to discharge vs 7% in control and 0.6% in non-activity
- More importantly, only 1 in 159 patients in the no cardiac activity group survived to hospital discharge with no comment on neurologic outcome

Design and Results

- Single center Retrospective observational study. Patients >19 years old, no DNR, presenting in cardiac arrest. Tertiary center in Canada in 2010-2014. 223 patients were included, 180 had POCUS performed by providers
- Cardiac activity defined as "sustained coordinated contractility of the left ventricle, with visible valve movement" on initial POCUS
- POCUS grp had longer resuscitations (27.3min) if they had cardiac activity and shorter resuscitations if no activity (11.5min) when compared to control group (14.4min)
- 76% ROSC in patients with cardiac activity -- compared to 19% ROSC in non-cardiac activity group (40% ROSC in control)

Criticisms

- **Unblinded**, retrospective, observational study. Suspect many confounders (EtCO2 on arrival, down time of patient's prehospital, etc.) not described.
- This observational study came out in the era of multiple publications about US in cardiac arrest, and given that this was unblinded, physician's decisions to terminate earlier were likely impacted by US results, as illustrated by patients not receiving epinephrine/intubation. Ceasing resuscitation efforts earlier will obviously have worse rates of survival/ROSC.
- "Pauses were minimized as per ACLS recommendations, however, actual delays in CPR were not recorded"

References

- Ultrasound use during cardiopulmonary resuscitation is associated with delays in chest compressions.
- https://www.annemergmed.com/article/S0196-0644(17)31376-8/fulltext
- https://www.resuscitationjournal.com/article/S0300-9572(16)30478-6/fulltext
- The POCUS pulse check: a randomized controlled crossover study comparing pulse detection by palpation versus by point-of-care ultrasound Badra K, Coutin A, Simard R, et al. Resuscitation. 2019;139:17-23.
- Comparison of manual pulse palpation, cardiac ultrasonography and Doppler ultrasonography to check the pulse in cardiopulmonary arrest patients