Blood Pressure and Antihypertensive Medications

Circulation
- Two systems
  - Pulmonary (low pressure)
  - Systemic (high pressure)
  - Aorta 120 mmHg
  - Large arteries 110 mmHg
  - Arterioles 40 mmHg
  - Arteriolar capillaries 30 mmHg
  - Venous capillaries 18 mmHg
  - Venules 16 mmHg
  - Muscular Veins 12 mmHg
  - Central Veins 7 mmHg
  - Right atrium -5 mmHg

Arterial flow
- Pressure gradient
  - Heart generates pressure
  - Arteries contract or dilate to control flow and pressure
- Resistance to blood flow
  - Vessel diameter
  - Vessel length
  - Blood viscosity

Venous Return
- Mostly against gravity
  - Follows pressure gradient (small effect)
  - Constriction of venous SMC
  - Constriction of skeletal muscles
  - One way venous valves

Regulation of Cardiac Output
- CO ~ 5 liters/min
- CO = HR X SV
- Average HR 70 bpm, average SV 70ml
  - CO = 70 X 70 = 4900 ml/min = 4.9 liters/min
Heart Rate
- Autonomic nervous system innervates SA node
  - HR increases
    - Sympathetic stimulation
    - $\beta_1$ adrenergic receptors
  - HR decreases
    - Parasympathetic impulses
    - Muscarinic Receptors
    - Vagus nerve

Stroke Volume
- Myocardial contractility
  - Cardiac stretch (Starling’s law of the Heart)
  - Sympathetic stimulation ($\beta_1$ receptors)
- Cardiac preload
- Cardiac afterload

Starling’s Law of the Heart
- More stretch
- More contraction
- Up to a point

Preload
- Stretch applied to cardiac muscle prior to contraction
- Stretch is determined by amount of blood in ventricle at the end of diastole
  - End-diastolic volume
  - End-diastolic pressure
- How does preload affect Stroke Volume?

Control of Preload
- Affected by drugs
  - Venous tone
  - Blood volume
- Not affected by drugs
  - Skeletal muscle contractions
  - Resistance to flow in veins (e.g. thrombus)
  - Right atrial pressure
Systemic-Pulmonary Balance

- Right and Left heart **MUST** pump same amount of blood
- Very small disturbance can result in death
  - Fun with Math

Afterload

- Load against which a muscle (myocardium) must contract
- Operationally afterload is blood pressure

Arterial Pressure

- MAP = CO $\times$ TPR
  - CO = ?
  - TPR regulated by dilation/constriction
- Control mechanisms
  - ANS
  - RAAS
  - Kidneys
  - Local

ANS control of MAP

- Adjusts CO and peripheral resistance
- CO = ?
- Arteries
  - Sympathetic stimulation causes constriction
    - $\alpha$-1 receptors in arteries
  - No parasympathetic innervation
  - Complete removal of sympathetic tone reduces MAP by half

Control of ANS

- Baroceptor reflex
  - Carotid sinus
  - Aortic arch
- When drop in MAP is sensed
  - Constriction of arterioles
  - Constriction of veins
  - Acceleration of heart rate
- Baroceptor resetting

Renin-Angiotensin Cascade

- Angiotensinogen
- Renin
- Angiotensin I
- Angiotensin II
- Bradykinin
- AT_1
- AT_2
- AT_n
- Non-renin (e.g., tPA)
- Non-ACE (e.g., chymase)
- ACE
- Inactive peptides

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RAAS

• Angiotensin II
  – Constriction of arterioles
    • Hours
• Aldosterone
  – Retention of sodium and water
    • Days
  – Remodeling of heart and muscle
    • Weeks – Months

Renal Retention of Water

• Ultimate control of blood pressure!!!
  – Goal is to maintain renal perfusion
• Under influence
  – GFR
  – RAAS
  – ADH
  – Natriuretic peptides

Natriuretic Peptides

• Peptides that reduce vascular volume and
  – ANP (atrial) – produced by atrial myocytes
  – BNP (brain) – ventricular myocytes and brain
    • Both cause
      – Natriuresis
      – Diuresis
      – Increase vascular membrane permeability
      – Promote vasodilation (inhibition of sympathetic impulses)
  – CNP (endothelium)
    • vasodilation

Hypertension Etiology

• Primary (essential) hypertension
• Secondary - caused by something else
  – Accuracy of Diagnosis
  – Apnea (obstructive sleep)
  – Aldosteronism
  – Bruit (renal)
  – Bad kidneys
  – Catecholamines
  – Coarctation of Aorta

Hypertension Pathogenesis

• Disease of degree
• Hypertension begets hypertension
• End organ damage
  • Heart
  • Brain
  • Kidneys
  • Arteries
  • Eye

Hypertension Etiology

• Secondary Hypertension – continued
  – Cushing’s Syndrome
  – Drugs
  – Diet
  – Erythropoietin (excess)
  – Endocrine disorders
Hypertension Pathogenesis

- Arteries
  - Higher pressure causes physical damage
  - Scars elastic arteries
  - Increased risk for atherosclerosis
    - Turbulent blood flow – decreases endothelial function
    - Pressure causes more blood particles to enter intimal space
  - Resetting of baroceptors – causes body to think hypertension is normal
- Heart
  - Ventricular hypertrophy
    - Vicious cycle
      - Results in smaller chambers → less Cardiac output
      - Less output → has to work harder
      - Works harder → hypertrophies more
  - More at risk for ischemia
  - More vulnerable to coronary artery disease
- Brain
  - Increased risk of atherosclerotic stroke
  - Increased risk of hemorrhagic stroke
- Kidney
  - Glomerulus is artery, not capillary
  - Increased pressure causes increased GFR
- Eye
  - Retinal arteries sensitive to pressure damage

Hypertension Clinical Manifestations

- The Silent Killer
  - DUN DUN DUN DUN
  - Headache
  - Double vision
  - Lightheadedness
  - Nose bleeds
  - Anxiety
  - Palpitations
  - Sweating
  - Increased urine output
  - Weakness
  - Hematuria
  - Retinal changes
  - Hyperemic ears and mucous membranes
  - Hyperemic conjunctiva
  - Subconjunctival bleed

Approaches to Hypertension Treatment

- Inhibit Sympathetic impulses
  - Inhibit Cardiac contractility and heart rate
  - Inhibit vasoconstriction
- Inhibit RAAS
- Inhibit vasoconstriction
- Inhibit Renal retention of water

Antihypertensive Classes

- Diuretics – Inhibit Renal Retention
- Beta blockers – inhibit heart sympathetic
- Alpha-1 blockers – inhibit artery sympathetic
- Alpha-2 agonist – inhibit both sympathetic
- Calcium channel blockers – inhibit cardiac and/or arterial muscle constriction
- ACE inhibitors – inhibit RAAS
- ARBs – inhibit RAAS
- Direct vasodilators – self explanatory