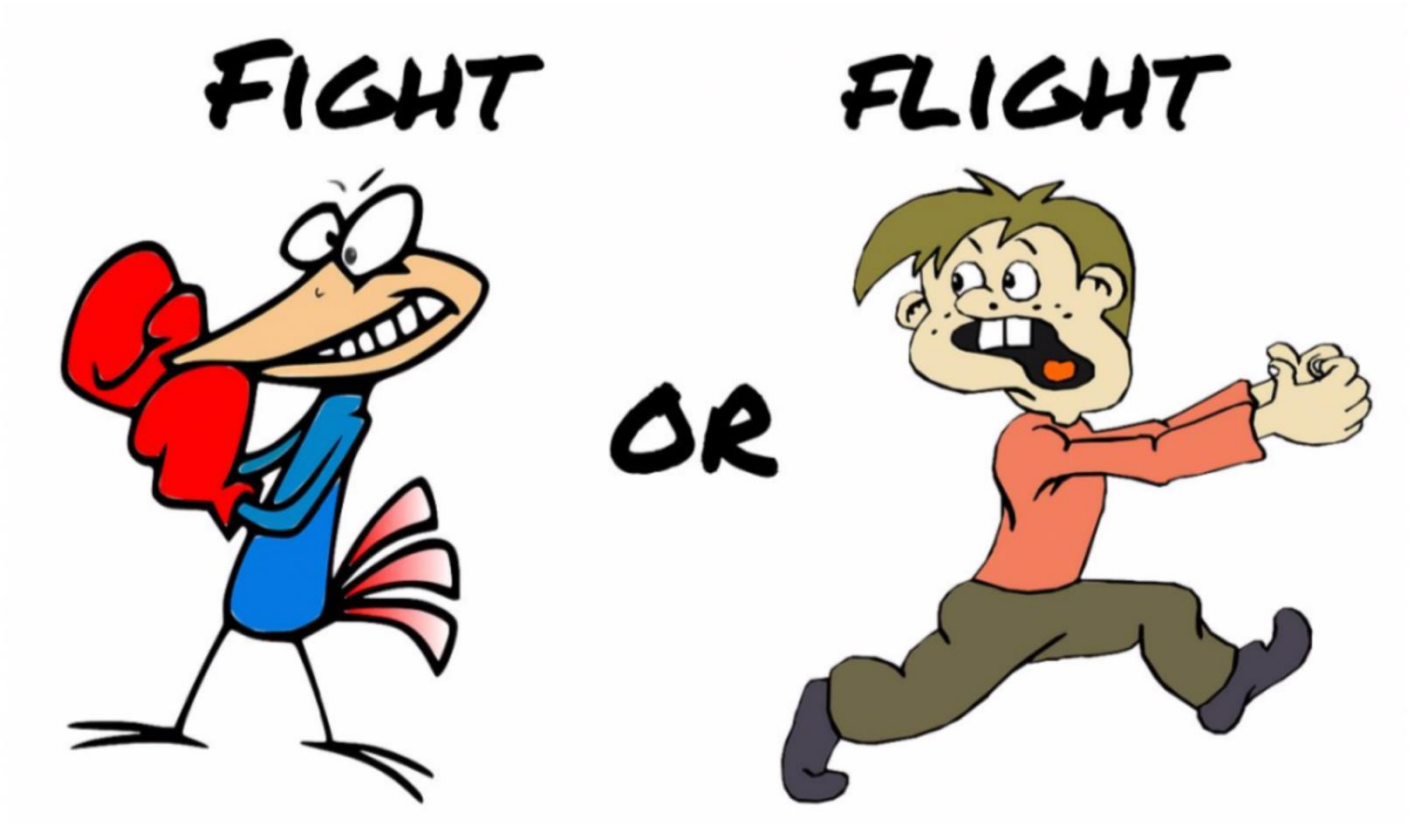
Inotropes Vasopressors
&
Shock

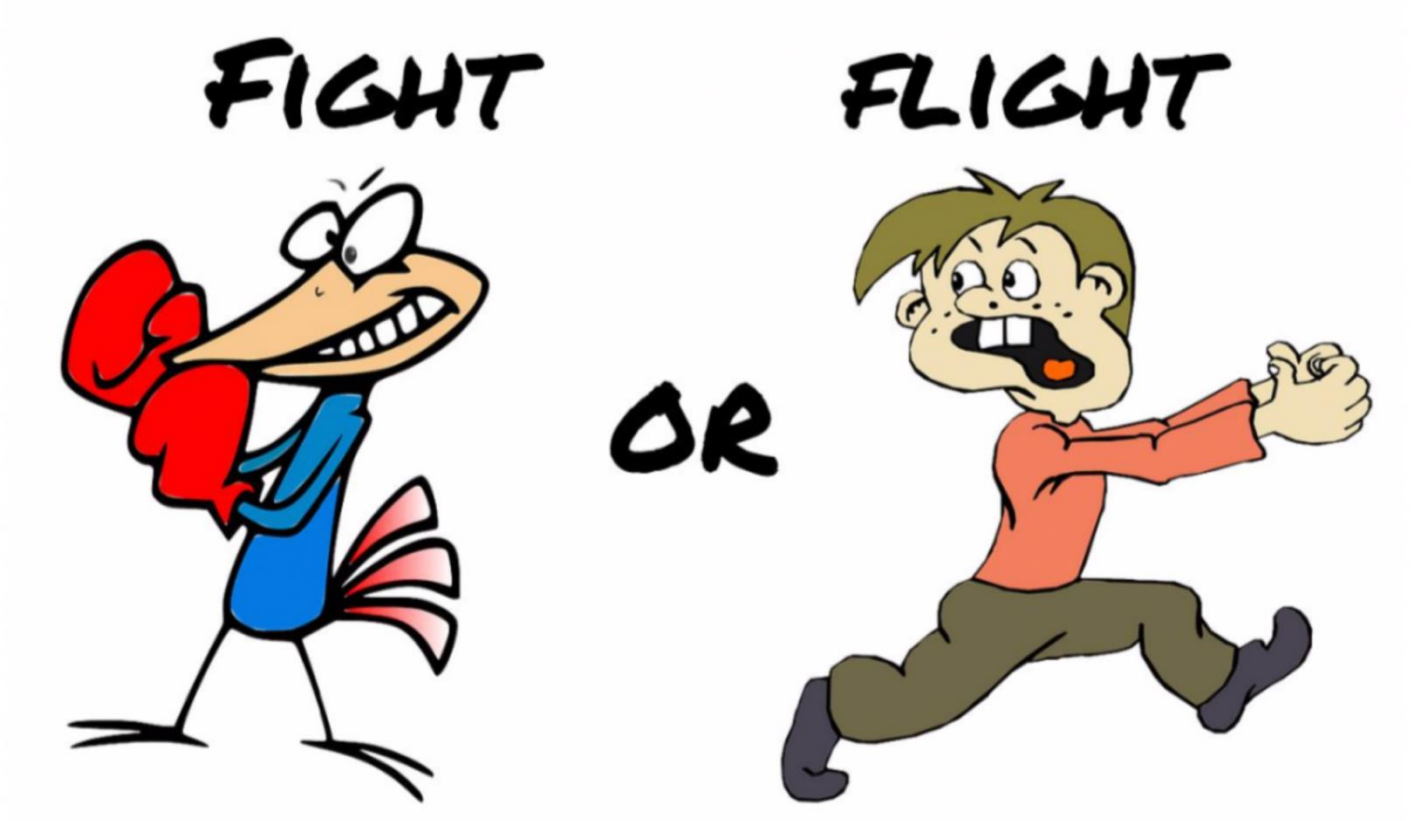
What is the physiologic response to "fight or flight?"



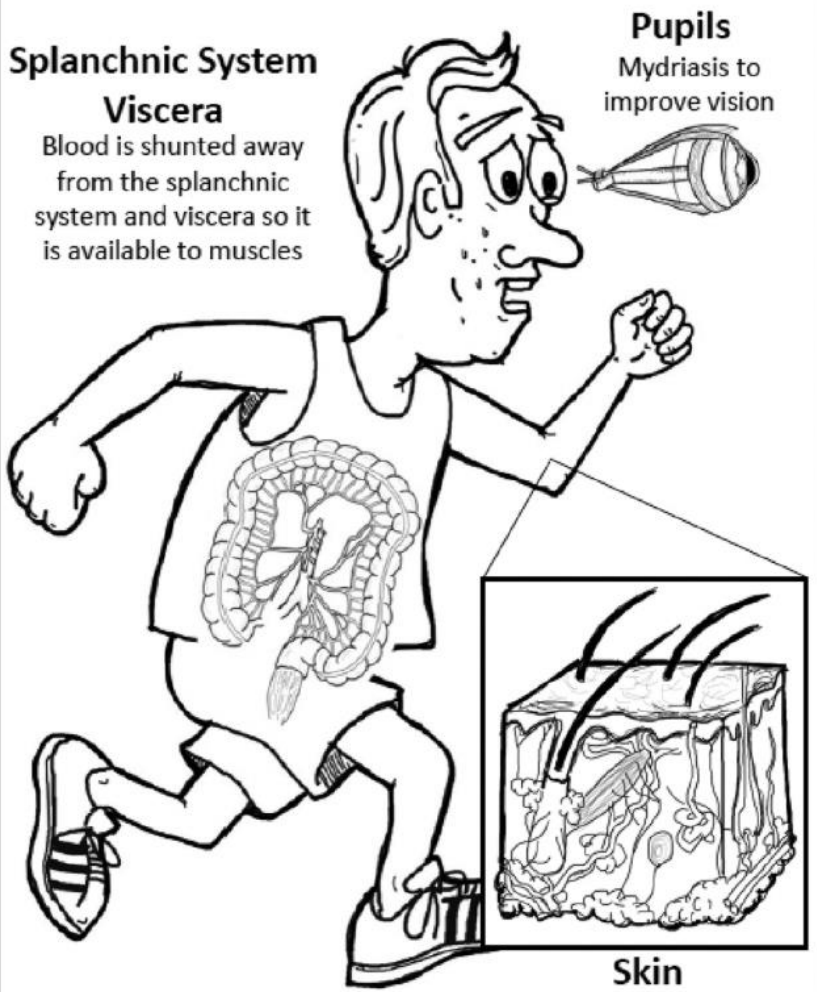
Physiologic Response to "Fight or Flight"

- Sympathetic nervous system is activated
- Release of endogenous catecholamines
  - Epinephrine
  - Norepinephrine
- Excitation of adrenoreceptors
  - α_1
  - B_1
  - B_2
  - (Dopminergic)
- Hypothalamo-pituitary-adrenal (HPA) axis activation
  - Stress hormone release (i.e cortisol & ADH)

What are the key effects of each adrenoreceptors? α_1? B_1? B_2?



Alpha-1



Splanchnic System Viscera

Blood is shunted away from the splanchnic system and viscera so it is available to muscles

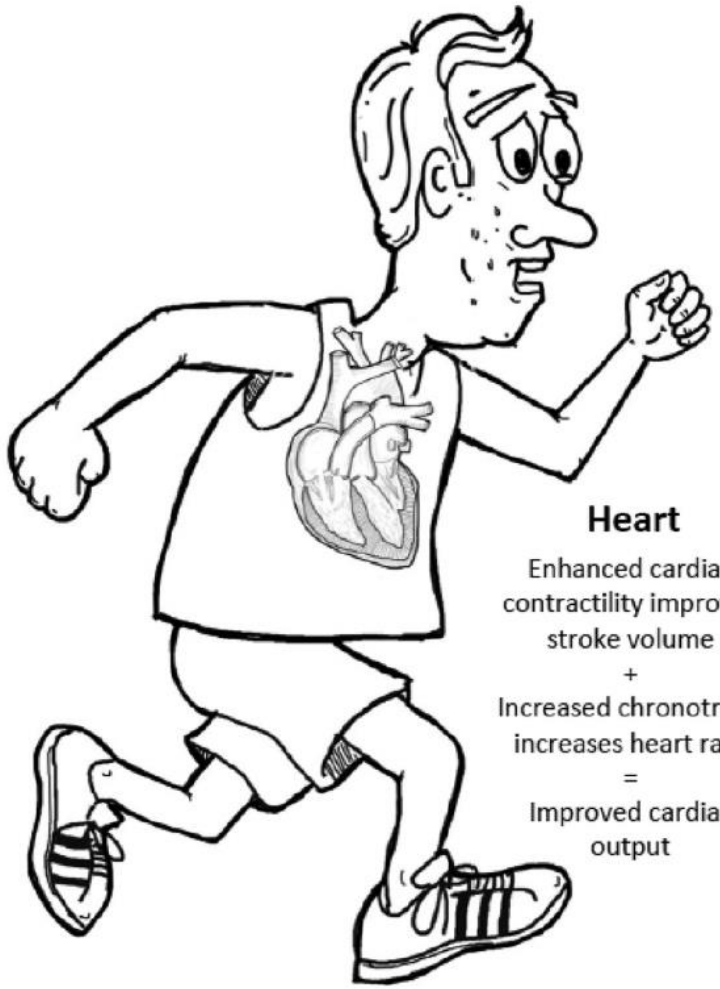
Pupils

Mydriasis to improve vision

Skin

Blood is shunted away from the skin so it is available to muscles

Beta-1



Heart

Enhanced cardiac contractility improves stroke volume

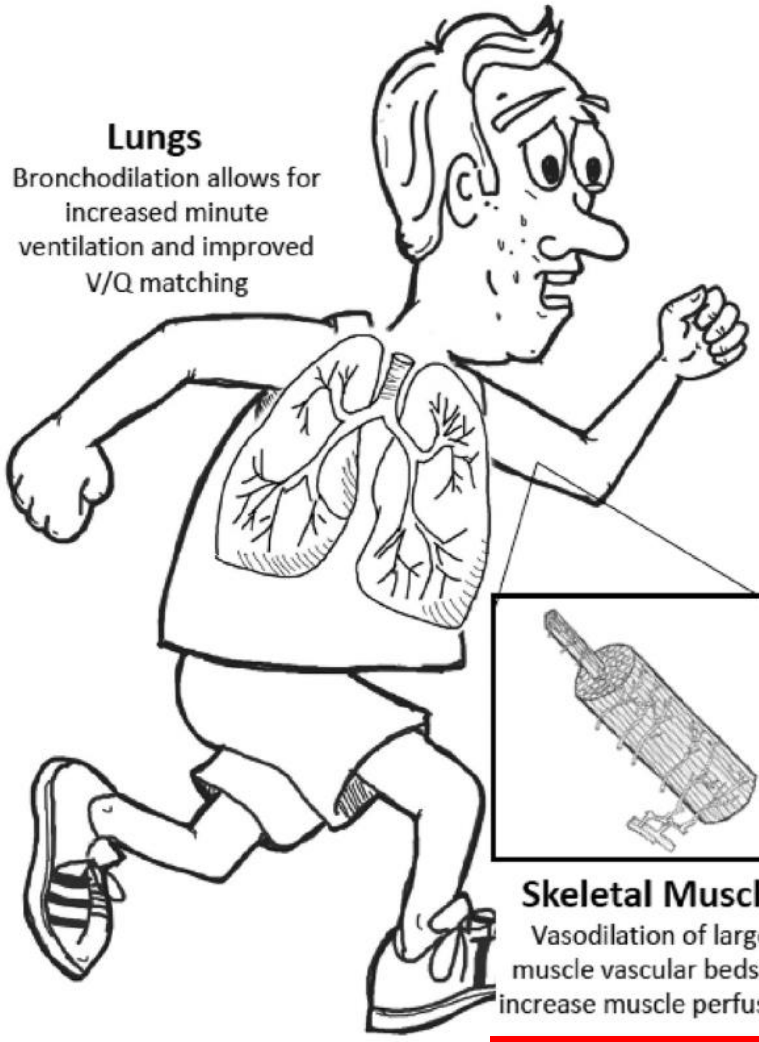
+

Increased chronotropy increases heart rate

=

Improved cardiac output

Beta-2



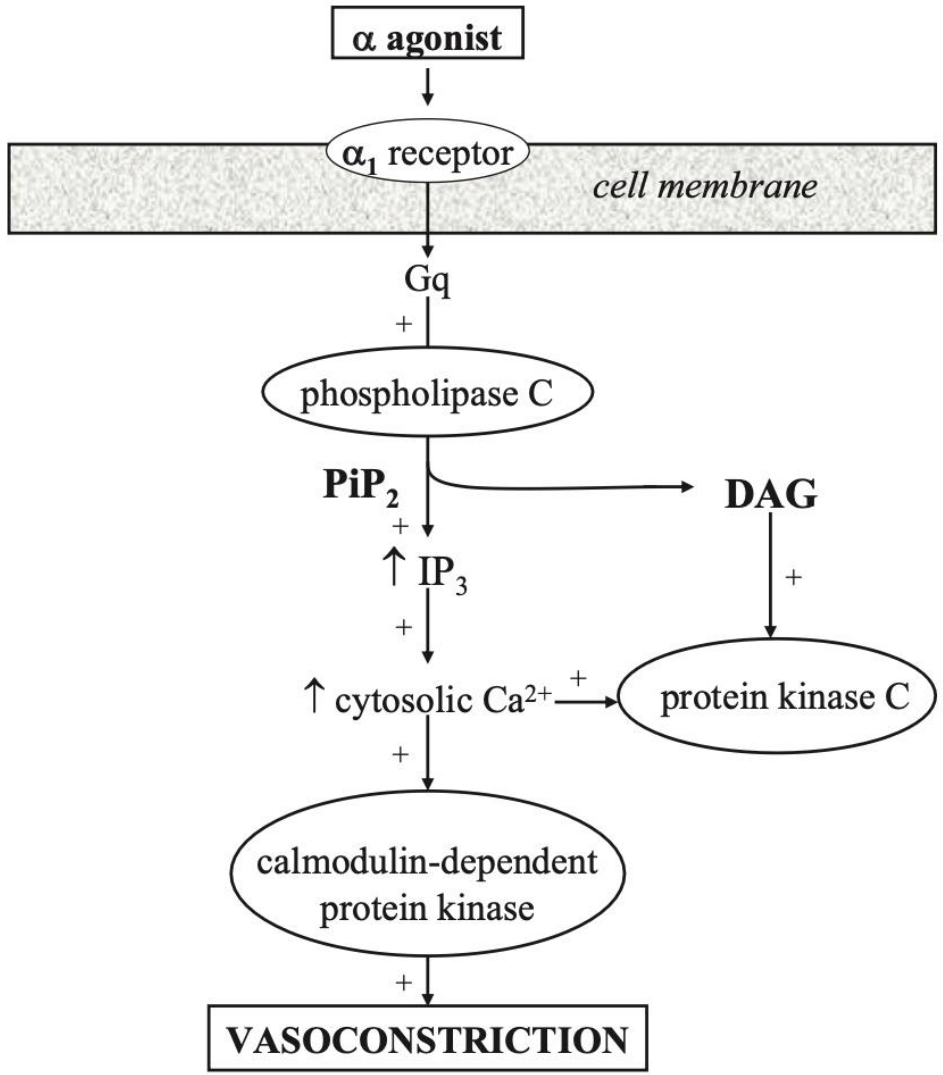
Lungs

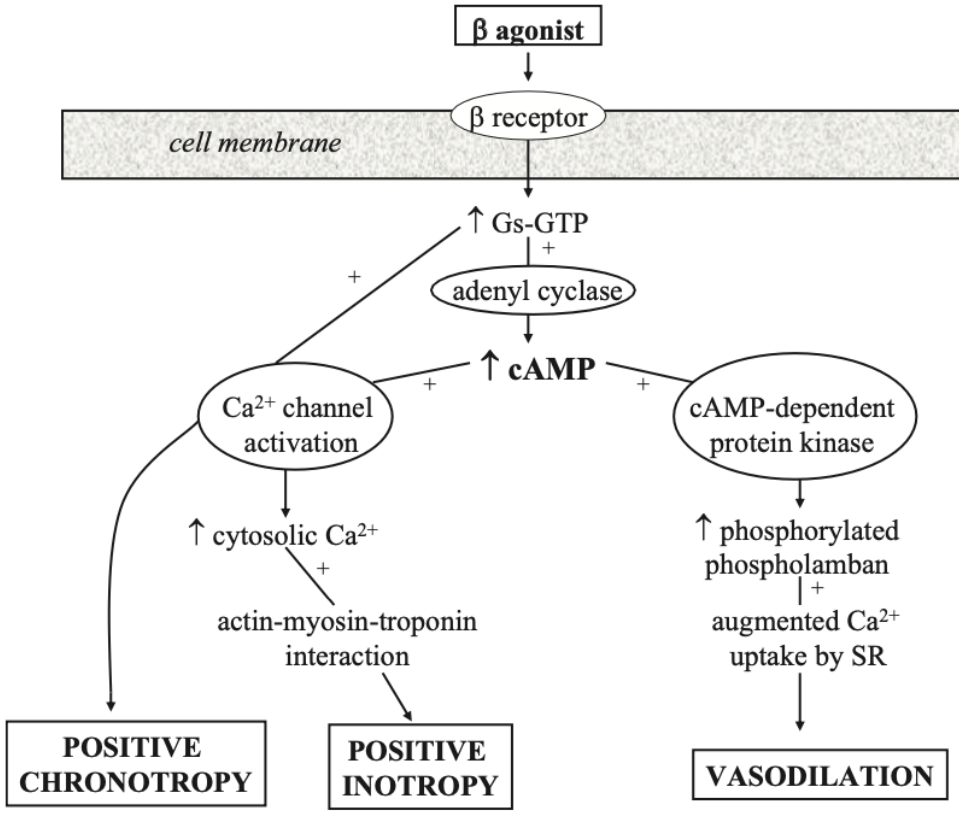
Bronchodilation allows for increased minute ventilation and improved V/Q matching

Skeletal Muscle

Vasodilation of large muscle vascular beds to increase muscle perfusion

Releases lactate as a rapidly available fuel source

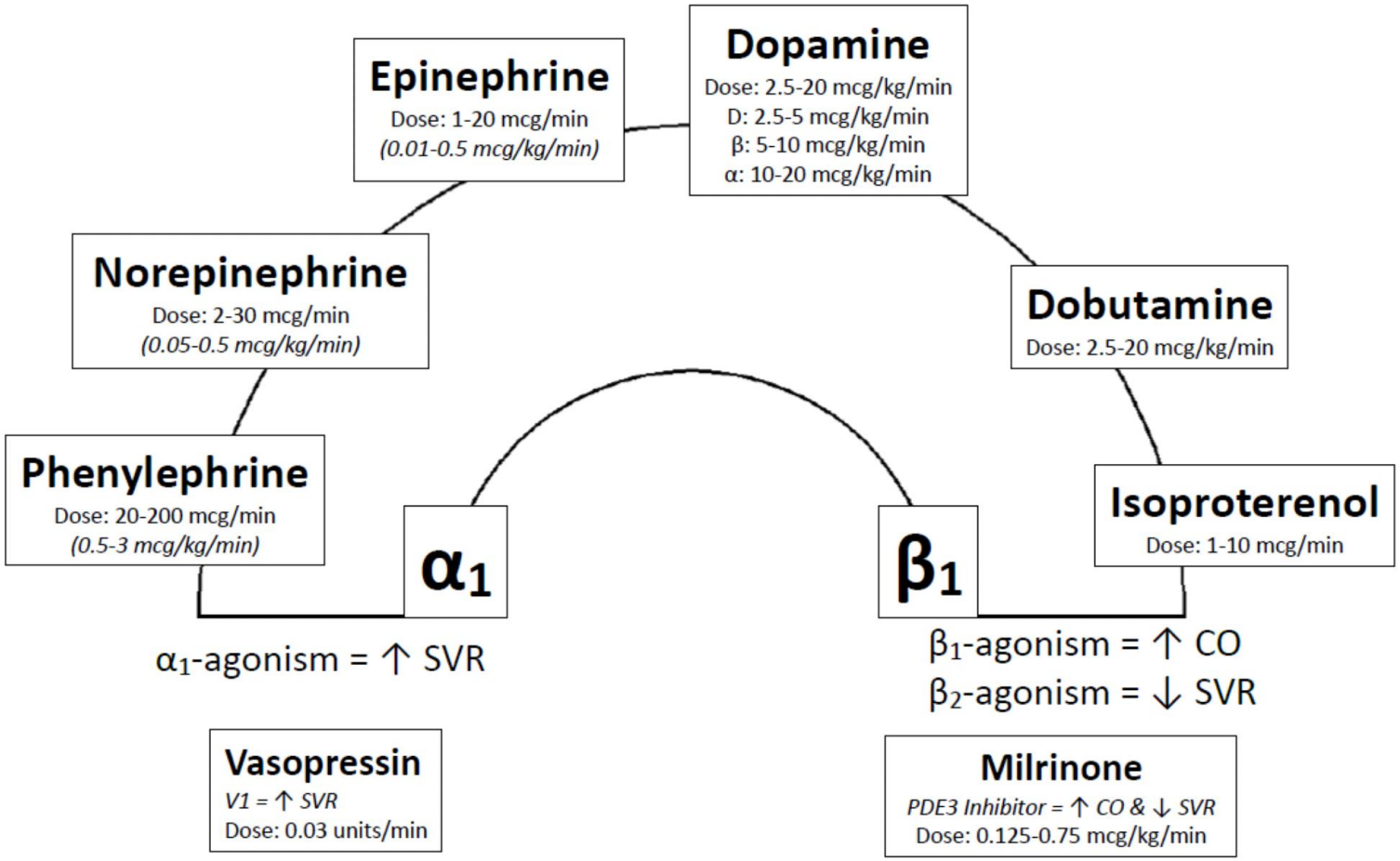

α agonist
α1 receptor
cell membrane
Gq
+
phospholipase C
PiP2
DAG
+
↑ IP3
+
+
↑ cytosolic Ca2+
+
protein kinase C
+
calmodulin-dependent
protein kinase
+
VASOCONSTRICTION


β agonist
β receptor
cell membrane
↑ Gs-GTP
+
adenyl cyclase
+
↑ cAMP
+
+
Ca2+ channel
activation
cAMP-dependent
protein kinase
↑ cytosolic Ca2+
+
actin-myosin-troponin
interaction
↑ phosphorylated
phospholamban
+
augmented Ca2+
uptake by SR
POSITIVE
CHRONOTROPY
POSITIVE
INOTROPY
VASODILATION

Adrenergic Receptors

Receptor	Location	Action	Effect
α1 *Vasopressors*	Systemic Vasculature	Vasoconstriction	↑ SVR
β1 *Inotropes*	Myocardium	↑HR ↑contractility	↑ CO
β2 *Vasodilators*	Systemic Vasculature	Vasodilation	↓ SVR

Vasopressors and Inotropes



Epinephrine

- Action - α1, β1, β2 agonism
  - Lower dose: β > α (inotropy)
  - Higher dose: α > β (vasoconstriction)
- Dose
  - 1-20 mcg/min or *0.01 - 0.5* mcg/kg/min
- Clinical Use
  - Refractory shock, adjunct (2nd or 3rd line)
  - Consider in patients with cardiogenic shock component
  - Anaphylaxis (B2 bronchodilates, mitigates airway mucosal edema)
  - Cardiac arrest

Norepinephrine (Levophed)

- Action - α1 >> β1, β2 agonsim
  - Primary vasoconstrictor - increases SBP, DBP, PP
  - Weak inotrope, Minimal chronotropy

- Dose
  - 2-30 mcg/min or *0.05-0.5* mcg/kg/min

- Clinical Use
  - 1st line septic shock (surviving sepsis guidelines)
  - Suggested for undifferentiated & cardiogenic shock

- Note
  - Potential rate limiting tachycardia/tachyarrythmias

Phenylephrine

- Action: Pure α agonist

- Dose
  - 20-200mcg/min
  - Bolus dose: 100-200 mcg Q 3-5 min
- Clinical Use
  - Septic shock in patients who do not tolerate norepinephrine
  - Anesthetic induced hypotension
  - Shock in pts w/ Aortic/Mitral Stenosis
  - Hypotension from simultaneous ingestion sildenafil & nitrates
  - To decrease outflow tract gradient in pts w/ obstructive hypertrophic cardiomyopathy
- Notes
  - Least arrhythmogenic
  - Potential for reflex bradycardia
  - Unopposed alpha – ischemic effects

Vasopressin (ADH)

- Action: Vasopressin rec agonsim
  - V1→ Vasoconstricts vascular smooth muscle = ↑ SVR
  - V2 → Reabsorbs H20 from renal collecting duct = ↓ UOP
  - ↑ vascular sensitivity to catecholamines (augments pressor effect)
  - Attenuates ATP activated K channels & NO production (BP augmentation)
  - Reverses adrenergic rec down regulation
- Dose: 0.04 units/min
- Clinical Use
  - Adjunct to Norepinephrine in refractory shock
  - Pts with Aortic/Mitral Stenosis, pulmonary HTN
  - GI Hemorrhage
  - Hemorrhagic shock (post hemorrhage control)
- Notes
  - ***Preserved effect in acidosis & hypoxia*** **(unlike catecholamines)**

Dopamine

- Action – dose dependent
  - Low dose (2.5-5 mcg/kg/min) - D1 & D2 (vasodilation & increased blood flow)
  - Medium dose (5-10 mcg/kg/min) - β
  - High dose (10-20 mcg/kg/min) - α
  - Unclear relationship in clinical practice
- Clinical Use
  - ACLS Guidelines for management of symptomatic bradycardia not responsive to atropine or pacing
- Notes
  - High arrhythmogenicity
    - ↑ myocardial oxygen demand

Dobutamine

- Action: Strong β, minimal α agonism
  - B1:β2 - binds 3:1 ratio
  - Stronge inotrope, weaker chronotropy
- Dose
  - 2.5-20mcg/kg/min (usual inotropic range: 5-10 mcg/kg/min)
- Clinical Use
  - Shock with ↓ CO
  - Decompensated HF
- Notes
  - Hypotension (Start with low doses and titrate up, may need concurrent vasopressor)
  - Tolerance (days)
  - Increases myocardial oxygen demand
  - Arrhythmogenic (malignant ventricular arrythmias)

Isoproterenol

- Action: Pure β agonism
  - Strong chronotrope & inotrope
  - Strong systemic & mild pulmonary vasodilatory effects
- Dose
  - 1-10 mcg/min
- Clinical Use
  - Brady arrhythmias, Heart Block, Torsade de Pointes
- Notes
  - Generally restricted to Cardiology

Phosphodiesterase inhibitors (i.e. Milrinone)

- Action: PDE 3 inhibition - Increased intracellular cAMP
  - Potent inotrope & vasodilator
  - Diastolic relaxation (lusitropy)
  - Reduces preload, afterload, SVR
- Dose
  - 0.125- 0.75 mcg/kg/min
- Clinical Use
  - Shock with ↓ CO
  - Decompensated HF, if adrenergic recs downregulated/desensitized in chronic HF
- Notes - Increases myocardial oxygen demand

Others

- **Methylene Blue** (inhibition guanylate cyclase – reducing NO production, refractory shock)
- **Angiotensin II** (vasodilatory shock, refractory)
- **Calcium-Sensitizing agents** (levosimendan, heart failure)

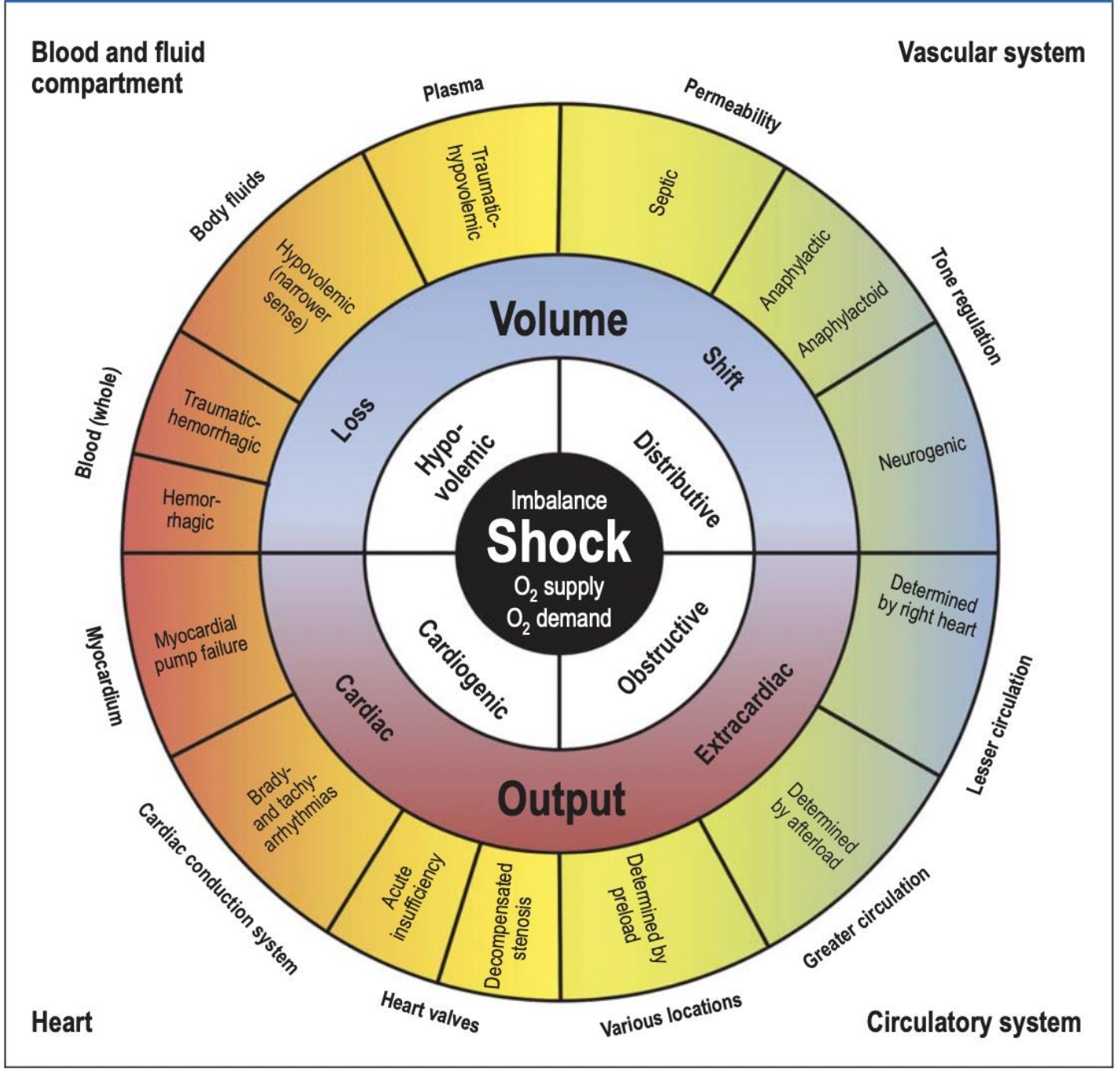
Shock =
Supply Demand
Mistmach

Types of Shock?

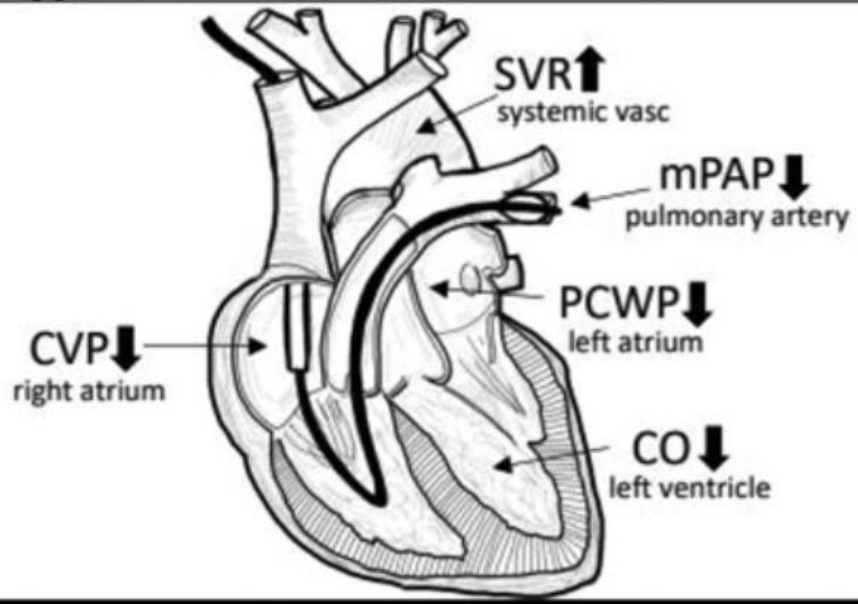
Classifications of Shock

- **Hypovolemic**
  - Hemorrhagic
  - Critical reduction circulating plasma volume
- **Distributive**
  - Septic
  - Neurogenic
  - Anaphylactic
- **Cardiogenic**
- **Obstructive**
  - Tamponade, tension PTX, massive PE
  - IVC compression
  - High PEEP

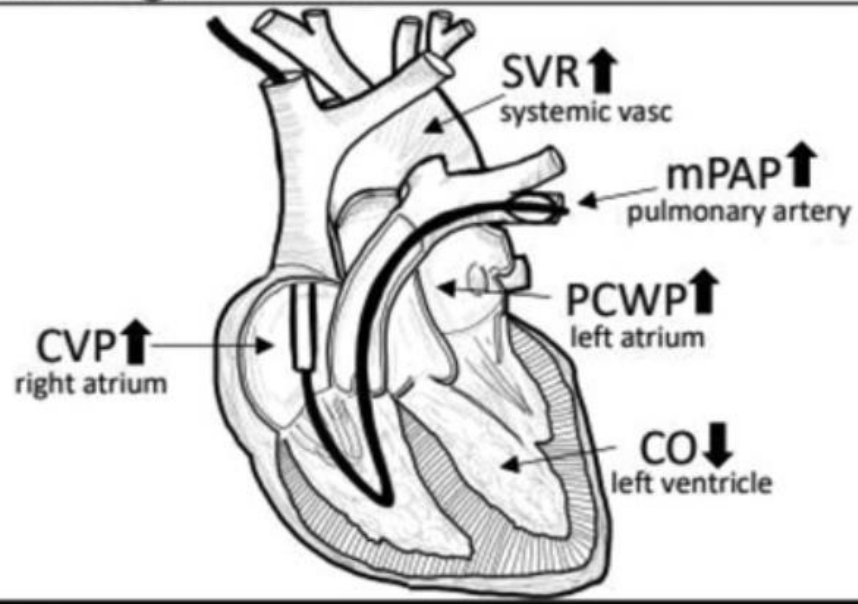
FIGURE 1


Blood and fluid compartment
Vascular system
Plasma
Permeability
Body fluids
Tone regulation
Blood (whole)
Lesser circulation
Myocardium
Greater circulation
Cardiac conduction system
Heart valves
Various locations
Heart
Circulatory system
Traumatic-hypovolemic
Septic
Hypovolemic (narrower sense)
Anaphylactic
Anaphylactoid
Traumatic-hemorrhagic
Neurogenic
Hemor-rhagic
Myocardial pump failure
Determined by right heart
Brady- and tachy-arrhythmias
Determined by afterload
Acute insufficiency
Decompensated stenosis
Determined by preload
Volume
Loss
Shift
Hypo-volemic
Distributive
Imbalance
Shock
O_2 supply
O_2 demand
Cardiogenic
Obstructive
Cardiac
Extracardiac
Output

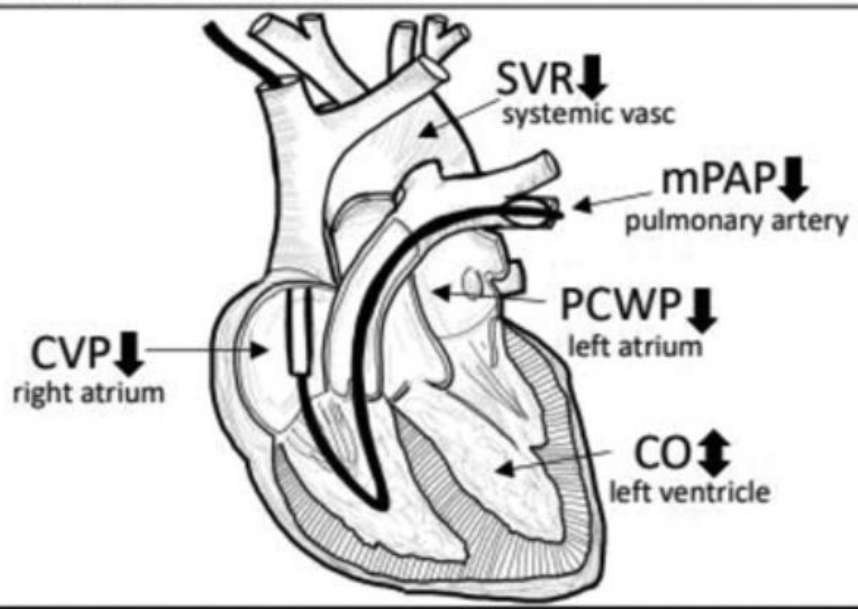
Hypovolemic Shock



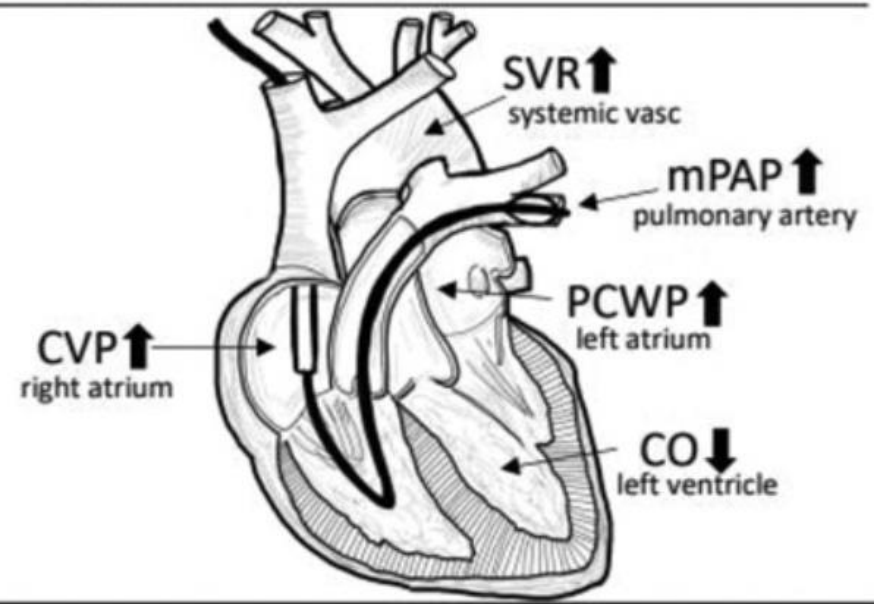
Cardiogenic Shock



Distributive Shock



Obstructive Shock



Type	CO	HR	CVP	PCWP	SVR	02 Sat
Cardiogenic	↓	↑	↔ ↑	↑	↑	↓
Hypovolemic	↓	↑	↔ ↓	↓	↑	↓
Septic	↑	↑	↔ ↓	↓	↓	↑
Neurogenic	↓	↓	↔ ↓	↓	↓	↓
Anaphylactic	↓	↑	↔ ↓	↓	↓	↓