Vasoactive Drugs
Do I have to choose?

Dr. Vandewiele Bert
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What is what?

• **Inotrope**
  – A substance that alters the force of muscular contraction (positive/negative)

• **Vasopressor**
  – An agent producing vasoconstriction and a rise in blood pressure, usually understood to be systemic arterial pressure unless otherwise specified.

• **Vasodilator**
  – An agent that causes dilation of the blood vessels

• **Chronotrope**
  – A substance that alters the rate of a regularly recurring phenomenon such as the heartbeat (positive/negative)

• **Inodilator**
  – An agent with both positive inotropic and vasodilator effects

• **Lusitrope**
  – Relaxation functions of cardiac muscle and chambers

• **Dromotrope**
  – Alteration in impulse conduction (positive/negative)
Shock

- Shock is a clinical state which occurs when an imbalance between oxygen supply and demand results in the development of tissue hypoxemia

  - NOT always hypotension
  - NOT always reduced oxygen delivery
Shock

Physiologically

• Hypoxic
  – Low PaO2

• Anaemic
  – Low haemoglobin level

• Stagnant
  – Low Cardiac output
  – Maldistribution

• Histotoxic
  – Eg Cyanide poisoning

Clinically

• Cardiogenic
  – Myocardial disease

• Extracardiac Obstructive
  – Pulmonary embolus / tamponade

• Hypovolemic
  – Uncontrolled haemorrhage
  – Excessive fluid loss

• Distributive
  – Sepsis
Initial priority

• Maintain reasonable hemodynamics
  – Fluid resuscitation (*How Much?*)
    • Fluid responsiveness
      – Vasopressor therapy
      – Inotropic therapy

...
Vasoactive Agents

- **Vasopressors**
  - Raise **Blood Pressure**

- **Inotropes**
  - Raise **Cardiac Output**

- Most vasoactive agents have mixed effects

- **Blood pressure ≠ blood flow ≠ perfusion**

- **Which cardiac output is adequate in shock (which shock) and how to measure it?**
Vasoactive agents

• Individual effects
• Mixed effects
• Overlapping effects
• Dose dependent effects

• Receptor specific
  – α1-receptor
  – β1-receptor
  – β2-receptor
  – Dopaminerg-receptor
α1-receptor

- Vasoconstriction of arteries (inclusive coronary arteries)
- Vasoconstriction of veins
- Other areas of smooth muscle contraction are:
  - Ureter, vas deferens, hair (arrector pili muscles), uterus (when pregnant), urethral sphincter, bronchioles, gastrointestinal tract
- Glycogenolysis and gluconeogenesis from adipose tissue and liver
- Secretion from sweat glands
- Na+ reabsorption from kidney.
β1-receptor

• **Increase cardiac output, by**
  – **positive chronotropic effect**
  – **positive dromotropic effect**
  – **positive inotropic effect**
    ➔ increasing the volume expelled with each beat (increased ejection fraction).

• **Increase renin secretion from juxtaglomerular cell of kidney**
\[ \beta_2 \text{-receptor} \]

- **Dilate arteries to skeletal muscle**
- Glycogenolysis and gluconeogenesis
- Smooth muscle relaxation, e.g. in bronchi, GI tract (decreased motility).
Dopamine-Receptor

• **Dose dependent**

• < 5 µg/kg/min: Dopamine receptors
  – Vasodilation in renal bed
  – Vasodilation in mesenteric bed

• 5 – 10 µg/kg/min: β1-adrenergic effects
  – Inotropic effects

• > 10 µg/kg/min: α1-adrenergic effects
  – Vasopressor effects
Dopamine-Receptor

**Activation of DA1 Receptors in Kidney - Induces Diuresis**

**Activation of Beta1 Receptors in the Heart** produces an increase in contractile force.

**Increase in peripheral resistance via alpha-receptors will increase the work of the heart. Increases in heart rate could induce arrhythmias.**

Effect

**Window of selectivity for therapeutic effect**

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Vasopressors

• The principles
• The choices
  – Norepinephrine
  – Dopamine
  – Epinephrine
  – Phenylephrine
  – Vasopressin
• The Complications
Vasopressors

• Endpoint = Arterial Pressure
• Minimal BP for autoregulation → Below this pressure flow is directly dependent on pressure
  – Animal studies: MAP < 60 mmHg compromises
    • Coronary / Renal / Central nervous system vascular bed
  – Guidelines in Sepsis recommend MAP > 60 / 65 mmHg
  – Dependent on baseline bloodpressure

Vasopressors

• Principal use:
  – Vasodilatory shock: Sepsis

• Other use
  – Cardiogenic shock
    • Coronary perfusion
  – Obstructive shock
    • Temporize
    • Treat Life threatening hypotension
  – Hypovolemic shock
    • Temporize
    • Treat Life threatening hypotension
Noradrenaline = Norepinephrine
Noradrenaline = Norepinephrine

- Potent α-adrenergic agonist with limited β-adrenergic agonist effects
  - Increase of MAP by vasoconstriction
  - Small increase in SV and CO
  - Filling pressures unchanged to modestly increased (1-3 mmHg)
- Dose: 0.01 – 3.3 µg/kg/min (Due to downregulation of α-receptors)
Noradrenaline: The downside

• Potential to decrease bloodflow when insufficiently fluid-resuscitated
  – Renal
  – Splanchnic
  – Peripheral
Dopamine
Dopamine

• Natural precursor of Noradrenaline and Adrenaline

• Dose dependent effects with overlap
  • < 5 µg/kg/min: Dopamine receptors
    – Vasodilation in renal bed
    – Vasodilation in mesenteric bed
  • 5 – 10 µg/kg/min: β1-adrenergic effects
    – Inotropic effects
  • > 10 µg/kg/min: α1-adrenergic effects
    – Vasopressor effects

• Increase in MAP and CO due to an increase in SV and a lesser extent HR

• Renal dose of dopamine? (2 µg/kg/min)
Dopamine: The downside

- Lymphocyte apoptosis
  \[\Rightarrow\] immunosuppression
- More arrhythmic events in patients with cardiogenic shock
- Decreased Prolactin release

Use of dopamine in acute renal failure: A meta-analysis

John A. Kellum, MD; Janine M. Decker, RN

Conclusions: The use of low-dose dopamine for the treatment or prevention of acute renal failure cannot be justified on the basis of available evidence and should be eliminated from routine clinical use. (Crit Care Med 2001; 29:1526–1531)

Data Extraction: Data were abstracted regarding design characteristics, population, intervention, and outcomes. Results of individual randomized clinical trials were pooled using a fixed effects model and a Mantel-Haenszel weighted chi-square analysis.

Data Synthesis: We identified a total of 58 studies (n = 2149). Of these, outcome data were reported in 24 studies (n = 1019)

Conclusions: The use of low-dose dopamine for the treatment or prevention of acute renal failure cannot be justified on the basis of available evidence and should be eliminated from routine clinical use. (Crit Care Med 2001; 29:1526–1531)

Key Words: dopamine; acute renal failure; kidney; randomized clinical trials; meta-analysis; acute tubular necrosis; radiocontrast media; sepsis; oliguria; diuretics
Comparison of Dopamine and Norepinephrine in the Treatment of Shock

Daniel De Backer, M.D., Ph.D., Patrick Biston, M.D., Jacques Devriendt, M.D., Christian Madl, M.D., Didier Chochoz, M.D., Cesar Aldecoa, M.D., Alexandre Brasseur, M.D., Pierre Defrance, M.D., Philippe Gottignies, M.D., and Jean-Louis Vincent, M.D., Ph.D., for the SOAP II Investigators*
RESULTS
The trial included 1679 patients, of whom 858 were assigned to dopamine and 821 to norepinephrine. The baseline characteristics of the groups were similar. There was no significant between-group difference in the rate of death at 28 days (52.5% in the dopamine group and 48.5% in the norepinephrine group; odds ratio with dopamine, 1.17; 95% confidence interval, 0.97 to 1.42; $P=0.10$). However, there were more arrhythmic events among the patients treated with dopamine than among those treated with norepinephrine (207 events [24.1%] vs. 102 events [12.4%], $P<0.001$). A subgroup analysis showed that dopamine, as compared with norepinephrine, was associated with an increased rate of death at 28 days among the 280 patients with cardiogenic shock but not among the 1044 patients with septic shock or the 263 with hypovolemic shock ($P=0.03$ for cardiogenic shock, $P=0.19$ for septic shock, and $P=0.84$ for hypovolemic shock, in Kaplan–Meier analyses).

CONCLUSIONS
Although there was no significant difference in the rate of death between patients with shock who were treated with dopamine as the first-line vasopressor agent and those who were treated with norepinephrine, the use of dopamine was associated with a greater number of adverse events. (ClinicalTrials.gov number, NCT00314704.)
Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008

F. Vasopressors

1. We recommend mean arterial pressure (MAP) be maintained $\geq 65$ mm Hg (Grade 1C).

2. We recommend either norepinephrine or dopamine as the first choice vasopressor agent to correct hypotension in septic shock (administered through a central catheter as soon as one is available) (Grade 1C).

3a. We suggest that epinephrine, phenylephrine, or vasopressin should not be administered as the initial vasopressor in septic shock (Grade 2C). Vasopressin .03 units/min may be subsequently added to norepinephrine with anticipation of an effect equivalent to norepinephrine alone.

3b. We suggest that epinephrine be the first chosen alternative agent in septic shock that is poorly responsive to norepinephrine or dopamine (Grade 2B).
Adrenaline

- Potent α- and β-adrenergic agonist effects
- Increase MAP
  - Increase in CO
  - Increase in peripheral vascular tone
- Increase in Oxygen delivery
AND CONSUMPTION
Adrenaline:
The downside

• Decrease of regional bloodflow
  – Splanchnic
  – Gastric
  – Peripheral (Ischaemia extremities)

• Increase in heart rate (HR) + potential to induce tachyarrhythmias

• Induces Hypoglycemia

• Increase Lactate concentration
Adrenaline vs Noradrenaline

• 2 Studies
• NO DIFFERENCE IN
  – Time to hemodynamic success
  – Vasopressor withdrawal
  – 28-day mortality
  – ICU mortality
  – Hospital mortality

Phenylephrine
Phenylephrine

• Selective $\alpha_1$-adrenergic agonist
  – Rapid onset
  – Short duration
  – Primary vascular effects
• Second line in septic shock
• Indicated in
  – Spinal shock
  – Vasoplegia after cardiac bypass
  – Medication induced hypotension
Vasopressine
Vasopressine

• Synthesized in the hypothalamus and stored in the pituitary gland
• Released in response to
  – Decreased blood volume
  – Decreased intravascular volume
  – Increased plasma osmolality
• Effects
  – Constricts vascular smooth muscle via V1 receptor
  – Increase responsiveness to catecholamines
  – Inhibition of vascular smooth muscle NO production
  – K+ - ATP channels
Vasopressine: How to use?

• Vasopressin (0.03 U/min) added to norepinephrine appears to be as safe and effective as norepinephrine in fluid-resuscitated patients with septic shock, and may be more effective in patients on lower doses of norepinephrine than when started as rescue therapy.

• Vasopressin should be thought of as replacement therapy for relative deficiency rather than as a vasopressor agent to be titrated to effect, and should be used only at low doses.

• What to do in patients with high vasopressor requirements despite vasopressin infusion remains uncertain.

Complications of vasopressors

- Tachycardia and tachyarrhythmias
- Myocardial ischemia and infarction
  - Coronary artery constriction
- Decreased stroke volume in the presence of myocardial dysfunction
  - Decreased DO2
- Limb ischemia and necrosis
- Impaired bloodflow to the splanchnic bed
  - Stress ulceration
  - Ileus
  - Malabsorption
  - Bowel infarction
WE NOW PAUSE FOR TECHNICAL DIFFICULTIES....
Inotropes

• The principles
• The choices
  – Dobutamine
  – Phosphodiesterase inhibitors
  – Levosimendan
Inotropes: the principles

• Improving myocardial contractility
• Monitor cardiac output as a substitute for contractility (easier and more relevant)
  – Swan Ganz
  – Vigileo
  – Picco
  – Nico
  – Lidco
  – TEE / TTE
• Indicated in cardiogenic shock (other shocks less clear cut)
• increasing cardiac output to predetermined “supranormal” levels in all patients does not improve outcomes

The principles
Dobutamine

• Predominant β1 adrenergic effects
  – Positive Inotropic
  – Positive chronotrophic
• Initial agent of choice in cardiogenic shock
  – Cave increased myocardial oxygen consumption
• Initial agent of choice in septic shock with low CO and adequate filling pressure (small group)
Phosphodiesterase inhibitors

• Increase intracellular cAMP independent of the β-receptor ➔ Inotropic effect
• Fewer chronotropic and arrhythmogenic effects
• One important note is the differential effects of increased cAMP in smooth muscle compared to cardiac muscle. Increased cAMP will promote relaxation in smooth muscle and hypotension
• Milrinone is a more potent pulmonary vasodilator than dobutamine, and so is often preferred in cases of predominant right heart failure
Calcium sensitizers: Levosimendan

- Increases cardiac myocyte calcium responsiveness
- Opens ATP dependent potassium channels
  - Inotropic effects
  - Vasodilatory properties
- No increase in myocardial oxygen consumption
- Cardiogenic and septic shock
"That’s the skip-forward button. Great for jumping to conclusions."
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Vasoactive Agents

- **Vasopressors**
  - Raise Blood Pressure
- **Inotropes**
  - Raise Cardiac Output

- Most vasoactive agents have mixed effects

- Perfusion adequacy is important!!!
  - Restore effective tissue perfusion (In all organs) and normalize cellular metabolism
The key to succes
The key to succes

• Identify etiology and pathogenesis of shock
  ➔ ADAPT AND TREAT

• Choose a vasoactive agent in the context of the goals of therapy
  – Increase cardiac output
  – Increase SVR
  – Decrease SVR
  – Decrease PVR

SV X HR
  • Preload
  • Afterload
  • Contractility
Set ultimate goals of therapy

- Restore effective tissue perfusion for all tissues
- Normalize cellular metabolism for all cells
- Monitor parameters of tissue perfusion and cellular metabolism
parameters of tissue perfusion and cellular metabolism

**Clinically**
- Oliguria
- Clouded sensorium
- Delayed capillary refill
- Cool skin
- Mixed venous oxygen saturation
  - $\text{ScvO2} = \text{ScO2} \, ?$
- Lactate
  - Hypoperfusion or cellular metabolism

**Directly**
- Splanchnic Circulation
  - Hepatic vein oxygen saturation
  - Gastric mucosal pH
  - Gastric mucosal PCO2
- Sublingual circulation
  - Near infrared spectroscopy
- Sublingual capnometry
Figure 2. Protocol for Early Goal-Directed Therapy.
CVP denotes central venous pressure, MAP mean arterial pressure, and ScvO₂ central venous oxygen saturation.
References

References