Vasoactive Medications

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Objectives

- List components of physiology involved in blood pressure
- Review terminology related to vasoactive medications
- Discuss the difference between an agonist and an antagonist
- Review catecholamine receptor basics
- Define shock and how it may be identified
- Summarize the basic principles of volume resuscitation.
- Explain the rationale for the use of specific Vasopressors.
What Goes Into Blood Pressure?

- Blood Pressure
  - Cardiac Output
  - Systemic Vascular Resistance

- Stroke Volume
  - Heart Rate
  - Preload
  - Afterload
  - Contractility
Why Does it Matter?

![Graph showing renal blood flow vs. mean arterial pressure with an autoregulatory range marked between 100 and 180 mmHg.](image)
Terminology Review

- **Inotropy**: Augments cardiac contractility
- **Chronotropy**: Increases heart rate
- **Vasopressor**: Induces vasoconstriction
Agonist vs. Antagonist

Before Drug
- Natural chemical
- Receptor site
- Normal cellular activity

Agonist Drug
- Natural chemical
- Receptor site
- Agonist drug
- Enhanced cellular activity

Antagonist Drug
- Natural chemical
- Receptor site
- Antagonist drug
- Blocked cellular activity
Receptor Review

- Alpha (α) receptors
- Beta (β) receptors
- Dopamine (D) receptors
- Vasopressin (V) receptors
$\alpha$-1 vs $\alpha$-2

- $\alpha$-1: smooth muscle
α-1 vs α-2

- α-2: pre-synaptic neurons
β-1 vs β-2 vs....β-3?

Beta₁ Receptors

1. Increase the force of myocardial contraction.

Activation of the Beta₁ Receptor

Heart Rate

2. Increase the rate of contraction.

3. Excess stimulation leads to arrhythmias.

Agonist vs. antagonist
β-1 vs β-2 vs....β-3?

- β-2: bronchial smooth muscle
  - β-2 agonist: dilation of bronchial tree, increase in heart rate (albuterol)
  - β-2 antagonist: constriction of bronchial tree (beta-blockers)
β-1 vs β-2 vs....β-3?

- β-3: adipose tissue
  - When stimulated, will induce thermogenesis
Dopamine Receptors

- Several subtypes
- Brain, heart, vascular smooth muscle, and kidney
- Stimulation will increase CO, HR, and blood pressure, ↑ UO?
Vasopressin Receptors

- Subtypes 1-3
  - V1: Blood vessels
  - V2: Kidney
    - High density in vascular smooth muscle
  - V3: Pituitary
    - Activation leads to profound vasoconstriction
What is Shock?

- Cardiogenic
- Septic
- Hypovolemic
- Hemorrhagic
- Neurogenic
- Distributive
- Obstructive
- Anaphylactic
What is Shock?

[Diagram showing balance between Oxygen Supply and Oxygen Demand]
What is Shock?

Oxygen Supply

Oxygen Demand

Glycolysis

2 ADP + 2 $P_i$ → 2 ATP

Glucose → 2 NAD$^+$ → 2 NADH + $2H^+$

Regenerates NAD

2 Pyruvate → (anaerobic respiration in some bacteria & animal cells)

2 Lactate

(b) Lactic acid fermentation
Managing Patient in Shock

Blood Pressure

Cardiac Output

Systemic Vascular Resistance

Stroke Volume

Heart Rate

Preload

Afterload

Contractility
What is Preload?

- Left ventricular end diastolic volume (LVEDV)
  - At the end of diastole, amount of blood volume in the left ventricle
    - Measure of stretch of the left ventricle
- Why does it matter?? → Think NICOM
Optimizing Preload

- IV Fluids (crystalloids)
  - Normal saline
  - LR
- Colloids
  - Albumin
- Blood

![Graph showing relationship between SV (ml) and LVEDP (mmHg)](image)
OK, So Which Fluid?

- Crystalloid = Colloid
- Pro’s and con’s of each strategy

- Replace blood with blood
- Replace plasma with colloid
  - Burns
- Resuscitate with colloid and/or crystalloid
- Replace ECF depletion with saline (Loss of water and salt)
  - Dehydration
What’s Normal About Normal Saline?

<table>
<thead>
<tr>
<th></th>
<th>0.9% Saline</th>
<th>Blood Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺ (mEq/L)</td>
<td>154</td>
<td>134-145</td>
</tr>
<tr>
<td>Cl⁻ (mEq/L)</td>
<td>154</td>
<td>95-105</td>
</tr>
<tr>
<td>K⁺ (mEq/L)</td>
<td>0</td>
<td>3.6-5.0</td>
</tr>
<tr>
<td>Mg²⁺ (mg/dL)</td>
<td>0</td>
<td>1.5-2.5</td>
</tr>
<tr>
<td>Ca²⁺ (mg/dL)</td>
<td>0</td>
<td>8.5-10</td>
</tr>
<tr>
<td>HCO₃⁻ (mEq/L)</td>
<td>0</td>
<td>22-26</td>
</tr>
<tr>
<td>Osmolarity (mOsm/L)</td>
<td>308</td>
<td>285-295 (mOsm/kg)</td>
</tr>
<tr>
<td>pH</td>
<td>5.8 (4.5-7.0)</td>
<td>7.35-7.45</td>
</tr>
</tbody>
</table>
Ok, So how much sodium is that?

52 Small bags of chips in 1 liter!!!!
Saline Pearls

- Most widely used IVF (200 million liters sold in US!)
- Not “normal” from chemical or physiologic standpoint
- Only 25-35% stays within the blood vessel
- Administration of large volumes may lead to interstitial edema and acidosis
## Lactated Ringers Solution

<table>
<thead>
<tr>
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<th>0.9% Saline</th>
<th>Lactated Ringers</th>
<th>Blood Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Na⁺ (mEq/L)</strong></td>
<td>154</td>
<td>130</td>
<td>134-145</td>
</tr>
<tr>
<td><strong>Cl⁻ (mEq/L)</strong></td>
<td>154</td>
<td>109</td>
<td>95-105</td>
</tr>
<tr>
<td><strong>K⁺ (mEq/L)</strong></td>
<td>0</td>
<td>4</td>
<td>3.6-5.0</td>
</tr>
<tr>
<td><strong>Mg²⁺ (mg/dL)</strong></td>
<td>0</td>
<td>0</td>
<td>1.5-2.5</td>
</tr>
<tr>
<td><strong>Ca²⁺ (mg/dL)</strong></td>
<td>0</td>
<td>3</td>
<td>8.5-10</td>
</tr>
<tr>
<td><strong>HCO₃⁻ (mEq/L)</strong></td>
<td>0</td>
<td>0</td>
<td>22-26</td>
</tr>
<tr>
<td><strong>Osmolarity</strong></td>
<td>308 (mOsm/L)</td>
<td>273 (mOsm/L)</td>
<td>285-295 (mOsm/kg)</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>5.8 (4.5-7.0)</td>
<td>6.5 (6-7.5)</td>
<td>7.35-7.45</td>
</tr>
<tr>
<td><strong>Lactate</strong></td>
<td></td>
<td></td>
<td>28mmol/L</td>
</tr>
</tbody>
</table>
Lactated Ringers Pearls

- Developed in 1930’s → Hartmann’s solution
- Benefit is lack of effect on acid-base status…. BUT….

- Potassium → not good in renal patients
- Hypotonic → not good in TBI patients

AND it has lactate and we check lactic acid levels on EVERYONE???

- Lactate and lactic acid are different entities
- Unlikely to have any impact on serum lactate levels even in large volumes
What Happens to Lactate?

- Lactate $\rightarrow$ pyruvate OR $\text{CO}_2 + \text{H}_2\text{O}$
- $\text{H}_2\text{O} \rightarrow \text{H}^+ + \text{OH}^-$
- $\text{OH}^- + \text{CO}_2 \rightarrow \text{HCO}_3^-$

May PREVENT acidosis
Rule of Thumb

- Ensure volume status is addressed BEFORE initiating vasopressor
- ↓ Incidence of tachycardia
Managing Patient in Shock

- Blood Pressure
- Cardiac Output
  - Stroke Volume
    - Preload
    - Afterload
    - Contractility
  - Heart Rate
- Systemic Vascular Resistance

\[ \text{CO} = \text{SV} \times \text{HR} \]
Systemic Vascular Resistance (SVR)

- Resistance that blood "sees" as it travels through the circulatory system
- Most important parameter is the radius of the vessel
  - Also the easiest to change
- Radius of a vessel ↓, the resistance ↑
- Radius of a vessel ↑, the resistance ↓
Vasopressors

- Medications mimicking the effect of neurotransmitters that lead to contraction of the smooth muscles surrounding blood vessels
  - Decrease radius of the vessel
  - Increase SVR
  - Increase perfusion to organs
Vasopressor

- Catecholamines
  - Dopamine
  - Epinephrine
  - Norepinephrine
  - Phenylephrine
- Vasopressin
Catecholamines

\[
\text{DOPA} \quad \xrightarrow{3} \quad \text{L-Aromatic Amino Acid Decarboxylase} \\
\text{DOPAMINE} \quad \xrightarrow{4} \quad \text{(Dopamine } \beta\text{-Oxidase)} \\
\text{NOREPINEPHRINE} \quad \xrightarrow{5} \quad \text{(Phenylethanolamine N-Methyltransferase)} \\
\text{EPINEPHRINE}
\]
Catecholamine Effects

Via ↑ in SVR and CO
Dopamine

1-5 mcg/kg/min
- Dopamine Receptors
  - Urine output ↑

5-10 mcg/kg/min
- β-Receptors
  - HR ↑
  - Contractility ↑
  - CO ↑

>10 mcg/kg/min
- α-Receptors
  - Vasoconstriction

Renal blood flow ↑
Dopamine

- Typical dose range: 5-20mcg/kg/min
- Monitor: blood pressure, ECG, urine output
- Side effects: tachycardia, arrhythmia, chest pain, nausea and vomiting
- Clinical Pearls
  - CENTRAL LINE ONLY
  - NO MATTER WHAT DOSE
Dopamine

1-5 mcg/kg/min

- Dopamine Receptors
  - ↑ Renal blood flow
  - ↑ Urine output
  - ↑ Contractility
  - ↑ CO

5-10 mcg/kg/min

- β-Receptors
  - ↑ HR
  - ↑ Contractility
  - ↑ CO

>10 mcg/kg/min

- α-Receptors
  - Vasoconstriction
Local Concentration is Key

- Low concentration systemically
- High concentration locally

Total Blood Volume

Small Blood Volume

DRUG

Low concentration systemically

High concentration locally
EPINEPHRINE

Epinephrine

Low Dose
(<0.05-0.1 mcg/kg/min)
- β-1 predominantly
  - ↑HR
  - ↑ Myocardial contract
- SOME β-2
  - bronchodilator

High Dose
(> 0.1 μg/kg/min)
- α-1 predominantly
  - Vasoconstriction
    - ↓ Renal BF
    - ↓ Splanchnic BF
    - ↑ Glucose
Epinephrine

- Indication for continuous infusion are:
  - Low cardiac output state
    - $\beta$- effects will improve cardiac function
    - $\alpha$- effects $\uparrow$afterload and decrease cardiac output
  - Septic shock
    - Useful for both inotropy and vasoconstriction
Epinephrine

- Typical dose range: 0.05-2.0 mcg/kg/min
- Monitor: blood pressure, ECG, renal function, electrolytes
- Side effects: tremors, palpitations, arrhythmia, myocardial ischemia, ↓ mesenteric circulation, ↑ lactic acid, hyperglycemia

Clinical Pearls

- CENTRAL LINE ONLY
- Drug of choice for anaphylactic shock
- Second line agent in septic shock
Norepinephrine

- Catecholamine AND neurotransmitter
- Rapid acting $\alpha$- agonist
  - Potent vasoconstriction
- Small amount $\beta$- activity
  - May increase HR and stroke volume
Norepinephrine

- Typical dose range: 0.05-2.0 mcg/kg/min
- Monitor: blood pressure, ECG, renal function, electrolytes
- Side effects: bradycardia, arrhythmia, digital ischemia

Clinical Pearls

- CENTRAL LINE ONLY
- Drug of choice for septic shock
Phenylephrine

- Potent $\alpha$-agonist
- Intense peripheral vasoconstriction

<table>
<thead>
<tr>
<th>Agent</th>
<th>$\alpha_1$</th>
<th>$\alpha_2$</th>
<th>$\beta_1$</th>
<th>$\beta_2$</th>
<th>Dopaminergic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine</td>
<td>+</td>
<td>+</td>
<td>++++</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Dopamine</td>
<td>++++/+++++</td>
<td>?</td>
<td>++++</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>++++</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>+++</td>
<td>++++</td>
<td>+++</td>
<td>1/++</td>
<td>0</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>++++/+++++</td>
<td>+</td>
<td>?</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

$\alpha$, $\alpha$ adrenergic receptors; $\beta$, $\beta$ adrenergic receptors, DA, dopamine receptors. Activity ranges from no activity (0) to maximal activity (+++++) or ? when activity is not known. Reproduced with permission from Rudis et al. Is it time to reposition vasopressors and ionotropes in sepsis? Crit Care Med 1996;24:525–537.
Phenylephrine

- Typical dose range: 0.05-2.5mcg/kg/min
- Monitor: blood pressure, ECG, renal function, electrolytes
- Side effects: bradycardia, arrhythmia, ↑ UO
- Clinical Pearls
  - CENTRAL LINE ONLY
  - Appropriate option in patients with hypotension and profound tachycardia
Vasopressin

1. Hypothalamus detects too little water in blood
2. Pituitary gland releases ADH
3. Kidneys maintain blood water level
4. So less water is lost in urine (urine more concentrated)
5. Blood water level to normal
Vasopressin and Shock

- Pituitary depletion and impaired synthesis
- Constricts vascular smooth muscle via V1 receptor
- Increases responsiveness of vasculature to catecholamines
- Inhibits smooth muscle nitric oxide production
Vasopressin

- Typical dose: 0.03-0.04U/min
- Monitor: blood pressure, HR, urine output
- Side effects: myocardial ischemia, ↓ mesenteric circulation

Clinical Pearls
- ALWAYS second line agent
- Replacing a deficiency ➔ not a titratable “pressor”
Which Agent to Remove First

- Often, the decision to remove norepinephrine or vasopressin is based on expert opinion alone → Does it matter?

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>VP DC first (n=62)</th>
<th>VP DC second (n=92)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension requiring intervention, n (%)</td>
<td>42 (67.8)</td>
<td>10 (10.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NE dose increased after VP DC’d</td>
<td>31 (50)</td>
<td>----</td>
<td></td>
</tr>
<tr>
<td>VP added back after DC’d</td>
<td>21 (33.9)</td>
<td>5 (5.4)</td>
<td></td>
</tr>
<tr>
<td>NE added Back after DC’d</td>
<td>----</td>
<td>5 (5.4)</td>
<td></td>
</tr>
</tbody>
</table>

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Managing Patient in Shock

Blood Pressure

Cardiac Output

Systemic Vascular Resistance

Stroke Volume

Heart Rate

Preload

Afterload

Contractility
Contractility

- Also know as inotropy
- Measure of “how hard” the heart contracts
- As inotropy ↑ → stroke volume ↑
Improving Contractility

- Dobutamine
  - β-1 agonist
    - Primary effect is on myocardium
    - ↑ strength of contraction
    - Typical dose rage: 2.5-20mcg/kg/min
    - Monitor: blood pressure, ECG
    - Side effects: tachycardia, arrhythmia, chest pain
  - Clinical Pearls
    - No central venous access needed if ≤10mcg/kg/min
Improving Contractility

- Milrinone
- Inotrope and a vasodilator
  - ↑ the force of contractility of the heart and causes vasodilation in the periphery
  - Typical dose range: 0.375-0.75 mcg/kg/min
  - Monitor: blood pressure, ECG, renal function, electrolytes
  - Side effects: arrhythmia, chest pain, headache
  - Clinical Pearls
    - No central venous access
Review

- Blood pressure is a combination of several physiologic variable
- Preload $\rightarrow$ fluids
- SVR $\rightarrow$ vasopressors
- Contractility $\rightarrow$ inotropes
Vasoactive Medications

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