Use and Abuse of Inotropes and Vasopressors

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Vasopressors: Alpha

- Phenylephrine alone
- Norepinephrine
- NE vs Dop in sepsis
- NE plus or minus Vaso

Bolus vasopressors: Phenylephrine vs ephedrine

Phenylephrine
- Pure alpha
- HR decrease, SVR increase, CO DECREASE
- Venoconstrictor: Preload increase
- Direct only

Ephedrine
- Alpha and Beta
- HR increase, SVR increase, CO increase
- Venoconstrictor: Preload increase
- Direct and indirect, so diminished effect if catecholamine depleted (cocaine, MAOs, sustained shock)

In our OR, phenylephrine is the “alpha dog” for post-propofol hypotension

When is this approach potentially harmful?
- Patients with poor cardiac function
  - Pts are afterload-sensitive, so better to give them back what they lost (SVR and contractility)
  - Ephedrine makes more sense unless HR>80 bpm and/or something like very tenuous CAD or AS.
  - If there is a very low LVEF (say < 0.30) from post-ischemic cardiomyopathy and no active angina/ST changes/reversible WM abn: Pt may NEED a fast HR to compensate for limited increase SV with increased filling time. (we’re talking LVEF < 0.30)

Renal Failure Independent Predictors

Renal Failure Independent Predictors
Kheterpal S, Anesthesiology 2007;107:892-902

Observational Database study, first in noncard surgery, N>15,000

No disclosures

Strong assists from Drs. John Butterworth, Pierre Moine, David Abts, and Kevin Arnold
**Number of Risk Factors vs Risk**

*Kheterpal S, Anesthesiology 2007;107:892-902*

<table>
<thead>
<tr>
<th>Preoperative Risk Class</th>
<th>Acute Renal Failure, n (%)</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I (0 risk factors)</td>
<td>n = 5,778</td>
<td>16.0 (1.7-3.6)</td>
</tr>
<tr>
<td>Class II (1 risk factor)</td>
<td>n = 5,841</td>
<td>2.0 (1.1-3.6)</td>
</tr>
<tr>
<td>Class III (2 risk factors)</td>
<td>n = 2,625</td>
<td>4.7 (2.6-8.5)</td>
</tr>
<tr>
<td>Class IV (3+ risk factors)</td>
<td>n = 938</td>
<td>16.0 (8.9-29.6)</td>
</tr>
</tbody>
</table>

Seven independent preoperative predictors were identified (p < 0.05): age ≥69 yr, emergent surgery, liver disease, body mass index ≥30 kg/m², high-risk surgery, perioperative vasopressor use, and chronic obstructive pulmonary disease necessitating chronic bronchodilator therapy.

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**Recent Clinical Tug-of-War**

- Clear trend toward more conservative fluid administration intraoperatively
- Especially: Intra-abdominal, esophageal, intrathoracic
  - But also high risk procedures for ARF
- Bedside impression in supervising residents, CRNAs, AAs:
  - Increasing use of vasopressors (alpha mainly)
  - Often taken for granted as better than fluid administration. Masking hypovolemia/low CO?
- Set-up for ARF, especially if prolonged in high-risk Pt

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**More benefit ascribed to PA Cath, CI/DO₂, and supranormal targets**

*Hamilton MA Anesth Analg 2011;112:1392*

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of studies</th>
<th>No. of patients</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CI/DO₂</td>
<td>9</td>
<td>804</td>
<td>0.76 (0.41-1.37)</td>
</tr>
<tr>
<td>Other</td>
<td>15</td>
<td>3811</td>
<td>0.36 (0.19-0.65)</td>
</tr>
<tr>
<td>Therapy</td>
<td>5</td>
<td>400</td>
<td>0.61 (0.37-1.05)</td>
</tr>
<tr>
<td>Fluids</td>
<td>10</td>
<td>700</td>
<td>0.44 (0.19-1.06)</td>
</tr>
<tr>
<td>Vasopressors</td>
<td>19</td>
<td>4105</td>
<td>0.47 (0.29-0.76)*</td>
</tr>
<tr>
<td>Goals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CI/DO₂</td>
<td>17</td>
<td>3395</td>
<td>0.38 (0.21-0.69)*</td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td>894</td>
<td>0.75 (0.44-1.37)</td>
</tr>
<tr>
<td>Resuscitation</td>
<td>3</td>
<td>581</td>
<td>0.43 (0.15-1.19)</td>
</tr>
<tr>
<td>Target</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supranormal</td>
<td>8</td>
<td>0.29 (0.18-0.47)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>21</td>
<td>0.88 (0.66-1.13)</td>
<td></td>
</tr>
</tbody>
</table>

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**How does this relate to Vasopressors/Inotropes?**

- Kheterpal et al. also analyzed intra-operative factors
- In highest quartile of pre-op risk, vasopressor bolus frequency (5 vs 3 equipotent boluses) and vasopressor infusion use (18% vs 4%) were the strongest predictors
  - Included phenylephrine, ephedrine, and epi
  - SAP and MAP thresholds, furosemide/mannitol less consistent, U.O. NS

*Kheterpal S, Anesthesiology 2007;107:892-902*

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**A Systematic Review and Meta-Analysis on the Use of Preemptive Hemodynamic Intervention to Improve Postoperative Outcomes in Moderate and High-Risk Surgical Patients**

*Anesth Analg 2011;112:1392*

- 29 studies, 2,420 Pts, most interventions were fluids/inotropes (not pressors), goals were a mix dominated by CI and DO₂
- Types of surgery not given, no known trials in thoracotomy Pts (Abdominal>Total hip>>others)
- Mortality OR 0.48 (0.33-0.70) unless isolated to higher Jadad (quality) scores, then 0.62 (0.39-1.01=NS). But Cx reduced either way (OR 0.43-0.44, CI 0.28-0.59)

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**What will best help us balance fluids vs vasopressors?**

- I like (non-invasive) cardiac output
  - Gives you a sense of when a vasopressor is masking low CO
- (But lactate has good support in sepsis and CPB settings )
- Noninvasive Tissue O₂ shows promise in sepsis
Surviving Sepsis 2012

- Update of 2008 Guidelines
- Hemodynamic aspects, 1st 6 hrs:
  - MAP ≥65 mmHg
  - CVP 8-12 mmHg
  - UO ≥0.5 ml/kg/hr
  - Normalize lactate if ≥4 mmol/L
  - SvO2 > 70% (SVC) or >65% (PA)
- Use vasopressors if initial fluid resuscitation fails to achieve MAP ≥65 mmHg

Which vasopressor(s)?

Dellinger RP, Intens Care Med 2013;39:165

- 1st Line: Norepinephrine
  - Vasopressin 0.03 U/min (1.8 U/hr) added to NE to raise MAP or reduce NE
    - Not recommended as sole agent
    - Not recommended in dose > 0.04 U/min unless not responding to other agents
  - Epi either w/ or instead of NE if not responding to NE
  - NOT Dopamine unless bradycardic
  - NOT phenylephrine unless NE is causing arrhythmias or NE/vaso isn’t achieving MAP goal

Inotropes and sepsis

Dellinger RP, Intens Care Med 2013:39:165

- Use selectively when filling pressures high and CO low, or with signs of hypoperfusion despite adequate MAP and intravascular volume
- Recommend dobutamine up to 20 ug/kg/min
  - [Do they know about potential decrease in NE potency?]
- Avoid targeting predetermined supranormal CI
  - Use markers of perfusion adequacy (lactate, SvO2) to determine if supranormal CI is needed

Vasopressin in Septic Shock


- Reduces dose requirement for NE
- May decrease mortality in combination with NE (vs NE alone) in milder septic shock
- Low-dose Vaso with corticosteroids decreased mortality vs NE with corticosteroids (retrospective finding)
- Lower HR than with NE alone

VASST Trial

Dopamine versus norepinephrine in the treatment of septic shock: A meta-analysis

Dellinger RP, Intens Care Med 2013:39:165

- Observational trials (N=5: 1360 Pts): When trial with high heterogeneity excluded, dopamine increased RR of death (1.25, 1.05-1.43, P < 0.01)
- Randomized trials: No heterogeneity (N=6, 1408 Pts): Dopamine RR of death 1.12 (1.01-1.20, P=0.035)
- 2 trials reported arrhythmias: Dopamine RR 2.34 (1.46-3.77, P=0.001)
Adverse effects of Vasopressin (Sepsis)
Russell JA, Crit Care 2011:15:226

• Decrease in CO: Expected from any predominant vasoconstrictor
• Hyponatremia
• Thrombocytopenia
• Animal studies: Decreased myocardial contractility after ischemia/reperfusion
  – But probably less renal ischemia than alpha-agonists
  – Dose dependent: beware > 0.06 U/kg/hr
• Liver: Increased bilirubin/transaminases in some studies

Refining Vasopressin Use
Russell JA, Crit Care 2011:15:226

• If cardiac output is inadequate: add dobutamine or levosimendan
  – May also decrease Pulmonary vascular resistance
• Receptor selectivity: Blockade of V2 receptor (emphasizing V1a) improves tissue perfusion and LVSWI and decreased liver and renal dysfunction in sheep
• Genotype identified that is associated with increased vasopressin clearance and increased mortality in sepsis

A Double-Blind Randomized Trial: Prophylactic Vasopressin Reduces Hypotension After Cardiopulmonary Bypass
David L. S. Morales, MD, Mauricio J. Garrido, MD, John D. Madigan, RA, David N. Holman, MD, Joseph Fahey, RA, Matthew R. Williams, MD, Donald W. Landay, MD, FACS, and Mehmet C. Cit, MD
Departments of Surgery and Medicine, Columbia University College of Physicians and Surgeons, New York, New York

Background: Inhibition of angiotensin-converting enzyme (ACE) predisposes patients to cardiovascular complications after cardiopulmonary bypass (CPB). This complication has been correlated with increased vasopressin deficiency and can be corrected by its replacement. In patients receiving ACE inhibition, no investigational agent (inhibition of renin or angiotensin) would provide adequate compensation until the renin-angiotensin system is established.

Methods: Cardiac surgery patients on CPB and CPB were randomized to receive vasopressin (UFL Ultra) in a 5:1 ratio in an initial volume of normal saline to a MI starting 90 minutes before CPB.

Results: Vasopressin did not change pre-CBP mean arterial pressure or pulmonary artery pressure. After CPB, the vasopressin group had a lower peak mean arterial pressure than the placebo group. The difference was statistically significant. All study patients received a second dose of vasopressin at 30 minutes post-CPB. This dose also reduced systolic blood pressure by 6 mmHg without affecting heart rate, MAP, or CVP. Systemic arterial pressure decreased by 10% after CPB, but the vasopressin group remained hemodynamically stable.

Vasopressin effects

Renal:
• Decreased RBF, UO, Na excretion
• Increased RVR, O2 extraction, GFR, FF
• All support efferent arteriolar vasoconstriction
• Dose dependent, but suggests some “plateauing” between 2.4 and 4.8 U/hr
• Fully reversible

Vasopressin effects

Systemic
• Decreased CO (10%), PAP, PVR, HR
• Increased CVP, PAOP (slight – 1-1.5 mmHg)
• Unchanged Stroke volume, MAP
• Little or no dose dependency
• Fully reversible
In patients who start with normal hemodynamics

- Possibly harmful renal effects if sustained
- Compromised CO (afterload) without any increase in MAP: CO decrease matched by SVR increase
  - With phenylephrine, would get increased SVR "overmatching" decreased CO with net increase in MAP
  - Also with phenylephrine, would get dose-dependent MAP increase

Methylene Blue in Cardiac Surgery

- Excellent Pro/Con in JTCA August 2011 by Riha/Augustides and Andritsos
- Vasoplegia Syndrome is a bad thing and has certain risk factors
  - VADs are highest risk group (30-40%)
  - Other factors: ACE/ARB, B-blockers (!), long CPB times
  - Mortality as high as 50%
- 3 prospective studies assessed prophylactic use in CPB Pts with favorable outcomes: ICU stays, vasoplegia, higher SVRs, even mortality (1 study)

When would we want to increase preload more than afterload?

- Anesthetic technique reduces preload as much or more than afterload: spinal/epidural, possibly propofol-based TIVA
- You want to avoid liberal fluid administration: Gut anastomoses, pneumonectomy
  - And you’re pretty sure you’ve given sufficient volume

Alpha vs Beta Agonist vs Mixed: Venous return

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total change to a volume of 100 ml (L)</th>
<th>Change in MAP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylephrine (µg)</td>
<td>1000</td>
<td>2.0 ± 1.9</td>
</tr>
<tr>
<td>Phenylephrine (µg)</td>
<td>1500</td>
<td>1.5 ± 2.3</td>
</tr>
<tr>
<td>Phenylephrine (µg)</td>
<td>2000</td>
<td>1.0 ± 2.4</td>
</tr>
<tr>
<td>Dobutamine (µg)</td>
<td>1000</td>
<td>1.5 ± 2.7</td>
</tr>
<tr>
<td>Dobutamine (µg)</td>
<td>1500</td>
<td>1.0 ± 2.3</td>
</tr>
<tr>
<td>Dobutamine (µg)</td>
<td>2000</td>
<td>0.5 ± 2.1</td>
</tr>
</tbody>
</table>

Dopamine vs Dobutamine: SVR and venous return
So if you want to *venoconstrict*

- *Beta is better than alpha!*
- Mixed alpha-beta is better than alpha
- Dopaminergic agonists further augment
- Dopamine might be 1st choice
  - Try 3-5 ug/kg/min
  - (Hopefully minimal HR increase)

Factors associated with inotropic drug support in elective coronary surgery

- Older age
- Female sex
- Cardiac enlargement on chest radiograph
- Reduced Left ventricular ejection fraction
- Greater LV end-diastolic pressure
- Prolonged duration of cardiopulmonary bypass and aortic clamp times


Where you have your elective CABG determines whether you will likely receive a positive inotrope!

- **Overall N=1217**

Post-CPB Vasoactive Drug Selection

High-risk CABG, 50 high-volume centers

- Greater MR (but 7.8 vs 6.5/6.4%)
- More previous CV interventions (33 vs 26/30%)
- Longer CPB time (130 vs 122/108)
- Longer X-clamp time (92 vs 86/78)
- Higher % post-op transfusion (57 vs 51/47)
- **NOT ENOUGH TO EXPLAIN THE DIFFERENT FREQUENCY OF USE PATTERNS**

Williams JD, J Card Surg 2011;26:572

University HealthSystem Consortium 2000 CABG Database

Williams JD, J Card Surg 2011;26:572
Did Inotrope/Vasopressor Use Influence Outcomes?

**NOPE**

- ND among high/med/low use centers in
  - Operative or 30-day mortality
  - Post-op renal failure
  - Atrial fibrillation
  - Acute limb ischemia
- Retrospective design precludes conclusions about relative safety of high/med/low or of individual drugs chosen

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Routine myocardial dysfunction and recovery after CABG


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Myths about β-AR agonists

- “Epinephrine causes more tachycardia than dobutamine”
- “Norepinephrine lacks β₂-AR activity”
- There is such a thing as “renal dose” dopamine

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Dobutamine increases HR more than epinephrine after CABG

- 52 patients recovering from CABG in the ICU
- Dob 2.5 & 5 μg/kg/min; Epi 10 & 30 ng/kg/min
- After high dose, stroke volume index similar; Dob ↑HR more than Epi

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Drug Interactions

- Drugs can interact additively, synergistically, or antagonistically
- Interaction between β-AR agonists and PDE inhibitors is at least additive, possibly synergistic
- Interaction between Ca salts and β-AR agonists is antagonistic
- Interaction between dobutamine (partial agonist) and epinephrine (full agonist) can be antagonistic