Vasopressors and Inotropes

Jennifer Salotto, MD
Trauma, Acute Care, and Critical Care Fellow
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Critical Care Lecture Series
Key Points

- Overview of the pathophysiology of shock, or, why do we care?
- What are vasopressors and how do they work?
- What are inotropes and how are these different from vasopressors?
- Which agent to choose and why?
- What is the evidence?
Introduction

- Vasopressors are drugs which elevate Mean Arterial Pressure (MAP) via vasoconstriction
- Inotropes increase cardiac contractility
- Both lead to improved cardiac output and are utilized when cardiac output is insufficient to maintain end-organ perfusion
End-organ Autoregulation

- Can compensate for decreased MAP in a given range
- Below threshold MAP, autoregulation may be lost and perfusion linearly dependent on pressure

Curr Opin Anesthesiol 21: 141-147
Indications

- Why do we use vasopressors?
  - To improve MAP
  - Improve oxygen delivery to the periphery
  - Redistribute cardiac output
  - To limit fluid volumes

- To choose the right agent, identify the etiology of shock
Principles of Vasopressor Use

- **Indications:**
  - Map < 60 mmHg and
  - Evidence of end-organ dysfunction from hypoperfusion

- **Be sure to correct hypovolemia first!**

- **Place an arterial line with vasopressor use**
  - Peripheral perfusion impaired with shock;
  - Cuff may be inaccurate
Vasopressor

- Increase blood pressure via constriction of blood vessels
- $= \text{Increase SVR, } = \text{increase venous return to the heart.}$
Inotrope

- Increases muscular contraction of the heart
- Increases stroke volume -> increased cardiac output
Cardiac Output

Cardiac factors:
- Heart rate
- Myocardial contractility

Coupling factors:
- Preload
- Afterload
Goal: increase O2 delivery to the periphery

\[ \dot{D}O_2 = \dot{Q} \cdot C_aO_2 \]

Where \( \dot{D}O_2 \) = oxygen delivery

\( \dot{Q} \) = cardiac output (dL/min)

\( C_aO_2 \) = oxygen content of arterial blood

(\( mL \text{ O}_2/100 \text{ mL blood} \))

- **Pressor**: increase SVR, increase Venous return, increase stroke volume, increase CO

- **Inotrope**: increase SV, increase CO
How do vasopressors work?

- Systems to modulate vascular tone:
  - Sympathetic nervous system outflow
  - Vasopressin
  - Plasma angiotensin

- Sympathetic Outflow
  - Effects of catecholamines range from pure alpha agonist to pure beta agonist
  - Dopamine: dopamine receptors
Alpha-1 Adrenergic Receptors

- Present in:
  - Arteriolar walls
    - Induces significant vasoconstriction
  - Heart
    - Positive inotropy
Beta-1 Receptors

Heart

- Increased chronotropy and inotropy
- Increased AV-node conduction velocity

Renal juxtaglomerular cells

- Increased renin release
Beta-2 Agonists

- Bronchial smooth muscle
- Uterine muscle
- Bronchodilation
  - Uterine relaxation (tocolysis)

- Bladder detrusor muscle: Relaxation
- Eye ciliary muscle: Relaxation
- GI tract: Decreased motility
- Liver: Increased glucose metabolism, lipolysis
- Smooth muscle: Relaxation
Dopamine Receptors

- Present in renal, splanchnic, coronary, and cerebral vascular beds
- Low dose dopamine = D1A receptors
  - vasodilation of renal and mesenteric circulation
Vasopressors

- Phenylephrine
- Norepi
- Dopamine
- Epinephrine
- Vasopressin
Most vasopressors have a combination of effects
Which vasopressor to choose?
56 year-old obese man with COPD and OSA, who was initially admitted to the medicine floor for acute COPD exacerbation secondary to community-acquired pneumonia, was found to be in ARF.

Versed and Succinylcholine were given for emergent intubation. Vitals after intubation: Temp 99.8F, BP 74/48, Hr 74. What is the most appropriate 1st line agent?

A. Phenylephrine
B. Dobutamine
C. Norepinephrine
D. Dopamine
Phenylephrine

- Pure alpha-1 = pure vasoconstriction
- Increases SVR, increases MAP
- Use in:
  - distributive shock with tachyarrhythmia
  - Reversal of hypotension after spinal anesthesia
  - good in pregnancy
- Cons:
  - reflex bradycardia
  - impaired cardiac output in heart dysfunction
  - hypoperfusion of gut and kidneys
A 58 yo F is found to be hypotensive with unknown etiology. While workup is initiated she has a decline in mental status and is intubated. A central line is placed and several fluid boluses are given but she is still unstable. A continuous drip is started and after administration her HR remains at 105, her CO drops to 2.8 from 3.3 L/min and SVR increases from 500 to 1150 dynes.s/cm5. Based on the changes, which drug was most likely administered?

A. Dobutamine
B. Dopamine
C. Phenylephrine
D. Epinephrine
E. Milrinone
Question

- 72 yo F with DM type II, HTN and CKD is admitted for altered mental status. Her vitals upon arrival: Temp 101F, BP 70/45, Hr 140, RR 20, Sat 95% RA. Lab findings: WBC 21, Cr 3.5, Lactic Acid 3.4, Positive UA.

- After IVF resuscitation, pt continues to remain hypotensive BP 60-70s/30-40s and tachycardic Hr 130s. What is the most appropriate 1st line agent?

  A. Epinephrine
  B. Dobutamine
  C. Norepinephrine
  D. Dopamine
Norepinephrine

- Endogenous mediator of sympathetic nervous system
- Released in response to stress
- Strong alpha, less beta-1.
  - Increases systolic and diastolic pressure (alpha)
  - Increased chronotropic function (beta)
Norepinephrine

- **Uses**
  - Catecholamine of choice in septic shock
  - Remember: mortality equal for EPI, NE, and dopamine…. BUT… NE fewer ADRs
  - Ok for distributive shock, neurogenic shock

- **Pros:**
  - safe, easy to titrate
  - reliable dosing profile
  - does not cause tachycardia/increased myocardial oxygen demand

- **Cons:** systemic vasoconstriction
Dopamine

- Precursor of norepinephrine and epinephrine
- Stimulates alpha, beta and dopaminergic receptors in a dose-dependent fashion

- 0-3 ug/kg/min: vasodilation to renal and splanchnics, diuresis
- 3-10 ug/kg/min: beta stimulation, inotropic and chronotropic effects; periph vasodilation
- >10 ug/kg/min: alpha effects, pure vasoconstriction- increases afterload, reduce SV
Dopamine

**Uses:**
- Second line agent in septic shock
- Reasonable choice in cardiogenic shock with IABP
- IABP preferred in cardiogenic shock

**Cons:**
- Sinus tachycardia and Afib in 25%
- Difficult dosing profile
- Increased intraocular pressure
- Delayed gastric emptying
- Extravasation = tissue necrosis
### TABLE 7. Norepinephrine Compared With Dopamine in Severe Sepsis Summary of Evidence

**Norepinephrine compared with dopamine in severe sepsis**

- **Patient or population:** Patients with severe sepsis
- **Settings:** Intensive care unit
- **Intervention:** Norepinephrine
- **Comparison:** Dopamine

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Assumed Risk</th>
<th>Corresponding Risk</th>
<th>Relative Effect (95% CI)</th>
<th>No. of Participants (Studies)</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term mortality</td>
<td></td>
<td></td>
<td>RR 0.91 (0.83 to 0.99)</td>
<td>2043 (6 studies)</td>
<td>moderate³</td>
<td></td>
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<tr>
<td></td>
<td>Dopamine</td>
<td>Norepinephrine</td>
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<tr>
<td></td>
<td>530 per 1000</td>
<td>482 per 1000 (440 to 524)</td>
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<td>Serious adverse events —Supraventricular arrhythmias</td>
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<td></td>
<td>RR 0.47 (0.38 to 0.58)</td>
<td>1931 (2 studies)</td>
<td>moderate³</td>
<td></td>
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<tr>
<td></td>
<td>Dopamine</td>
<td>Norepinephrine</td>
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<tr>
<td></td>
<td>229 per 1000</td>
<td>82 per 1000 (34 to 195)</td>
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<tr>
<td>Serious adverse events —Ventricular arrhythmias</td>
<td></td>
<td></td>
<td>RR 0.35 (0.19 to 0.66)</td>
<td>1931 (2 studies)</td>
<td>moderate³</td>
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</tr>
<tr>
<td></td>
<td>Dopamine</td>
<td>Norepinephrine</td>
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<tr>
<td></td>
<td>39 per 1000</td>
<td>15 per 1000 (8 to 27)</td>
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</table>

*The assumed risk is the control group risk across studies. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI: CI = confidence interval, RR = risk ratio).

³Strong heterogeneity in the results (I² > 85%), however this reflects degree of effect, not direction of effect. We have decided not to lower the evidence quality.

³Effect results in part from hypovolemic and cardiogenic shock patients in De Backer, *N Engl J Med* 2010. We have lowered the quality of evidence one level for indirectness.
Epinephrine

- Adrenergic hormone of adrenal medulla
- High dose: Potent alpha-1
  - Venous and arterial vasoconstriction
  - Lesser increase in MAP than norepinephrine
- Low dose: B1 and B2 effects
  - Increased HR, SV
- May increase skeletal muscle production of aerobic lactate, may prevent use of lactate clearance to guide resuscitation
Epinephrine

**Uses:**

- Cardiac arrest
- Drug of choice in anaphylactic shock
- More potent increase in SV and HR than NE or dopamine
Epinephrine

- **Cons:**
  - Greater risk of cardiac stimulation, increases myocardial oxygen demand
  - Hyperglycemia via inhibition of insulin secretion
  - May impair splanchnic blood flow in severe septic shock
  - May lead to an increase in lactate secondary to an increased rate of glycolysis
Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: Which is best?

Daniel De Backer, MD, PhD; Jacques Creteur, MD, PhD; Eliézer Silva, MD, PhD; Jean-Louis Vincent, MD, PhD, FCCM

- Prospective, randomized, open-label study
- 20 pts w septic shock on dopamine (10 moderate, 10 severe)
- Replacement of dopa with NE and then Epi to maintain MAP
- Measured systemic and splanchnic circulation
  - PA catheter, indocyanine green and hepatic v. cath

Crit Care Med 31 (2003) 1659-1667
Figure 1. Study protocol synopsis. At each step, only one of the three vasopressor agents was administered. MAP, mean arterial pressure.
Results:

- Cardiac Index similar to dopamine and NE but greater with Epi
- In moderate septic shock, splanchnic blood flow was similar
- In severe septic shock, splanchnic blood flow was decreased with Epi
Vasopressin

- Antidiuretic hormone
- V1 receptor: vasoconstrictive properties
- Increases MAP, SVR, UOP in patients with pre-existing peripheral vasodilation
- Use in: catecholamine resistant shock
  - Septic, anaphylactic, autonomic insufficiency, vasodilation after anesthesia
Rationale to supplement vasopressin in septic shock

- Relative vasopressin deficiency
- Potential for synergism between NE and Vaso
- Vasopressin-mediated vasoconstriction
- Exogenous vasopressin may decrease the catecholamine requirement
Vasopressin

- Use a low dose, don’t titrate
- Adverse effects uncommon with infusions <0.04U/hr
- Higher doses associated with cardiac, digital, and splanchnic ischemia
Multicenter, double-blind RCT

Norepi or Vasopressin infusions

Endpoint: mortality 28 days

n= 778

No difference in mortality at 28, 90 days
Lactate and renal function were unaffected by the two treatments

Survival of patients with less severe shock was improved in the vaso group (p=0.05)
Inotropes

- Augments cardiac output via increasing contractility
- No literature supports a mortality benefit
Dobutamine

- Synthetic adrenergic agent
- B1: ++, B2 +
- Net increase in HR, SV
- Decrease in SVR
- BP usually net unchanged, but response may vary
- Ensure adequate volume load prior to initiation
Dobutamine

**Use:**
- In non-cardiogenic shock when contractility is compromised
- Septic shock with tissue hypoperfusion despite adequate intravascular volume and MAP

**Cons:**
- Increases myocardial oxygen demand - not a first line in decompensated heart failure or ischemia
- May cause significant tachycardia
- Tolerance after 72 hours
Digoxin

- Uncertain mechanism
- Improves hemodynamics without affecting heart rate or blood pressure
- Does not increase myocardial oxygen demand and does not decrease coronary perfusion
- Use in heart failure with Afib - controls HR
- Must closely follow levels
Milrinone

- A phosphodiesterase inhibitor
- Enhances myocardial contractility and relaxation
- Vasodilator - more likely to cause hypotension
- Lusitropic: improvement in diastolic function
- No data for milrinone over dobutamine
- Favored in:
  - Patients on beta blockade
  - May improve pulm HTN and RV function
Milrinone

- **Avoid in:** renal failure

- **Cons:**
  - T1/2: 50 minutes
  - Bolus may cause hypotension
  - atrial arrhythmias
Specific Shock Scenarios:

- Septic Shock
- Cardiogenic Shock
- Neurogenic Shock
Surviving Sepsis Campaign

International Guidelines for Management of Severe Sepsis and Septic Shock: 2012

- Initial guidelines: 2004
- Outlines early, goal directed therapy
  - CVP 8-12
  - MAP > 65
  - UO > 0.5cc/kg/hr
  - Mixed venous 65%

Crit Care Med. 2013; 41:580-637
Crystalloids the initial fluid of choice (1B)
Continue fluid challenge as long as there is hemodynamic improvement
Vasopressors for refractory hypotn, >65mmHg
Surviving Sepsis, 2012

- Norepinephrine: first choice (1B)
- Epinephrine: first alternative (2B)
- Vasopressin 0.03 U/min added to NE
  - Raise MAP or decrease NE dose
  - Greater than 0.04 U/min as a salvage measure only
- Dopamine only in low risk tachyarrhythmia or bradycardia (2C)
- Phenylephrine only if: (1C)
  - NE = arrhythmia
  - CO known to be high and MAP low
  - salvage

Crit Care Med. 2013; 41:580-637
Inotropic Therapy:
- Dobutamine trial alone or added to a vasopressor if:
  - Myocardial dysfunction
  - Ongoing hypoperfusion despite adequate intravascular volume and adequate MAP

Crit Care Med. 2013; 41:580-637
Meta-analysis of RCTs reporting mortality rates with pressors and inotrope use in septic shock

- 14 studies, 2811 patients
- NE or NE + vaso associated with reduced mortality vs. dopamine; but not EPI
- Addition of an inotrope did not reduce mortality
- No concrete evidence supports NE vs dopa as 2nd agent

A 70 y.o. man with HTN undergoes repair of AAA. He gets 9 L LR and 4 prbc intraop. Post-operation, BP is 90/60, HR is 110 bpm, CVP is 7 mmHg, PAP is 30/10 mmHg, Cardiac output = 2.0 L/min UO is 15 mL/hr, and hematocrit is 30%. Next step?

1. Give a diuretic to increase urine output
2. Give vasopressor agent to increase B.P.
3. Administer fluid challenge
4. Give vasodilating agent
5. Observation
Cardiogenic Shock

- Decreased contractility of heart leading to malperfusion of periphery
- CO and CI down, HR up, SBP down, PAP, CVP may be elevated
- Inotropes increase CO but use has been complicated by increased mortality secondary to
  - Tachycardia, increased myocardial O2 demand= increased arrhythmia and MI, hypotension
Inotropes and Cardiogenic Shock: Indications

- Stabilize patients in acute heart failure with signs of end-organ hypoperfusion
- Use as bridge to revascularization, IABP, ECMO, transplant
- Inotrope-dependent patients: impaired renal function without dobutamine, milrinone
Cardiogenic Shock: Agents

- **Digoxin**: heart failure and Afib
- **Dobutamine**: positive inotrope, increases HR
- **Milrinone**: better for pulm HTN, R heart failure, in myocardial ischemia
- **Dopamine**: no benefit over placebo
A 22 yo M is involved in a MVC and is found to have a T6 fracture and paraplegia. The patient is hypotensive with a systolic BP of 70mmHg and bradycardic. Which is the appropriate initial therapy?

A. Isotonic fluid
B. Steroid administration
C. Intubation
D. Alpha-agonist
E. Dobutamine
The same 22 yo M with a T8 injury has now been given 2 Liters of isotonic fluid. His MAP is now 55. What is the appropriate therapy?

A. more fluid
B. phenylephrine
C. dobutamine
D. obtain an ECHO
E. norepinephrine
Neurogenic Shock

- Characterized by hypotension, may see bradycardia; skin is warm
- Common after injuries of T4 and below
- Above T4: heart unable to receive sympathetic input- treat with pure alpha (phenylephrine)
- Below T4: alpha agonist may aggravate reflex bradycardia; choose norepinephrine or dopamine
Take Home Points

- Vasopressors are drugs which elevate Mean Arterial Pressure (MAP) via vasoconstriction
- Inotropes increase cardiac contractility
- Many drugs have properties of both
- Both lead to improved cardiac output
Take Home Points

- Attempt to ID type of shock prior to treatment
- For septic shock, there is no mortality benefit with different agents, BUT rates of ADRs are least with Norepinephrine
- Any agent which increases HR will increase myocardial oxygen demand
- Try to make evidence-based choices in your clinical practice
- Use available guidelines to assist your choices
References


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   Related citations

   Bartel B.
   PMID: 24851468 [PubMed - indexed for MEDLINE]
   Related citations

5. The shock index as a predictor of vasopressor use in emergency department patients with severe sepsis.
   Wira CR, Francis MW, Bhat S, Ehrman R, Conner D, Siegel M.
   Related citations

6. Coefficient of Variation of Coarsely Sampled Heart Rate is Associated With Early Vasopressor Independence in Severe Sepsis and Septic Shock.

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