Vasopressors in Sepsis – A Little of Everything

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Introduction

Septic shock is characterized by acute circulatory failure leading to tissue hypoperfusion, and potentially resulting in multi-organ failure.

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Hypotension in septic shock is due to 3 major hemodynamic disorder:

- Hypovolemia
- Vascular failure
- Heart failure
• Vascular dysfunction is characterized by:
  1. Microvascular dysfunction
  2. Endothelial dysfunction
  3. Vascular hyporesponsiveness

• Vascular dysfunction will cause vasopressor-refractory hypotension & death
Fluid responsiveness

- An ability of left ventricle to increase stroke volume 10-15% after a fluid challenge of 500 mls of crystalloids in 10-15 minutes

- Also known as volume responsiveness

- Fluid responsiveness does not equal to patients need fluid
Vasopressor responsiveness?

• Critically ill patients vary considerably in how they respond to vasopressor

• Uncontrolled vasodilation or vasoplegia can be assessed clinically by increasing vasopressor requirement & low diastolic BP.

• Mechanism of vasoplegia
  1. Sustained (+) SNS by cytokines causing dysautonomia & loss CVS variability and inappropriate tachycardia
  2. Downregulation of adrenergic, vasopressin (V1) and Angiotensin 1 (AT1) receptors.
  3. Increase iNOS activity leading to increase Nitrit Oxide level 1000 fold in sepsis.

Vasopressors are agents that induce vasoconstriction & increase in MAP.

Many vasopressors also increase contractility & have inotropic properties.

Cornerstone therapy in the management of shock syndromes
To date, no vasopressor has consistently been proven to be superior to the others in term of clinical outcomes

Cochrane Database Syst Rev. 2016;2
Norepinephrine is first choice vasopressor (Strong recommendation, MQE)
Vasopressin as second vasopressor to increase MAP or to reduce norepinephrine dose (weak recommendation, MQE)
Epinephrine as second vasopressor (weak recommendation, WQE)
Allow us to provide the best care to our patients at the bedside

Surviving Sepsis Campaign: Retract the SSC 2018 Guidelines

by: Emcri P
recipient: Clinicians Worldwide

5,642 SUPPORTERS 10,000 GOAL
• Norepinephrine is first-choice vasopressor with no recommendation for maximum dose and early administration is associated with improved survival

• Pharmacodynamically, catecholamines show a linear increase in effect with the logarithmic increase of the concentration

• Consequently, high doses of norepinephrine may be necessary to maintain mean arterial pressure (MAP) above 65 mmHg

Is epinephrine a bad vasopressor? (Cardiogenic Shock)

The authors concluded that use of epinephrine associated with a 3-fold increase in short term mortality.

- 16 trials included (12 observational studies, 4 RCTs)
- Only 1 trial compared epinephrine and norepinephrine on clinical outcome
Is epinephrine a bad vasopressor?

• Epinephrine or norepinephrine has been to be comparable in term of efficacy, dose and clinical outcomes.

• Myburg (2008) reported that both drugs were equipotent and produced same results:
  ✓ time taken to achieve target MAP
  ✓ vasopressor free days
  ✓ No difference in CVP, urine output and net fluid balance
  ✓ Epinephrine caused tachycardia & lactic acidosis but no difference in incidence of tachyarrhythmias

Epinephrine vs Norepinephrine

Dose of epinephrine & norepinephrine vs MAP

Serum lactate vs vasopressor

Single or multiple vasoactive drugs?

- CATS Study showed that in septic shock it’s quite safe to use epinephrine alone as compared to combination of norepinephrine and dobutamine.

- The results showed that:
  - early & late mortality were no different
  - No significant difference in rate of severe arrhythmias, myocardial events, length of stay and time to pressor withdrawal
  - Lactate significantly increased in epinephrine group at day 1 only (P=0.003); pH significantly lower in epinephrine group from day 1-4

Lancet 2007; 370: 676–84
How high you can go?

Many studies defined high dose norepinephrine is more than 1 mcg/kg/min with mortality approaching 80-100%.

Dilemma for clinician to further increase beyond 1 mcg/kg/min.

The ETHICUS study showed that the most common reason for withholding or withdrawing vasopressor therapy was lack of response to maximal therapy.

• 106 patients were subjected to high dose vasopressor in ICU (defined as 1 mcg/kg/min)
• The mortality rate was 60.4% at 28 days and 65.1% at 90 days
• High dose Norepinephrine stronger predictor of mortality than SOFA score alone.
• Combination of SOFA > 10 and norepinephrine > 0.75 µg/kg/min caused mortality 85.2%
Fig. 5 Correlation between WMD > 0.75 μg/kg/min, SOFA > 10 and mortality.
1. Metabolic effects
   • ↓ insulin release
   • Inhibition of lipolysis
   • ↑ hepatic glucose production & glycogen breakdown
   • ↑ Skeletal muscle glycogenolysis and lactate production

2. Endocrine effects
   • ↓ Serum concentrations of anterior pituitary hormones: prolactin, TRH, hGW, and LH (Dopamine)
   • ↓ TSH secretion (Dopamine)
   • Stabilization of the hypothalamic-pituitary axis (Vasopressin)
3. Immunological effects

- Transient T-cell hyperresponsiveness (Dopamine)
- ↓ Endotoxin mediated release of pro-inflammatory cytokines (Norepinephrine and Epinephrine)
- Upregulation of anti-inflammatory cytokines (Norepinephrine and Epinephrine)
- Potential stimulation of bacterial growth (Norepinephrine and Epinephrine)
- ↓ Levels of circulating proinflammatory cytokines (Levosimendan, Vasopressin)
- ↓ IL-6 levels and nitrite/nitrate levels (Selepressin)

Annane D. Intensive Care Med(2018);44;6:833-846
Duration on vasopressors is important too…
Any role of non-catecholamine vasopressors?
1. Vasopressin

- Equipoise results of vasopressin trials in term of mortality
- VANISH Trial compared early vasopressin vs norepinephrine on kidney failure in septic shock showed that:
  a. vasopressin has potential to be front line vasopressor as norepinephrine in septic shock
  b. those treated with vasopressin less likely to require dialysis (25.4 vs 35.3, p = 0.03)
  c. vasopressin treated group had lower creatinine level and higher urine output

Serum Creatinine Over the First 7 Days (vasopressin vs Norepinephrine)
Urine output Over the First 7 Days (vasopressin vs Norepinephrine)
• 5 RCT studies showed reasonably strong evidence vasopressin improves renal function

• Other advantage is catecholamine sparing effect (avoiding excessive β adrenergic stimulation)

• Prevention of AKI and renal replacement therapy in septic shock is important in term of mortality and cost.
<table>
<thead>
<tr>
<th>Vasopressin is preferred</th>
<th>Cathecholamine is preferred</th>
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<tbody>
<tr>
<td><strong>Hyperdynamic sepsis</strong></td>
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</tr>
<tr>
<td>• Hyperkinetic LV</td>
<td>• Normal/depressed LV</td>
</tr>
<tr>
<td>• Increased CO</td>
<td>• Normal/ depressed CO</td>
</tr>
<tr>
<td><strong>Marked tachycardia</strong></td>
<td></td>
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<tr>
<td></td>
<td>Normal heart rate/bradycardia</td>
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<tr>
<td><strong>Arrythmias</strong></td>
<td>Vasoconstriction</td>
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<tr>
<td>• Atrial fibrillation with fast ventricular rate</td>
<td>• Mesentric ischemia</td>
</tr>
<tr>
<td>• Ventricular arrythmias</td>
<td>• Raynaud’s disease</td>
</tr>
<tr>
<td><strong>Central access available</strong></td>
<td>Peripheral access only</td>
</tr>
<tr>
<td><strong>Threatened renal failure</strong></td>
<td>Good urine output/low risk of renal failure</td>
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<tr>
<td><strong>Pulmonary hypertension</strong></td>
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**Vasoconstriction**

- Mesentric ischemia
- Raynaud’s disease

**Inotropy**

- Epinephrine
- Norepinephrine
- Vasopressin
Ang II has emerged as promising therapy to raise BP in vasodilatory shock.

Use of Ang II has dated back 50 years ago & interest re-ignited after ATHOS -3 trial, confirming its effectiveness in raising BP.

2. Angiotensin II (Ang II)
Physiological effects of Ang II

• Action via AT-1 receptor
  ▪ Vasoconstriction
  ▪ Na+ reabsorption
  ▪ Release of aldosterone
  ▪ Constricts efferent > afferent arteriole, thus maintain GFR
  ▪ (+) release of vasopressin & ACTH
  ▪ (+) release of norepinephrine
  ▪ Pro-inflammatory
  ▪ Pro-oxidant
  ▪ Pro-coagulant

• Action via AT-2 receptor
  ▪ (+) natriuresis
  ▪ Anti-inflammatory
  ▪ Anti-oxidant
  ▪ Vasodilation
  ▪ Anti-proliferation
  ▪ Nitric oxide release

<table>
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<tr>
<th><strong>ATHOS-3 Trial</strong></th>
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<tr>
<td>344 patients with vasodilatory shock randomized to either Ang II or placebo</td>
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<tr>
<td>All patients received norepinephrine &gt; 0.2 µg/kg/min</td>
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<tr>
<td>Intervention group were commenced on 20ng/kg/min of Ang II</td>
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<tr>
<td>In both groups, catecholamines were not allowed to be increased</td>
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<tr>
<td>The maximum rate of drugs during the first 3 hours was equivalent to a dose of 200ng/kg/min</td>
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Results

**Primary outcome:**
- % of patients in Ang II achieved MAP 75 mmHg or 10 mmHg higher than baseline significantly higher
  - 69.9 vs 23.4 (P <0.001)
  - Mean doses of background Norepinephrine were significantly less in the Ang II group

**Secondary outcome**
- no change in SOFA score at 48 hours in both groups
- No difference in mortality at 7 and 28 days (tendency lower in Ang II)
- Adverse events were almost the same
Angiotensin II for the Treatment of Vasodilatory Shock

CONCLUSIONS

Angiotensin II effectively increased blood pressure in patients with vasodilatory shock that did not respond to high doses of conventional vasopressors. (Funded by La Jolla Pharmaceutical Company; ATHOS-3 ClinicalTrials.gov number, NCT02338843.)
A Game Changer?

• Probably will not change our practice at the moment
• Signals from ATHOS-3 trial:
  1. Primary outcome was not clinically meaningful
  2. Increased in MAP did not translate into improvement in SOFA score and organ function
  3. Patients with low cardiac output were not included hence safety of Ang II in distributive shock with low cardiac output is not tested
Safety issues with Ang II

• Physiological effects of Ang II may not be safe in septic shock patients
  ✓ pro inflammatory activity
  ✓ pro coagulant/thrombotic

• Pure vasopressor which is not suitable as stand alone drug in septic shock
3. Methylene blue (MB)

- In vasodilatory shock, there is marked upregulation of nitric oxide (NO) which causes vasodilation or vasoplegia.

- Inflammatory mediators e.g. TNF, IL-1, IL-6, augment iNOS enzyme causing 1000 folds increase in NO.

- NO mediated increase in cGMP is responsible for vasoplegia.

- Increase in cGMP also affects cardiac muscle causing reduced contractility.
Methylene Blue: Magic Bullet for Vasoplegia?

Leila Hosseinian, MD,* Menachem Weiner, MD,* Matthew A. Levin, MD,* and Gregory W. Fischer, MD*†

Anesth Analg 2016;122:194–201
Evidences of MB use in septic shock

• Most studies are small but demonstrated MB significantly increase MAP without effect on mortality.

• El Adawy (2018) randomized 40 patients into 2 groups;
  a) MB group received IV MB 1 mg/kg bolus followed 0.5 mg/kg/hr over 4 hours.
  b) Vasopressin group received vasopressin infusion 0.02 U/kg/hr over 6 hours.

  • MB significantly increased MAP at 6 and 24 hours (p < 0.05)
  • Dose of catecholamine significantly lower in MB group
• Though the study was small & with potential bias it gave signal the effectiveness of MB as non-adrenergic vasopressor

• MB also had bee used in vasoplegic syndrome post cardiac surgery and in liver transplantation.
• No vasopressor has been proven to be superior to others in term of clinical outcomes
• At the moment norepinephrine is the first choice vasopressors but epinephrine gives similar results.
• High dose catecholamines associated with mortality & should be weaned with reasonable target MAP
• Use of vasopressin associated with improve renal function
• Angiotensin II and methylene blue are additional armament in septic shock, awaiting larger trials.
Thank you