VASOACTIVE DRUGS AND THEIR USE IN SHOCK

October 13, 2016

David Castillo, PharmD, BCPS
Emergency Department Lead Clinical Pharmacist
Peacehealth Southwest Medical Center
DCastillo@peacehealth.org

Learning Objectives

- Explain the differences between inoconstrictors, pure vasoconstrictors, and inodilators
- Review hemodynamic equations and understand how vasoactive drug fundamentals can help treat different forms of shock
- Describe how to titrate vasoactive drugs and the parameters we should monitor during titration
- Recognize some reasons for refractory shock and describe how they can be treated

Shock

- “Any state in which the oxygen delivery to end organs is insufficient to sustain normal metabolic processes”
- Clinical significance:
  - Shock affects 1/3 of patients admitted to the ICU
  - Vasopressor-dependent shock carries an average 28-day mortality of 35-50% regardless of etiology
  - Septic shock carries a 40-50% mortality rate
  - Cardiogenic shock complicated by a myocardial infarction carries a mortality rate that approaches 50%
Shock Progression

- **Pre-shock**: compensatory mechanisms are utilized to compensate for diminished tissue perfusion
- **Shock**: compensatory mechanisms become overwhelmed and signs/symptoms of organ dysfunction start appearing
- **End organ dysfunction**: shock progresses, organ dysfunction leads to organ failure, and death ensues

---

Etiology

- Finding the underline cause:
  - Physical exam: trauma, FAST exam, qSOFA, vitals, oliguria, etc.
  - **PMH**: recent infection, HF, cardiac history, clotting history, etc.
  - Labs/tests: serum lactate, CMP, CBC w/diff, EKG, Troponin, cardiac enzymes, BNP, PT/INR, aPTT, and blood gas. UA, CXR, or echocardiogram if needed.

---

Types of Shock

- **Hypovolemic**: hemorrhagic, non-hemorrhagic (GI or renal losses, burns, etc.)
- **Distributive**: septic, neurogenic, anaphylactic, drugs & toxins, endocrine shock (i.e. adrenal crisis), etc.
- **Cardiogenic**: MI, ADHF, atrial tachycardia, complete heart block, valvular insufficiency, etc.
- **Obstructive**: PE, pulmonary hypertension, tension pneumothorax, pericardial tamponade, etc.
- **Undifferentiated** or mixed shock
Treatment

- IV Fluids / blood
- Antibiotics
- Vasoactive drugs
- Steroids
- Thyroid replacement
- Cathlab / Thrombolytic
- Surgery
- Etc.

Hemodynamic Equations & Drug Fundamentals

Hemodynamic Mechanisms

- Hemodynamic Equations
  1. BP = CO x SVR
  2. CO = HR x SV

Preload Afterload Inotropy

BP = blood pressure, CO = cardiac output,
SVR = systemic vascular resistance,
HR = heart rate, SV = stroke volume
Shock and Hemodynamic Equations

**Hypovolemic**: hemorrhagic, non-hemorrhagic (GI or renal losses, burns, etc.)

\[ \downarrow BP = \downarrow CO \times SVR \uparrow \]
\[ \downarrow CO = \uparrow HR \times SV \downarrow \]
\[ \downarrow Preload \quad \downarrow Afterload \quad \uparrow Inotropy \]

**Key**:
- • = Primary issue
- ○ = Compensatory response
- ● = Effects with time

Shock and Hemodynamic Equations

**Distributive**: septic, neurogenic, anaphylactic, drugs & toxins, endocrine shock (i.e. adrenal crisis), etc.

\[ \downarrow BP = CO \times SVR \downarrow \]
\[ \downarrow CO = \uparrow HR \times SV \downarrow \]
\[ \downarrow Preload \quad \downarrow Afterload \quad \uparrow Inotropy \]

**Key**:  
- • = Primary issue
- ○ = Compensatory response
- ● = Effects with time

Shock and Hemodynamic Equations

**Cardiogenic**: MI, ADHF, atrial tachycardia, complete heart block, valvular insufficiency, etc.

\[ \downarrow BP = \downarrow CO \times SVR \downarrow \]
\[ \downarrow CO = \uparrow HR \times SV \downarrow \]
\[ \downarrow Preload \quad \downarrow Afterload \quad \uparrow Inotropy \]

**Key**:  
- • = Primary issue
- ○ = Compensatory response
- ● = Effects with time
Vasoactive Drug Fundamentals

- **Receptor effect**
  - Vasoactive drugs often activate multiple receptors

- **Dose-response curve**
  - Drug receptor activation is often dose dependent
  - Therefore at higher doses of a drug different receptors are activated vs. lower doses

- **Direct vs. reflex actions**
  - Drug actions often mimic the body's natural compensatory reactions to shock, so the clinician must distinguish between the two.

### Vasoactive medication receptor activity and clinical effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Receptor activity</th>
<th>Predominant clinical effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alpha 1</td>
<td>Beta 1</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>***</td>
<td>0</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Dopamine (mcg/kg/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5-1.0</td>
<td>0</td>
<td>***</td>
</tr>
<tr>
<td>1.0-3.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3.0-10.0</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>0</td>
<td>+++</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>0</td>
<td>+++</td>
</tr>
</tbody>
</table>

+++ = Very strong effect; ++ = Moderate effect; + = Weak effect; 0 = No effect.
*Doses between 2. and 3. mcg/kg/min have variable effects.

Recategorization of Vasoactive Drugs

- **Inoconstrictors** (vasopressor + inotrope)
  - Norepinephrine (NE)
  - Epinephrine (EPI)
  - Dopamine (DA)

- **Pure Vasoconstrictors** (vasopressor)
  - Phenylephrine
  - Vasopressin

- **Inodilators** (vasodilator + inotrope)
  - Dobutamine
  - Milrinone

Inoconstrictors

- Norepinephrine (NE)
- Epinephrine (EPI)
- Dopamine (DA)

Inoconstrictors — General Info

- Includes: NE, EPI, and DA
- Mechanism of action (MOA):
  - Mainly Alpha 1, beta 1, and beta 2 stimulation
  - Dose effects and response curve
- General Adverse Drug Reactions (ADRs):
  - Tachycardia, tachyarrhythmias, myocardial ischemia, tissue/cutaneous ischemia, mesenteric ischemia, hyperglycemia, and renal vasoconstriction
  - Extravasation risks
- Tachyphylaxis
**Inoconstrictor – Norepinephrine (NE)**

- **Indications:**
  - **PEARL:** NE is the 1st-line vasopressor for most forms of shock with severe hypotension.

- **Vasoconstriction potency:**
  - NE slightly lower than EPI, 3-5x more than phenylephrine, and ~100x more than DA for raising MAP.

- **Dosing:**
  - Sepsis/Septic shock: 0.01-3 mcg/kg/min
  - Post-cardiac Arrest (AHA): 0.1-0.5 mcg/kg/min

- **ADRs:**
  - Tachycardia is a risk at high doses due to beta 1 stimulation.

**Inoconstrictor – Epinephrine (EPI)**

- **Indications:**
  - Second-line for most other shock states.

- **Inotropic potency:**
  - 100x more potent an inotrope than DA or dobutamine.

- **Dosing effects:**
  - Low Dose: 0.01-0.1 mcg/kg/min – increases CO and/or HR.
  - High dose: 0.1-0.5 mcg/kg/min – causes vasoconstriction and inotropic effects (max studied dose: 5 mcg/kg/min).

**Inoconstrictor – Epinephrine (EPI)**

- **Anaphylaxis dosing:**
  - Pediatric bolus: 0.01 mg/kg SQ
  - Adult bolus: 0.2-0.5 mg SQ
  - Infusion: 5-15 mcg/min IV.

- **ADRs:**
  - May elevate lactate concentrations on initiation.
  - Can decrease splanchnic blood flow more than equipotent NE and DA doses.
Inoconstrictor – Dopamine (DA)

- **Indications:**
  - Alternative inoconstrictor for patients with low risk of tachyarrhythmias or bradycardia induced hypotension

- **Dosing effects:**
  - Defined dose-response curve
  - Low dose (renal dosing): < 4 mcg/kg/min
    - Minimal inotropic, chronotropic, and vasoconstriction effects
    - Mesenteric and renal vasodilation, can increase urine output
  - PEARL – Studies have failed to show clinical benefit for DA in preventing renal failure

Inoconstrictor – Dopamine (DA)

- **Dosing effects (continued):**
  - Moderate dose (inotropic dosing): 4 – 10 mcg/kg/min
    - Effects of DA on CO peak ~8 mcg/kg/min
    - >5-6 mcg/kg/min can increase LV filling pressures and exacerb pulmonary congestion
  - High dose (vasopressor dosing): >10 mcg/kg/min
    - MAP increases without further CO increase
    - Alpha effects appear to be weaker than that of NE

  PEARL – Many studies reveal increased ADEs and/or mortality with DA vs NE as the first-line vasopressor

SOAP II study
De Backer et al.

- Multicenter, double blinded, parallel-group RCT
- Included 1,679 patients with shock
  - Septic shock (62%), cardiogenic shock (16%), hypovolemic shock (16%), and other types of shock (6%)
  - Compared DA (5-20 mcg/kg/min) to NE (0.05-0.2 mcg/kg/min), with open-label NE added as needed to maintain MAP
- Primary outcome: Trend toward increased 28-day mortality with DA vs NE in shock patients, but no statistical significance was reached (48.5% vs 52.5%, OR 1.17, P= 0.1)
- Subgroup analysis showed greater mortality with DA use in patients with cardiogenic shock (P=0.03)
- The risks for tachyarrhythmias (i.e. Atrial fibrillation) was almost doubled with DA compared with NE (24.1% vs 12.4%, P< 0.001)
Pure Vasoconstrictors
Phenylephrine
Vasopressin

Pure Vasoconstrictors – General Info
- Includes: phenylephrine and vasopressin
- MOA: pure vasoconstriction without cardiac chronotropic or inotropic effects
- Benefit: these do not cause tachycardia / tachyarrhythmias
- ADRs
  - Impaired mesenteric organ perfusion compared with NE
  - Tissue, kidney, and myocardial ischemia

Pure Vasoconstrictor – Phenylephrine
- Indications:
  - Alternative vasopressor when inotropic stimulation is harmful (i.e. uncontrolled tachycardia/tachyarrhythmias)
  - Vasodilatory/distributive shock when SVR is low and CO is adequate
- MOA: Hits alpha 1 receptors without action on beta receptors
- Dosing:
  - Post-cardiac Arrest (AHA): 0.5-2 mcg/kg/min
Pure Vasoconstrictor – Phenylephrine

- **PEARL:** Should not be used for cardiogenic shock or neurogenic shock
- **ADRs:**
  - May cause reflex bradycardia
  - May decrease SV and CO in patients with cardiac dysfunction

1. \( BP = CO \times SVR \)
2. \( CO = HR \times SV \)

Preload  Afterload  Inotropy

Pure Vasoconstrictor – Vasopressin

- **Indications:**
  - Adjuvant vasopressor in vasodilatory shock (i.e. sepsis shock)
  - Central diabetes insipidus
- **MOA:**
  - Hits vascular vasopressin 1a receptors to cause vasoconstriction
  - Endogenous antidiuretic hormone analog. Can increase water retention & cause vasoconstriction

Pure Vasoconstrictor – Vasopressin

- **Dosing:**
  - **PEARL:** Low dose (0.03-0.04 u/min) can replete the relative vasopressin deficiency that may develop in shock
  - High dose (0.1 u/min) is reserved for salvage therapy in refractory vasodilator shock. Dosing NOT for regularly use
- **ADRs**
  - Reflexive bradycardia and decreased CO
  - Mesenteric ischemia and peristalsis in the GI tract (ischemic bowel)
### Pure Vasoconstrictor – Vasopressin

- **Clinical studies:**
  - Conflicting evidence on vasopressin mortality benefit in septic shock compared with NE
  - Conflicting evidence on vasopressin's ability to reduce kidney failure compared with NE

### Inodilators

- **Dobutamine**
- **Milrinone**

### Inodilators – General Info

- **Includes**: dobutamine and milrinone
- **MOA**:
  - **Dobutamine**: beta 1 agonists that increases chronotropy and inotropy, and may cause vasodilatation
  - **Milrinone**: selective phosphodiesterase inhibitor that increases inotropy & vasodilation. Has little effects on chronotropy
- **ADRs**:
  - Both may cause hypotension from vasodilation
### Inodilator – Dobutamine

<table>
<thead>
<tr>
<th>Indications:</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Cardiogenic shock with low CO and maintained blood pressure</td>
</tr>
<tr>
<td>□ Cardiac decompensation (i.e. ADHF)</td>
</tr>
<tr>
<td>□ Adjunct therapy in septic shock</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dosing:</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Cardiac decompensation, septic shock: 0.5-20 mcg/kg/min</td>
</tr>
<tr>
<td>□ Post-cardiac Arrest (AHA): 5-10 mcg/kg/min</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Benefits:</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Increases inotropy and may reduce afterload from vasodilation</td>
</tr>
<tr>
<td>□ Blood pressure may increase as CO increases</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADRs:</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ May cause tachycardia (dose related), and tachyarrhythmias</td>
</tr>
</tbody>
</table>

### Inodilator – Milrinone

<table>
<thead>
<tr>
<th>Indications:</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Inotrope in HF: 50 mcg/kg loading dose over 10 minutes, then infuse 0.1-0.75 mcg/kg/min</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Benefits:</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Less likely than dobutamine to cause tachycardia, arrhythmias, hypertension, and myocardial ischemia.</td>
</tr>
<tr>
<td>□ Preferred inotrope in patients with RV dysfunction and pulmonary HTN</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADRs:</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ More likely than dobutamine to cause hypotension</td>
</tr>
<tr>
<td>□ Can accumulate in patients with renal dysfunction</td>
</tr>
</tbody>
</table>
Drug Titration & Refractory Shock

Drug Titration

- Parameters to monitor
  - **Vitals:** MAP > 65 to 70 mmHg, BP (SBP > 90 mmHg), and HR
  - **Advanced hemodynamic parameters:** CI or CO, PCWP, CVP, SvO2, ScvO2, etc
  - **Other:** urine output (>0.5 ml/kg/hr), ana. declining lactate

- **Pearl: Vasoactive drugs have a non-linear dose response curve**
  - Titration should be based on stage of shock, type of shock, and vasoactive drug fundamentals / pharmacokinetics

Drug Titration

- **Up titration:**
  - **Inoconstrictors, dobutamine:** may increase infusion rate every 5-10 minutes
  - **Pure vasoconstrictors:** every 10-15 min
  - **Milrinone:** every 30 minutes

- **Down titration:**
  - Similar to “up titration” rates
  - Vasopressin should, however, be reduced slowly (0.01 units/min every 30 minutes) to avoid rebound hypotension
SEPSISPAM Study
Asfar et al.
- Multicenter open-label RCT
- Included 776 patients with septic shock
  - 338 patients used a low MAP target (65-70 mmHg), while 388 used a high MAP target (80-85 mmHg)
- Primary outcome: there was no significant difference in 28-day mortality (34% vs 36%, P=0.57) or 90-day mortality (42.3% vs 43.8%, P=0.74) between each group
- Patients with a higher MAP target had more incidence of AF (P=0.02)
- Patients with chronic hypertension with a higher MAP target required less renal-replacement therapy,
- There was no statistical difference between the two groups in other serious adverse events (i.e. MI, VF or VTach, mesenteric ischemia)

Refractory Shock
- Refractory shock is revealed when maximal doses of a first agent are unable to maintain BP and end-organ perfusion
- Reassessment:
  - Stage of shock, type of shock, and the vasoactive drug fundamentals
  - Causes: Receptor desensitization, inflammatory vasodilation, systemic acidemia, ionized hypocalcemia, and relative deficiency of vasopressin and corticosteroids

Refractory Shock
- Adjuvant Treatment:
  - EPI – useful when BP, HR, and/or CO are inadequate
  - Dobutamine – useful when CO is inadequate, but BP maintained
  - Vasopressin – useful when tachycardia/tachyarrhythmia present. May also help reduce NE dosages in septic shock
  - Phenylephrine – useful only when CO is adequate and when other vasoressors fail to increase BP

Pearl: If hypotension remains after use of 2 vasopressors, there’s no evidence that adding a 3rd agent is better than switching vasoactive drugs
Refractory Shock

- Hydrocortisone 200mg/day IV in septic shock
  - May reverse shock and reduce catecholamine requirements
  - Indicated only if adequate fluid and vasopressor therapy not able to restore hemodynamic stability (grade 2C)
  - No need to test ACTH before steroid use (grade 2B)
  - Lack of consistent evidence for mortality reduction

Vasoconstriction

- Phenylephrine
- Norepinephrine
- HD Epinephrine
- LD Epinephrine/Dopamine
- Dobutamine
- Milrinone

Positive inotropy

Vasodilation

- Nitroprusside

<table>
<thead>
<tr>
<th>References</th>
</tr>
</thead>
</table>

---

<table>
<thead>
<tr>
<th>References</th>
</tr>
</thead>
</table>

---

<table>
<thead>
<tr>
<th>References</th>
</tr>
</thead>
</table>
Extravasation

*Extra material*

- Many vasoactive drugs are vesicants and can cause blistering, severe tissue injury, or tissue necrosis when extravasated.

- Prevention:
  - Administer vesicants through a central line when possible.
  - If a central line is not available, give via a small bore needle (i.e. 20G) into a large peripheral vein. Avoid administration using smaller veins (i.e. in the hand, dorsum of the foot).
  - Educate patient to report signs of redness, swelling, pain/burning, tingling, etc. which could be the early signs of an extravasation.
  - Absence of blood return, IV flush resistance, or IV infusion interruption should raise suspicion of extravasation.
### Extravasation

**General management to extravasations:**
- Stop the infusion
- Do NOT remove the IV line
- Aspirate fluid out of the IV line
- Do NOT flush the line
- Give antidote if indicated (see treatment section)
- Remove the IV line
- Elevate the extremity
- Apply dry warm or cold compress when indicated
- Monitor the patient and document the event

- Consult your hospital policy on procedures for handling extravasations

### Extravasation

**Loubani et al.**

- Reviewed 85 articles describing local tissue injury or extravasation secondary to a vasopressor given through either a peripheral or central line
- 318 events occurred with peripheral line and 204 (64%) resulted in tissue injury
  - The median duration of vasopressor use before extravasation occurred was 24 hours
  - NE (80.4%), DA (9.3%), vasopressin (6.9%)
  - 85.3% of events happened at infusions sites distal to the AC
- EPI, phenylephrine had 1-2 case reports of tissue injury

### Extravasation

**Vasoactive drug extravasation treatment:**
- **Phentolamine (preferred):** Dilute 5-10 mg in 10-15 ml NS and inject/infiltrate into extravasation site
- **Nitroglycerin 2% ointment:** apply 1-inch or a 4 mm/kg thin ribbon to the affected area; repeat 8hrs after if needed
- **Terbutaline:** Dilute 1 mg in 1-10 ml NS and inject/infiltrate into extravasation site
  - Apply warm dry compress

- Dobutamine and milrinone are NOT vesicants