Use and Abuse of Inotropes and Vasopressors

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No disclosures

Strong assists from Drs. John Butterworth, Pierre Moine, David Abts, and Kevin Arnold

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)

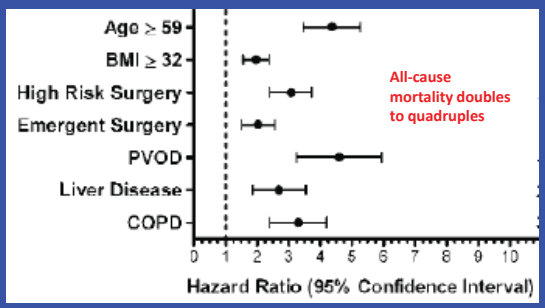
In our OR, phenylephrine is the "alpha dog" for post-propofol hypotension

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

Kheterpal S, Anesthesiology 2007;107:892-902



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

Number of Risk Factors vs Risk

Kheterpal S, Anesthesiology 2007;107:892-902

Table 4. Frequency and Hazard Ratio of Acute Renal Failure Based on Number of Preoperative Risk Factors

Preoperative Risk Class	Acute Renal Failure, n (%)	Hazard Ratio (95% Confidence Interval)
Class I (0 risk factors), n = 5,728	16 (0.3)	
Class II (1 risk factor), n = 5,841	32 (0.5)	2.0 (1.1–3.6)
Class III (2 risk factors), n = 2,625	34 (1.3)	4.7 (2.6–8.5)
Class IV (3+ risk factors), n = 908	39 (4.3)	16.0 (8.9–28.8)

Seven independent preoperative predictors were identified ($P < 0.05$): age ≥59 yr, emergent surgery, liver disease, body mass index ≥32 kg/m^2, high-risk surgery, peripheral vascular occlusive disease, and chronic obstructive pulmonary disease necessitating chronic bronchodilator therapy.

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

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*

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

Mark A. Hamilton, MRCP, FRCA, Maurizio Cecconi, MD, and Andrew Rhodes, FRCP, FRCA

- 29 studies, 2420 Pts, most interventions were fluids/inotropes (not pressors), goals were a mix dominated by CI and DO_2
- 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)

More benefit ascribed to PA Cath, CI/DO_2, and supranormal targets

Hamilton MA Anesth Analg 2011;112:1392

Table 2. Subgroup Analysis for Mortality

Subgroup	No. of studies	No. of patients	Odds ratio (95% CI)
Monitor			
ODM	9	894	0.75 (0.41–1.37)
PAFC	15	3511	0.35 (0.19–0.65)*
Other[a]	5	400	0.61 (0.27–1.35)
Therapy			
Fluids	10	700	0.44 (0.19–1.06)
Fluids and inotropes	19	4105	0.47 (0.29–0.76)*
Goals			
CI/Do_2	17	3350	0.38 (0.21–0.68)*
FTc/SV	9	894	0.75 (0.41–1.37)
Other[b]	3	561	0.43 (0.15–1.19)
Resuscitation target			
Supranormal	8	0.29 (0.18–0.47)	0.29 (0.18–0.47)*
Normal	21	0.86 (0.66–1.13)	0.86 (0.66–1.13)

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 O_2 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, SvO_2) to determine if supranormal CI is needed

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

(Crit Care Med 2012; 40:725–730)

Daniel De Backer, MD, PhD; Cesar Aldecoa, MD; Hassane Njimi, MSc, PhD; Jean-Louis Vincent, MD, PhD, FCCM

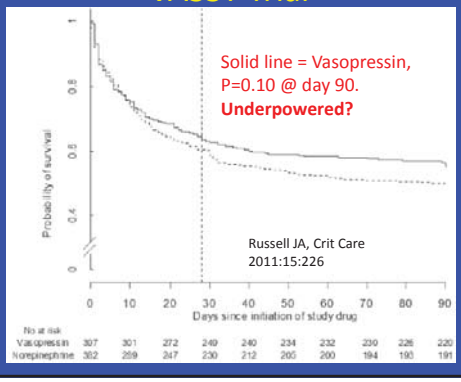
- Observational trials (N=5: 1360 Pts) : When trial with high heterogeneity excluded, dopamine increased RR of death (1.25, 1.05-1.43, P < 0.01)
- Randomized trials: No heterogeneity (N=6, 1408 Pts): Dopamine RR of death 1.12 (1.01-1.20, P=0.035)
- 2 trials reported arrhythmias: Dopamine RR 2.34 (1.46-3.77,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

Vasopressin in Septic Shock

Vasopressin and Septic Shock Trial, Russell JA, Crit Care 2011:15:226

- 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



Adverse effects of Vasopressin (Sepsis)

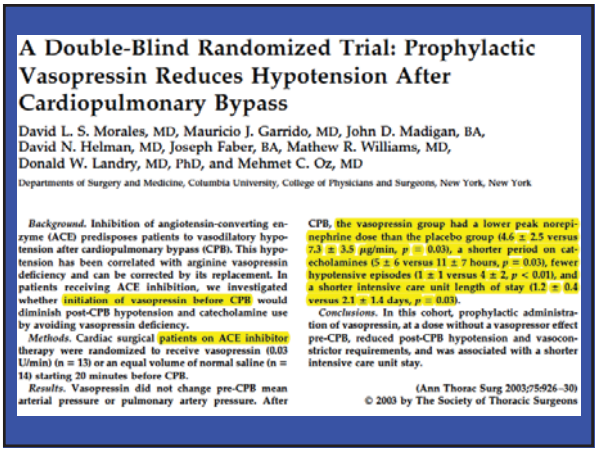
Russell JA, Crit Care 2011:15:226

- Decrease in CO: Expected from any predominant vasoconstrictor
- Hyponatremia
- Thrombocytopenia
- Animal studies: Decreased myocardial contractility after ischemia/reperfusion
- Focal ischemia: Mesentery/gut, skin/digits, sometimes myocardial
  - 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, BA, David N. Helman, MD, Joseph Faber, BA, Mathew R. Williams, MD, Donald W. Landry, MD, PhD, and Mehmet C. Oz, 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 vasodilatory hypotension after cardiopulmonary bypass (CPB). This hypotension has been correlated with arginine vasopressin deficiency and can be corrected by its replacement. In patients receiving ACE inhibition, we investigated whether initiation of vasopressin before CPB would diminish post-CPB hypotension and catecholamine use by avoiding vasopressin deficiency.

Methods. Cardiac surgical patients on ACE inhibitor therapy were randomized to receive vasopressin (0.03 U/min) (n = 13) or an equal volume of normal saline (n = 14) starting 20 minutes before CPB.

Results. Vasopressin did not change pre-CPB mean arterial pressure or pulmonary artery pressure. After CPB, the vasopressin group had a lower peak norepinephrine dose than the placebo group (4.6 ± 2.5 versus 7.3 ± 3.5 μg/min, $p = 0.03$), a shorter period on catecholamines (5 ± 6 versus 11 ± 7 hours, $p = 0.03$), fewer hypotensive episodes (1 ± 1 versus 4 ± 2, $p < 0.01$), and a shorter intensive care unit length of stay (1.2 ± 0.4 versus 2.1 ± 1.4 days, $p = 0.03$).

Conclusions. In this cohort, prophylactic administration of vasopressin, at a dose without a vasopressor effect pre-CPB, reduced post-CPB hypotension and vasoconstrictor requirements, and was associated with a shorter intensive care unit stay.

(Ann Thorac Surg 2003;75:926–30)

ACTA ANAESTHESIOLOGICA SCANDINAVICA
doi: 10.1111/j.1399-6576.2009.02037.x

Low-dose vasopressin increases glomerular filtration rate, but impairs renal oxygenation in post-cardiac surgery patients

G. Bragadottir, B. Redfors, A. Nygren, J. Sellgren and S.-E. Ricksten
Department of Cardiothoracic Anesthesia and Intensive Care, Sahlgrens University Hospital, Göteborg, Sweden

- 12 post-op cardiac surgery Pts on prop/MS infusions, hemodynamically stable, no inotropes/pressors: 10 CABG/2 valve
- Vasopressin 1.2, 2.4, and 4.8 U/hr given
- Hemodynamics: Systemic (PAC) and Renal (renal vein retrograde thermodilution)

Vasopressin effects

Bragadottir G, Acta Anaesth Scand 2009;53:1052

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

Bragadottir G, Acta Anaesth Scand 2009;53:1052

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

Perspective on Bragadottir study

Acta Anaesth Scand 2009;53:1052

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 JTCVA 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)

MB and Sepsis

- All studies performed have demonstrated that MB administration results in an increase in SVR, reflected by an increase in MAP and/or a decrease in vasopressor requirements.
- Adverse pulmonary effects noted in two of the prospective observational studies.
- Pulmonary vasoconstriction and reduced oxygenation coincided with higher MB dosing 3-4 mg/kg.

Paciullo, C.A., McMahon Horner, D., Hatton, K.W., Flynn, J.D. (2010). Methylene blue for the treatment of septic shock. *Pharmacotherapy, 30*(7), 702-715.

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

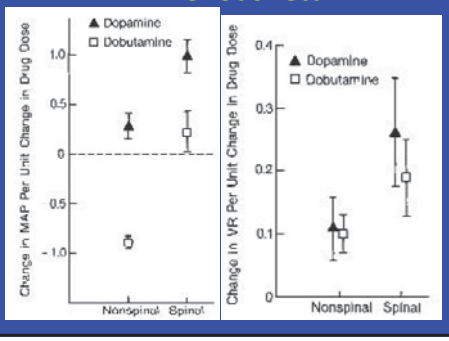
Alpha vs Beta Agonist vs Mixed: Venous return

Butterworth JF, Anesth Analg 1986;65:612

Table 1. Circulatory Response to Adrenergic Agonists during Total Spinal Anesthesia in Seven Dogs

Drug dosage	Total cumulative dose by end of measurement (μg/kg)	Change in MAP (%)	Change in P_{rs} (ml/kg)
Phenylephrine* (μg·kg⁻¹·min⁻¹)		(Baseline MAP = 46 ± 8 mm Hg)	
0.05	0.15 ± 0	2.0 ± 9.8	[illegible]
0.50	1.60 ± .07	1.8 ± 8.5	[illegible]
5.00	16.60 ± .07	24.4 ± 21.9	[illegible]
10.00	46.62 ± .07	74.4 ± 37.2*	[illegible]
20.00	106.61 ± .06	160.0 ± 31.8*	[illegible]
Isoproterenol* (μg·kg⁻¹·min⁻¹)		(Baseline MAP = 50 ± 7 mm Hg)	
0.005	0.015 ± 0	−2.7 ± 4.6	[illegible]
0.050	0.161 ± .006	−23.4 ± 19.3	[illegible]
0.500	1.661 ± .006	−37.7 ± 18.6	[illegible]
1.000	4.665 ± 0	−38.7 ± 14.7*	[illegible]
Ephedrine (μg/kg)		(Baseline MAP = 35 ± 4 mm Hg)	
200	200 ± 0	33.0 ± 16.9*	[illegible]
1000	1200 ± 0	91.0 ± 28.0*	[illegible]

Dopamine vs Dobutamine: SVR and venous return



Butterworth JF, Anesth Analg 1987; 66:209

So if you want to *veno*constrict

- ***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)

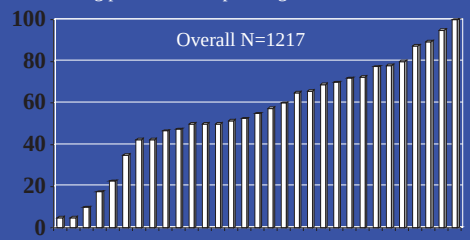
Factors associated with inotropic drug support in elective coronary surgery

- 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

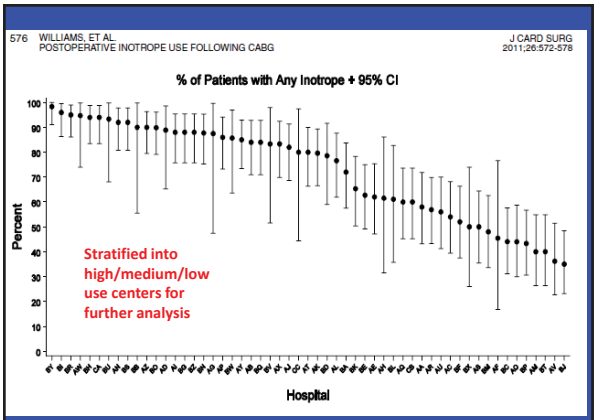
Royster. Anesth Analg 1991; 72:729-36

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

% receiving positive inotropic drugs at each of 31 sites

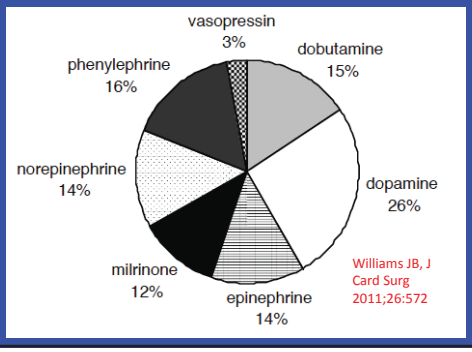


University HealthSystem Consortium 2000 CABG Database



Post-CPB Vasoactive Drug Selection

High-risk CABG, 50 high-volume centers



Highest tercile of Inotrope Use

Williams JD, J Card Surg 2011;26:572

- Greater MR (but 7.8 vs 6.5/6.4%)
- More previous CV interventions (33 vs26/30%)
- 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

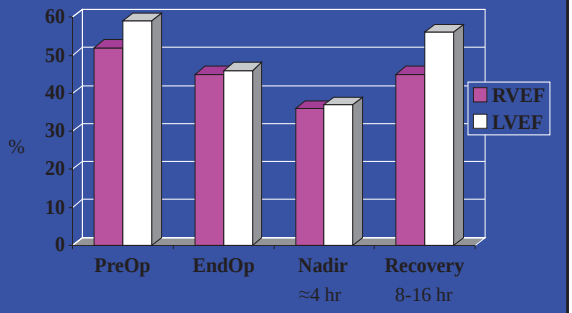
Did Inotrope/Vasopressor Use Influence Outcomes?

Williams JD, J Card Surg 2011;26:572

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

Routine myocardial dysfunction and recovery after CABG



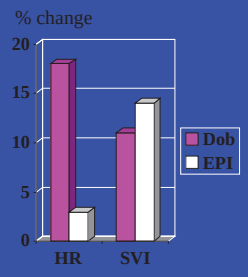
Breisblatt. J Am Coll Cardiol 1990;15:1261-9

Myths about β-AR agonists

- "Epinephrine causes more tachycardia than dobutamine"
- "Norepinephrine lacks β_2-AR activity"
- There is such a thing as "renal dose" dopamine

Dobutamine increases HR more than epinephrine after CABG

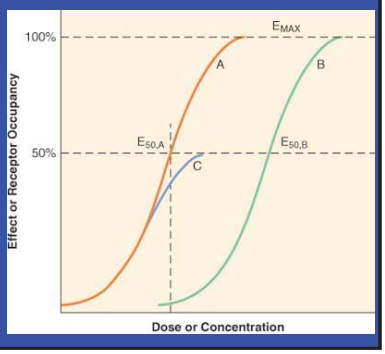
- 52 patients recovering from CABG in the ICU
- Dob 2.5 & 5 μg/kg/min; Epi 10 & 30 ng/kg/min
- After high dose, stroke volume index similar; Dob ↑HR more than Epi



Butterworth. J Cardiothorac Vasc Anes 1992;6:535-41

Strong vs Weak Agonist

Gupta DK, Henthorn TK Chapter 7 in Clinical Anesthesia, Barash et al. Editors, Philadelphia, Wolters Kluwer,, 2013,



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