Vasopressors

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Overview

- Define shock states
- Review drugs commonly used to treat hypotension
- Overview of drug management of shock states
- Describe recent studies on pharmacologic management of hypotension in septic shock
  - VASST - Vasopressin versus Norepinephrine for septic shock
  - European study - Epinephrine vs Norepinephrine + dobutamine
  - Portuguese Study - Dopamine versus Norepinephrine
Shock States

- Cardiogenic
- Hypovolemic
- Obstructive - Impairment of normal flow of blood
  - Obstruction of outflow - PE, pulmonary HTN, severe AS
  - Obstruction of inflow - Cardiac tamponade, pneumothorax
- Medication effects
  - Neuraxial local anesthetics
  - Systemically active drugs
- “Distributive” - Low vascular tone, increased vascular capacitance
  - Sepsis and other systemic inflammatory processes
  - Acute adrenal insufficiency
  - Neurogenic shock
Drugs Commonly Used to Treat Shock in ICUs

- **Adrenergic Agents**
  - **Phenylephrine**
  - **Norepinephrine**
  - **Epinephrine**
  - **Dopamine**
  - **Dobutamine**
  - **Isoproterenol**

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<th>α</th>
<th>β1</th>
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<tr>
<td>Phenylephrine</td>
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<td>Norepinephrine</td>
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- **Vasopressin**
Phenylephrine

- **Receptors:** $\alpha$
- **Vascular effects:** Potent vasoconstritor
- **Cardiac effects - Reflex**
  - Bradycardia
  - Decreased cardiac output
- **Uses**
  - Epidural and spinal anesthesia/analgesia
  - Vasodilation (autonomic instability, vasodilators)
  - To temporize while awaiting access for other agents
  - When agents with $\beta$-adrenergic activity cause tachycardia
Norepinephrine

- **Receptors:** α and β₁, minimal β₂ - α > β
- **Vascular effects:** Potent vasoconstrictor
- **Cardiac effects**
  - Increased contractility
  - Increased heart rate/tachycardia (variable)
- **Uses**
  - Combined vasodilation and myocardial dysfunction
  - Sepsis/SIRS
Epinephrine

- **Receptors:** $\alpha$ and $\beta$ - $\alpha = \beta$
- **Vascular effects:** Potent vasoconstrictor
- **Cardiac effects**
  - More potent effect on contractility than norepinephrine
  - Increased heart rate/tachycardia
- **Uses**
  - When severe myocardial dysfunction is contributing to shock
  - Cardiac arrest - Can be given intra-tracheally
  - Anaphylaxis
- **Potential Problems**
  - Reduced splanchnic blood flow
  - Increased myocardial work load $\rightarrow$ ischemia, heart failure
Dopamine

- **Receptors:** $\alpha$, $\beta_1>\beta_2$, dopaminergic
- **Vascular effects:** Vasoconstricts at higher doses
- **Cardiac effects - Lower doses**
  - Increased cardiac output
  - Increased heart rate
- **Uses**
  - Shock from sepsis or other systemic inflammatory processes
  - To increase urine output (low dose, dopaminergic effect)
- **Potential problems**
  - Dysrhythmias - Atrial fibrillation, ST
  - Not a potent vasoconstrictor - often need additional pressors
Dobutamine

- Receptors: $\beta_1 > \beta_2$
- Cardiac effects: $\beta_1$
  - Increased cardiac output - Strong inotrope
  - Increased heart rate
- Vascular effects: $\beta_2$, Vasodilation
- Effect on BP variable
- Uses
  - Cardiogenic shock
  - Refractory shock from sepsis or other systemic inflammatory process
- Potential problems
  - Tachydysrhythmias
  - Hypotension can occur $\pm 2^\circ$ to $\beta_2$ effects
Vasopressin

- Hormone with many effects: vascular, renal, endocrine
- Vascular
  - Important role in BP regulation
  - Variable vasoconstriction and vasodilation of vascular beds
- Vasopressin levels are decreased in sepsis
- Uses
  - Shock from sepsis and other inflammatory processes - Low dose
  - Peri-cardiopulmonary bypass
  - Instead of epinephrine during cardiorespiratory arrest
  - Hypotension due to ACE inhibitor
- Potential problems
  - Reduced GI blood flow, even at low dose
  - Cardiac ischemia
Vasoactive Drug Management of Shock States
Cardiogenic Shock

- Dobutamine
- Norepinephrine
- Epinephrine
- Phosphodiesterase inhibitors - Amrinone/milrinone
Hypovolemic Shock

Fluid resuscitation!!
Obstructive Forms of Shock

- **Outflow problems - PE, Aortic coarctation, Aortic stenosis, pulmonary HTN**
  - Judicious fluids
  - Inotropes or mixed inotrope/vasoconstrictor - dobutamine, norepinephrine

- **Inflow problems - Cardiac tamponade, pneumothorax**
  - Fluids
  - Relieve source (pericardiocentesis, chest tube)
Medication-Induced Shock

- Pathophysiology
  - Vasodilation
  - Cardiac dysfunction
- Neuraxial blockade - Phenylephrine
- Systemic vasodilators - Phenylephrine or norepinephrine (depending on additional factors)
- Cardiac depressants
  - Inotrope such as dobutamine
  - Consider norepinephrine if suspect concomitant vasodilation
Shock Associated with Systemic Inflammatory Process
Shock Associated with Inflammation

- Agents used routinely to treat hypotension due to sepsis and other systemic inflammatory processes:
  - Norepinephrine
  - Dopamine
  - Vasopressin
  - Phenylephrine
  - Dobutamine
  - Epinephrine

- Physiology of hypotension in systemic inflammatory processes
  - Decreased vascular tone → increased vascular capacitance
  - Decreased myocardial contractility
VASST Trial:
Vasopressin versus Norepinephrine

- **Hypothesis:** Low dose vasopressin → decrease mortality vs norepinephrine (NE) in septic shock

- **Inclusion criteria**
  - SIRS w/ documented or suspected infection
  - NE at ≥ 5 μg/min
  - New organ dysfunction

- **Interventions**
  - Vasopressin 0.01-0.03U/min vs NE at 5-15 μg/min
  - Titrate other pressor(s) to achieve BP goals

- **Primary Endpoint:** 28 day mortality

  NEJM 2008; 28;358(9):877-87
Subjects - 778 patients randomized
- Vasopressin 396
- NE 382

Outcome
- Overall no reduction in 28d (Primary endpoint, P=0.26) or 90d mortality (P=0.11)
- No significant differences in serious adverse events
- Subgroups
  - More severe – NE > 15mcg/min – Higher mortality in vasopressin group
  - Less severe – NE 5-15 mcg/min - Lower mortality at 28d (P=0.05)
Recommendations about Vasopressin Based on Available Data

- Consider using vasopressin in:
  - Patients with septic shock that are on a mid-range dose of NE (5-15 mcg/min)
  - Patients that develop tachydysrhythmias on NE
  - Patients that are extremely acidemic so won’t respond as well to NE (vasopressin not inactivated by low pH)
  - Patients on extremely high doses of NE
  - ACLS – as an alternative to epinephrine
  - Peri-CPB
European Trial: Epinephrine versus Norepinephrine + Dobutamine

- **Hypothesis:** Epi may be better than NE + Dobutamine based on more β activity
- **Study Design:** Randomized trial of patients with septic shock
- **Subjects:** 330 patients randomized
  - Epinephrine 161
  - NE + Dobutamine 169
- **Outcome**
  - Overall no reduction in 28d mortality (Primary endpoint, P 0.31) or other secondary endpoints
  - No significant differences in serious adverse events
- **Conclusions**
  - No significant difference

*Lancet. 2007 Aug 25;370(9588):676-84*
Dopamine: Sepsis Occurrence in Acutely Ill Patients (SOAP) Study

- **Hypothesis:** DA worsens outcome in shock
- **Study Design:** Observational study in 198 ICUs
- **Subjects:** 1058 patients with shock; 462 patients with septic shock
  - NE: 80.2%; 31.8% received only NE
  - DA: 35.4%; 8.8% received only DA
  - Epi: 23.3%; 4.5% only epi
  - Dobutamine + catecholamines 33.9%

- **Outcome**
  - DA and epinephrine used more in non-survivors
  - DA an independent risk factor for mortality in patients with shock, and in the subcategory of patients with septic shock

 Crit Care Med. 2006;34(3):589-97
Portuguese Community Acquired Sepsis Study: Dopamine (DA) vs NE

- **Hypothesis:**
- **Study Design:** Multicenter, observational study of patients with community-acquired sepsis in 17 ICUs
- **Subjects:** 458 patients with septic shock
  - 73% received NE
  - 50.5% received DA
- **Outcome**
  - NE associated with worse outcome
  - NE independent risk factor for ICU mortality in septic shock

Crit Care Med. 2009;37(2):410-6
Surviving Sepsis Campaign: 2008 Guidelines

- **Vasopressors**
  - NE and DA are the initial vasopressors of choice
  - Epinephrine, phenylephrine, or vasopressin should not be administered as the initial vasopressor in septic shock
  - Vasopressin 0.03 units/min may be subsequently added to NE
  - Use epinephrine as the first alternative agent in septic shock when blood pressure is poorly responsive to NE or DA.
  - Do not use low-dose dopamine for renal protection

- **Inotropic therapy**
  - Use dobutamine in patients with myocardial dysfunction

*Crit Care Med. 2008 Jan;36(1):296-327*
Thank You!!

Gram-negative Bacteria
Terlipressin

- **Vasopressin analogue**
  - Longer acting than vasopressin (half-life ~ 6 hours versus 6 minutes)

- **Widely used in Europe**
  - Undergoing trials in US

- **Uses**
  - Shock associated with sepsis and other systemic inflammatory processes

- **Potential problems**
  - Decreased cardiac output