Project: Ghana Emergency Medicine Collaborative

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Inotropes and Vasoactives

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Objectives

- Review factors central to cardiac output
- Review physiology and receptors used by inotropic and vasoactive drugs
- Review different types of inotropic and vasoactive drugs

Physiology

- Vasopressor = Vasoconstriction
- Goal: Re-establish blood flow to organs
- Vasopressors are NOT a volume substitute

Physiology

- Sometimes, you need a drug that increases cardiac output without necessarily increasing blood pressure
  - Inotropic agents
  - Vasoconstrictors
  - Both

Cardiac Output

- Cardiac Output (Q) = HR x SV
- Heart rate
  - Chronotropism: increase in HR decreases filling time, increases O_2 consumption
  - Nature of HR important
- Stroke volume
  - Contractility (inotropic state of the myocardium)
  - preload and afterload dependent

Cardiac Output

- Preload
  - Volume of venous return that dictates cardiac output via the Frank-Starling Curve
  - How to increase?
    - Fluid boluses
    - increasing venous tone

Cardiac Output

- Afterload
  - The impedance to ventricular ejection
  - The factor in the equation that, when reduced, will increase the cardiac output
    - Measured (MAP) or calculated (SVR)
  - Becomes the dominant factor in determining cardiac output when contractility of the heart is impaired*

Cardiac Output

Inotropism

Increase in force and velocity of contraction

Lusitropism

Promoting diastolic relaxation to improve filling and coronary perfusion

Cardiac Output

Inotropism

Increase in force and velocity of contraction

Lusitropism

Promoting diastolic relaxation to improve filling and coronary perfusion

GOAL: IMPROVE CARDIAC FUNCTION

Understanding Receptors

- α-adrenergic receptors
- β-adrenergic receptors
- Dopaminergic receptors
- Vasopressin receptors

Understanding Receptors

Agent (typical dosages)	β-1	β-2	α-1
Isoproterenol (0.01–0.1 μg/kg/min)	+++	+++	O
Norepinephrine (0.05–1 μg/kg/min)	++	O	+++
Epinephrine (0.05–2 μg/kg/min)	+++	++	+++
Phenylephrine (0.5–5 μg/kg/min)	O	O	+++
Dopamine* (1–20 μg/kg/min)	+(++)	+	+(++)
Dobutamine (2.5–20 μg/kg/min)	+++	+	+

*Dopamine effects at "high-dose," which are typically greater than 3 to 5 μg/kg/min, are shown in parentheses. O, no effect; +, minimal effect; ++, moderate effect; +++, substantial effect.

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Understanding Receptors

- α_1-adrenergic receptors
  - Post-synaptic – constricts VSM

- Debates:
  - Existence of both α_{1a} and α_{1v}?
  - α_1 receptors located in the heart?

Understanding Receptors

- α_2-adrenergic receptors
  - Pre- and post-synaptic
    - Post-synaptic – constricts VSM (as for α_1)
    - Pre-synaptic – inhibit NE release into synaptic cleft
    - More α_2 receptors in the venous system
  - Central actions
    - Decrease SNS, Increase PSNS

Understanding Receptors

- β_1-adrenergic receptors
  - Receptors predominate in the myocardium
  - + rate, + contractility, + conduction velocity
  - Equally sensitive to EPI and NE
- β_2-adrenergic receptors
  - Mainly located in smooth muscles of blood vessels and bronchus
  - More sensitive to EPI than NE

Understanding Receptors

- Dopaminergic Receptors
  - Re: Dopamine is a precursor of NE and EPI
  - Two major DA receptors
  - DA_1 receptors
    - mainly post-synaptic on renal sm and mesentery
    - Vasodilation and increased blood flow
  - DA_2 receptors
    - Pre-synaptic: inhibit NE release
    - Post-synamptic: vasoconstriction

Understanding Receptors

- Vasopressin Receptors
  - V1R – Vasoconstrict vascular smooth muscle
  - V2R – Anti-diuretic effects
  - V3R - ACTH release from pituitary
  - OTR – Vasodilation

FINALLY!
The War Chest

- Norepinephrine (Levophed)
- Epinephrine
- Dopamine
- Dobutamine
- Milrinone
- Vasopressin
- Phenylephrine (Neosynephrine)

Norepinephrine (Levophed)

- Identical to endogenous catecholamine synthesized by adrenal medulla
- Effects on α_{1+2} and β_1 receptors
- Low doses: β effects predominate
- Higher doses: α effects predominate
  - Venoconstriction (venous > arterial)

Agent (typical dosages)	β-1	β-2	α-1
Isoproterenol (0.01–0.1 μg/kg/min)	+++	+++	O
Norepinephrine (0.05–1 μg/kg/min)	++	O	+++
Epinephrine (0.05–2 μg/kg/min)	+++	++	+++
Phenylephrine (0.5–5 μg/kg/min)	O	O	+++
Dopamine* (1–20 μg/kg/min)	+(++)	+	+(++)
Dobutamine (2.5–20 μg/kg/min)	+++	+	+

*Dopamine effects at "high-dose," which are typically greater than 3 to 5 μg/kg/min, are shown in parentheses. O, no effect; +, minimal effect; ++, moderate effect; +++, substantial effect.

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Norepinephrine (Levophed)

- Onset: < than 2 min
- Metabolism: Hepatic (mostly)
- Dosing: 0.01 – 1.0 mcg/kg/min
- !! - Rebound hypotension if rapid D/C
- Indicated mainly for distributive shock after adequate hydration

Norepinephrine (Levophed)

- At high doses, α_1 effects predominate - THINK about what this means in your patient!
  - Case I: Septic shock – dilated periphery
    - NE may increase organ perfusion
  - Case II: Hypotension with normal SVR
    - NE could dramatically increase afterload and increase the work of the LV (dangerous if ischemic myocardium)
    - Increased renal arterial constriction – worsening oliguria
- HR might decrease reflex increase in PS tone

Epinephrine

- Endogenous catecholamine produced, stored, released by adrenal medulla
- Usually: ACLS, Anaphylaxis, CT Surgery
- Has both α and β effects
- Bronchodilator
- Histamine antagonist

Agent (typical dosages)	β-1	β-2	α-1
Isoproterenol (0.01–0.1 μg/kg/min)	+++	+++	O
Norepinephrine (0.05–1 μg/kg/min)	++	O	+++
Epinephrine (0.05–2 μg/kg/min)	+++	++	+++
Phenylephrine (0.5–5 μg/kg/min)	O	O	+++
Dopamine* (1–20 μg/kg/min)	+(++)	+	+(++)
Dobutamine (2.5–20 μg/kg/min)	+++	+	+

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PD-INEL
Source Undetermined

Epinephrine

- Onset: < 2 min
- Elimination: Renal (predominantly)
- Dosing – as for norepinephrine
  - 0.01 – 1.0 mcg/kg/min
- Very Arrhythmogenic

Dopamine

- Endogenous precursor of norepinephrine
- Can affect multiple receptors
  - DA, α, and β depending on dose (in theory)
- Indications: MI, Sepsis, CHF, Renal insufficiency
- Contraindications: Pheochromocytoma or tachydysrhythmia

Agent (typical dosages)	β-1	β-2	α-1
Isoproterenol (0.01–0.1 μg/kg/min)	+++	+++	O
Norepinephrine (0.05–1 μg/kg/min)	++	O	+++
Epinephrine (0.05–2 μg/kg/min)	+++	++	+++
Phenylephrine (0.5–5 μg/kg/min)	O	O	+++
Dopamine* (1–20 μg/kg/min)	+(++)	+	+(++)
Dobutamine (2.5–20 μg/kg/min)	+++	+	+

*Dopamine effects at "high-dose," which are typically greater than 3 to 5 μg/kg/min, are shown in parentheses. O, no effect; +, minimal effect; ++, moderate effect; +++, substantial effect.

PD-INEL
Source Undetermined

Dopamine

- Onset of action: < 5 min
- Metabolism
  - Hepatic and renal* to inactive metabolites (75%) and NE (25%)
- Dosing: 1- 20 μg/kg/min
  - Low or “Renal dose” 0.5-2 μg/kg/min
  - Moderate doses 2-10 μg/kg/min
  - High doses > 10 μg/kg/min

Dopamine

- "Renal dose" 0.5-2 μg/kg/min
  - Mainly DA_1 and DA_2 receptors
    - DA_1 post-synaptic effects - mostly Vasodilation
    - DA_2 some vasoconstriction and inhibition NE release
- Moderate doses: 2-10 μg/kg/min
  - Activates β receptors
    - + HR and + Contractility
- High doses > 10 μg/kg/min
  - α-mediated vasoconstriciton > DA and β

Role of Dopamine

- Renal Effects
  - Pioneer work by Goldberg in 1974
  - Theoretical benefits...
    - blunting of the NE induced vasoconstriction (renal vasodilation to increase GFR) leading to better natriuresis and diuresis
  - Led to belief that “renal dose” dopamine might confer protection against ARF

Role of Dopamine

- Australian and New Zealand Intensive Care Society Group
  - No benefit in ARF, no improvement in outcome
- NA Septic Shock trial (NORASEPT)
  - No reduction in incidence of ARF, need for hemodialysis, or mortality from patients with oliguria

Role of Dopamine

- Conclusions
  - Benefits not confirmed in study
  - Any apparent benefit (i.e. increased diuresis) likely due to β effects and better cardiac output rather than renal tropism
  - This apparent Increase in diuresis may actually increase risk of ARF in normo- or hypovolemic pts

Dobutamine

- Mainly a β_1 stimulant (strong inotrop) with only a weak β_2 interaction (vasodilation)
- Weak chronotropic effect
  - HR may actually decrease
- Risk of arrhythmias due to myocardial O2 demand at higher dose

Agent (typical dosages)	β-1	β-2	α-1
Isoproterenol (0.01–0.1 μg/kg/min)	+++	+++	O
Norepinephrine (0.05–1 μg/kg/min)	++	O	+++
Epinephrine (0.05–2 μg/kg/min)	+++	++	+++
Phenylephrine (0.5–5 μg/kg/min)	O	O	+++
Dopamine* (1–20 μg/kg/min)	+(++)	+	+(++)
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PD-INEL
Source Undetermined

Dobutamine

- Doses range from 2 - 20μg/kg/min
- Onset of action: 1-2 min
- Renal excretion
- Mainly indicated for cardiogenic shock (low output heart failure states)
- Contraindicated in idiopathic hypertrophic subaortic stenosis

Milrinone

- Phosphodiesterase inhibitor
- Selectively inhibits PDE III
  - Eleates cAMP
    - increased protein kinase and activation of a similar cascade as adrenergic drugs
- Inotropic action
- Vasodilates* and afterload reduces (which is why we often use it with a PAC)

Milrinone

- Onset of action 5-15 minutes
- Requires bolus of 50μg/kg over 10 minutes
- Drip dose 0.25 - 0.75 μg/kg/min
- Indicated for severe heart failure, cardiogenic shock
- May result in less arrhythmias than Dobutamine

Vasopressin

- Identical to endogenous ADH
- Primary role: maintain serum osmolality
- Larger doses: stimulates V1R receptors in smooth muscles resulting in calcium release from sarcoplasmic reticulum
- Net effect is vasoconstriction

Vasopressin

- Onset of action immediate
- Usual dose of 0.02-0.04U/min
- Indications: ACLS, GI hemorrhage, and septic shock
- Pressor sparing?

Phenylephrine

- Mainly an α_1 agonist
- Vasoconstriction with minimal HR effect
- Onset is immediate
- Dose 25 – 100 mcg IV (typical)
- Infusion: 0.5 – 5 μg/kg/min

Agent (typical dosages)	β-1	β-2	α-1
Isoproterenol (0.01–0.1 μg/kg/min)	+++	+++	O
Norepinephrine (0.05–1 μg/kg/min)	++	O	+++
Epinephrine (0.05–2 μg/kg/min)	+++	++	+++
Phenylephrine (0.5–5 μg/kg/min)	O	O	+++
Dopamine* (1–20 μg/kg/min)	+(++)	+	+(++)
Dobutamine (2.5–20 μg/kg/min)	+++	+	+

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