Episode 19: Vasoactive medications

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In this episode I review the receptors that vasoactive drugs act on. I then review the main vasoactive medications used in the OR and the ICU to treat acute hypotension and the ones used to treat acute hypertension.

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Receptors

- α1 adrenergic receptor is Gq protein coupled receptor→ ↑ Ca^{2+} in smooth muscle cell → smooth muscle contraction
- α2 adrenergic receptor is Gio protein coupled receptor → presynaptic negative feedback
    - Eg. dexmedetomidine, clonidine
    - Antihypertensive, anxiolytic, sedation
- β1 adrenergic receptor is Gs protein coupled receptor
    - Found in cardiac muscle
    - ↑ cAMP → ↑ HR, contractility, and AV nodal conduction
- β2 adrenergic receptor is Gs protein coupled receptor
    - Smooth muscle relaxer peripherally in vasculature and lungs
- β3 adrenergic receptor leads to lipolysis
- Vasopressin 1 receptor is GPCR → smooth muscle contraction
- Dopamine receptor → smooth muscle contraction
- Phosphodiesterase (PDE) 3 breaks down cAMP
    - Inhibition prevents break down of cAMP → ↑ cAMP → ↑ HR, contractility, and AV nodal conduction in heart AND peripheral smooth muscle relaxation

Vasopressors

- Vasopressors = act as vasoconstrictors on peripheral vasculature
    - Eg. Epinephrine, norepinephrine, dopamine, phenylephrine, ephedrine
- Epinephrine: α1 α2, β1, and β2 agonist
    - Doses at 0.01 to 0.04mcg/kg/min → primarily β1 agonist
    - Doses at 0.08 to 0.1mcg/kg/min and above → α1, β1 agonist
    - Code doses have ↑ α1 agonist affect → vasoconstriction and relaxation of bronchial smooth muscles through β2 agonist
- Norepinephrine: α1, α2, and β1 agonist, with minimal β2 agonism
    - Effect is mostly positive inotropy and strong vasoconstrictor
- Dopamine: α1 α2, β1, β2 agonist, and all dopamine receptor agonism
    - Dopamine in theory causes increased blood flow to kidneys → not shown to improve renal outcomes clinically
- Phenylephrine: selective α1 agonist
    - Effect is peripheral vasoconstriction; no effect on heart
- Ephedrine acts indirectly by stimulating release of norepinephrine
    - Less effect with multiple doses in bolus form → not used as infusion

Inodilators

- Inodilators = medications that provide inotropy and peripheral vasodilation
    - Eg. dobutamine, milrinone, isoproterenol
- Dobutamine: β1 agonist and to a lesser degree β2 agonist
    - β1 effect → ↑ inotropy, ↑ CO, ↑ HR, ↑ AV nodal conduction
    - β2 effect → peripheral vasodilation → hypotension
    - Good for heart failure
- Milrinone: PDE3 inhibitor
    - ↑ cAMP in cardiomyocytes → ↑ inotropy, ↑ HR, ↑ AV nodal conduction

- ↑ cAMP in smooth muscles peripherally → peripheral vasodilation → ↓SVR
- Isoproterenol: mostly β1 agonist and some β2 agonist
  - Main effect is ↑ HR with some ↑ inotropy and AV nodal conduction
  - β2 peripheral effect is less pronounced

Side Effects

- Inodilators:
  - Systemic hypotension because of β2 activity
  - Risk of arrhythmias because of β1 activity → increased risk with higher dose
- Vasopressors:
  - β1 agonism → risk of arrhythmias
  - Peripheral vasoconstriction → peripheral and splenic ischemia
    - Digital ischemia with high doses and prolonged period of norepinephrine
    - Intestinal ischemia → worry about anastomosis

Treatment of Hypotension

- Don't treat a number, treat the mechanism
- Eg. hypotension after induction is most likely from propofol; treated with phenylephrine or ephedrine if HR is low
- Eg. septic shock; treated with norepinephrine ± vasopressin because dealing with peripheral vasodilation from sepsis → need strong vasoconstrictor
  - Epinephrine is third line
  - Dopamine inferior because causes more arrhythmia
  - No phenylephrine because ↓CO from ↑ SVR
- Eg. cardiogenic shock → need inotropy
  - If hypotensive → epinephrine
  - If poor CO, but not hypotensive → dobutamine or milrinone
- Eg. hemorrhagic shock → resuscitate instead of vasopressors
- Eg. aortic stenosis → heart pushing against fixed defect
  - Goal is to lower HR because need time for LV to fill and push out against stenotic valve
  - Use phenylephrine → α1 causes systemic vasoconstriction with reflex bradycardia
- Eg. tamponade → keep HR fast with increased inotropy
  - Use epinephrine
- Eg. pulmonary hypertension with systemic hypotension
  - Only vasopressor that doesn't affect pulmonary vascular resistance is vasopressin
  - Use vasopressin alone
- Eg. hypotension with arrhythmias
  - Phenylephrine or vasopressin → don't have β agonism
  - If patient is hypotensive because of arrhythmia → think about cardioversion rather than vasopressors

Vasodilators

- Nicardipine → Ca^{2+} channel blocker
  - IV infusion has onset 1 to 2 minutes; once infusion stopped, take ~30 minutes for effect to decrease by ½

    - Start around 5mg/hr and titrate up to 15mg/hr for effect
- Nitroglycerin → forms NO → increased cGMP → smooth muscle dilation primarily in coronary arteries and systemic veins → ↓ preload and small amount of ↓ afterload
    - Onset 30 seconds; offset 3 to 5 minutes
    - Start at 5mcg/min and titrate up to 400 mcg/min
    - Common side effects:
        - Headache
        - Tachyphylaxis → people need higher doses to get same effect
        - CANNOT be given to patients who have taken Viagra or similar medications
- Nitroprusside → direct action on arteriole and venous smooth muscle → ↓ afterload
    - Onset 1 minute; offset 1 to 10 minutes
    - Start 0.3mcg/kg/min to maximum of 2mcg/kg/min to avoid cyanide toxicity
    - Could go up to 10mcg/kg/min, but only able to do it for 10 minutes to avoid cyanide toxicity
- Labetalol → α and β blocker
    - IV labetalol has 7x stronger β blocker effect
    - PO labetalol has 3x stronger β blocker effect
    - Used as IV bolus 10 to 20mg to treat hypertension
    - Infusion dosage is 0.1mg/min to maximum of 8mg/min
    - Drug of choice for aortic dissection because ↓ BP and ↓ inotropy to ↓ Δpressure/Δtime (shearing force)
    - Onset 5 to 15 minutes; duration of action is up to 15 hours → do not use if worried about hypotension
    - Non-selective β blocker → not ideal for patients with asthma
- Nicardipine, nitroglycerin and nitroprusside could cause shunting
    - Dilatory effect interferes with hypoxic vasoconstriction → ↑ V/Q mismatch → poor oxygenation and shunting