Cardiac Hemodynamics – Part 1

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Review of CO

Cardiac output – the volume of blood pumped each minute by each ventricle

Cardiac output = stroke volume X heart rate

- Average heart rate = 70 bpm
- Average stroke volume = 70−80 ml/beat
- Average cardiac output = 5,500 ml/minute

Regulation of Cardiac Rate

- Spontaneous depolarization occurs at SA node when HCN channels open, allowing Na^+ in.
    - Open due to hyperpolarization at the end of the preceding action potential
    - Sympathetic norepinephrine and adrenal epinephrine keep HCN channels open, increasing heart rate.
    - Parasympathetic acetylcholine opens K^+ channels, slowing heart rate.
    - Controlled by cardiac center of medulla oblongata that is affected by higher brain centers

Regulation of Cardiac Rate

- Actual pace comes from the net affect of these antagonistic influences
    - Positive chronotropic effect – increases rate
    - Negative chronotropic effect – decreases rate

Regulation of Stroke Volume

- Regulated by three variables:
    - End diastolic volume (EDV): volume of blood in the ventricles at the end of diastole
        - Sometimes called preload
        - Stroke volume increases with increased EDV.
    - Total peripheral resistance: Frictional resistance in the arteries
        - Inversely related to stroke volume
        - Called afterload
    - Contractility: strength of ventricular contraction
        - Stroke volume increases with contractility.
        - Normally, about 60% -70% of the EDV is ejected – ejection fraction

Frank-Starling Law of the Heart

- Increased EDV results in increased contractility and thus increased stroke volume.

Intrinsic Control of Contraction Strength

- Due to myocardial stretch
    - Increased EDV stretches the myocardium, which increases contraction strength.
    - Due to increased myosin and actin overlap and increased sensitivity to Ca^{2+} in cardiac muscle cells
- Adjustment for rise in peripheral resistance
    - Increased peripheral resistance will decrease stroke volume
    - More blood remains in the ventricles, so EDV increases
    - Ventricles are stretched more, so they contract more strongly

Extrinsic Control of Contractility

- Contractility – strength of contraction at any given fiber length
- Sympathetic norepinephrine and adrenal epinephrine (positive inotropic effect) can increase contractility by making more Ca^{2+} available to sarcomeres. Also increases heart rate.
- Parasympathetic acetylcholine (negative chronotropic effect) will decrease heart rate which will increase EDV → increases contraction strength → increases stroke volume, but not enough to compensate for slower rate, so cardiac output decreases

Venous Return

- End diastolic volume is controlled by factors that affect venous return:
    - Total blood volume
    - Venous pressure (driving force for blood return)
- Veins have high compliance - stretch more at a given pressure than arteries (veins have thinner walls).
- Veins are capacitance vessels – 2/3 of the total blood volume is in veins
- They hold more blood than arteries but maintain lower pressure.

Factors in Venous Return

- Pressure difference between arteries and veins (about 10mm Hg)
- Pressure difference in venous system - highest pressure in venules vs. lowest pressure in venae cavae into the right atrium (0mm Hg)
- Sympathetic nerve activity to stimulate smooth muscle contraction and lower compliance
- Skeletal muscle pumps
- Pressure difference between abdominal and thoracic cavities (respiration)
- Blood volume

Blood Volume

Body Water Distribution

- 2/3 of our body water is found in the cells (intracellular).
- Of the remaining, 80% exists in interstitial spaces and 20% is in the blood plasma (extracellular).
- Osmotic forces control the movement of water between the interstitial spaces and the capillaries, affecting blood volume.
- Urine formation and water intake (drinking) also play a role in blood volume.
- Fluid is always circulating in a state of dynamic equilibrium

Tissue/Capillary Fluid Exchange

- Net filtration pressure is the hydrostatic pressure of the blood in the capillaries minus the hydrostatic pressure of the fluid outside the capillaries
    - Hydrostatic pressure at arteriole end is 37 mmHg and at the venule end is 17 mmHg
    - Hydrostatic pressure of interstitial fluid is 1 mmHg
    - Net filtration pressure is 36 mmHg at arteriole end and 16 mmHg at venule end

Colloid Osmotic Pressure (COP)

- Due to proteins dissolved in fluid
- Blood plasma has higher colloid osmotic pressure than interstitial fluid. This difference is called oncotic pressure.
    - Oncotic pressure = 25 mmHg
    - This favors the movement of fluid into the capillaries.

Edema

- Excessive accumulations of interstitial fluids
- May be the result of:
    - High arterial blood pressure
    - Venous obstruction
    - Leakage of plasma proteins into interstitial space
    - Myxedema (excessive production of mucin in extracellular spaces caused by hypothyroidism)
    - Decreased plasma protein concentration
    - Obstruction of lymphatic drainage

Regulation of Blood Volume by Kidneys

- The formation of urine begins with filtration of fluid through capillaries in the kidneys called glomeruli.
    - 180 L of filtrate is moved across the glomeruli per day, yet only about 1.5 L is actually removed as urine. The rest is reabsorbed into the blood.
    - The amount of fluid reabsorbed is controlled by several hormones and the sympathetic nervous system in response to the body's needs.

Role of the sympathetic nervous system

- Increased blood volume in the atria stimulates stretch receptors that leads to increased sympathetic stimulation to the heart and decreased stimulation to the kidneys
- Kidney arterioles dilate, increasing blood flow and increases urine production that will decrease blood volume

Antidiuretic Hormone (ADH or vasopressin)

- Produced by the hypothalamus and released from the posterior pituitary when osmoreceptors detect increased plasma osmolality.
- Plasma osmolarity can increase due to excessive salt intake or dehydration.
- Increased plasma osmolarity also increases thirst.
- ADH stimulates water reabsorption.
- Increased water intake and decreased urine formation increase blood volume.
- Blood becomes dilute, and ADH is no longer released.
- Stretch receptors in left atrium, carotid sinus, and aortic arch also inhibit ADH release.
- Stretch receptors in the atria also stimulated the release of atrial natriuretic peptide which increases excretion of salt and water from kidneys to reduce blood volume.

Regulation by Aldosterone

- Secreted by adrenal cortex *indirectly* when blood volume and pressure are reduced
    - Stimulates reabsorption of salt and water in kidneys
    - Does not change blood osmolality since both salt and water are involved
    - Regulated by renin-angiotensin-aldosterone system

Renin-angiotensin-aldosterone system

- When blood pressure is low, cells in the kidneys (juxtaglomerular apparatus) secrete the enzyme renin
    - Angiotensinogen is converted to angiotensin I by renin
    - Angiotensin I is converted to angiotensin II by ACE enzyme.
- Angiotensin II has many effects that result in a raise in blood pressure:
    - Vasoconstriction of small arteries and arterioles to increase peripheral resistance
    - Stimulates thirst center in hypothalamus
    - Stimulates production of aldosterone in adrenal cortex
- Can also work the opposite direction to reduce blood pressure

Renin

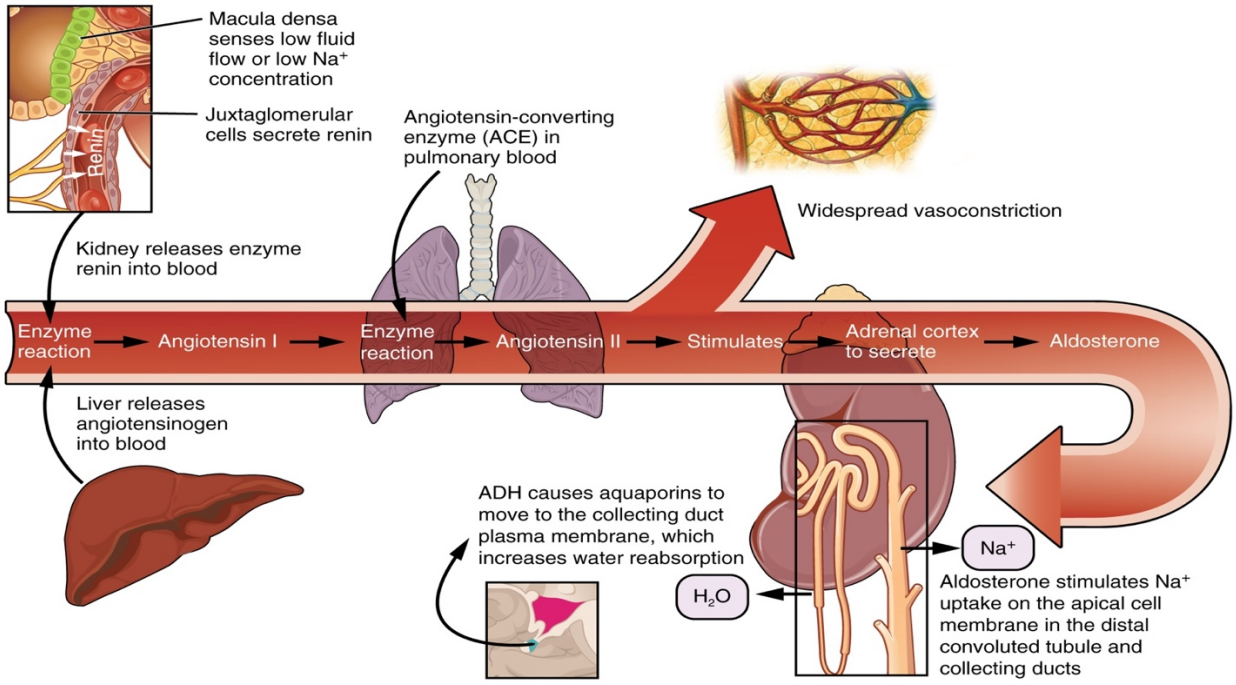
- Synthesized by and released from the juxtaglomerular cells (modified smooth muscle cells) of the renal afferent arteriole
- Release controlled by
    - renal arterial/arteriolar hydrostatic pressure: P ⇓ ⇒ renin ⇑; mechanism: decreased stretch of afferent arteriole granular cells
    - renal sodium at the distal tubule macula densa: Na+ ⇓ ⇒ renin ⇑
    - renal sympathetic activation ⇒ renin ⇑, due to:
        - fall in "central venous pressure", as mediated by the low-pressure (atrial & venous) baroreceptors; very sensitive
        - decrease in systemic arterial pressure; mediated by carotid and aortic baroreceptors; less sensitive
- Action: conversion of Angiotensinogen to Angiotensin I

Angiotensin

- Angiotensin-I is converted to Angiotensin II (A-II) in the presence of Angiotensin Converting Enzyme (ACE), an enzyme which is present in the capillary endothelium, especially in the pulmonary circulation

Actions of Angiotensin-II

- Powerful vasoconstriction, which increases blood pressure
- It increases cardiac output, which increases blood pressure
- Causes release of Aldosterone from the adrenal cortex.
    - Makes you thirsty to drink more water which increases blood volume



Atrial Natriuretic Peptide

- Also called atrial natriureticfactor (ANF), atrial natriuretic hormone (ANH), cardionatrine, cardiodilatin (CDD), or atriopeptin.
- Is a powerful vasodilator secreted by heart muscle cells.
- The main function of ANP is causing a reduction in expanded extracellular fluid (ECF) volume by increasing renal sodium excretion.
- Controlled by atrial stretch, when atrial (or "central venous pressure") increases.

Regulation by atrial natriuretic peptide

- Produced by the atria of the heart when stretch is detected from high volume or increased venous return
- Promotes salt and water excretion in urine in response to increased blood volume
- Inhibits ADH secretion
- Antagonist of aldosterone

Vascular Resistance to Blood Flow

Blood Flow to the Organs

- Cardiac output is distributed unequally to different organs due to unequal resistance to blood flow through the organs.

Physical Laws Describing Blood Flow

- Blood flows from a region of higher pressure to a region of lower pressure.
- The rate of blood flow is proportional to the differences in pressure.

Total Peripheral Resistance

- The sum of all vascular resistance in systemic circulation
- Blood flow to organs runs parallel to each other, so a change in resistance within one organ does not affect another.
- Vasodilation in a large organ may decrease total peripheral resistance and mean arterial pressure.
- Increased cardiac output and vasoconstriction elsewhere make up for this.

Extrinsic Regulation of Blood Flow

- Autonomic and endocrine control of blood flow
    - Sympathetic nerves
        - Increase in cardiac output and increase total peripheral resistance through release of norepinephrine onto smooth muscles of arterioles in the viscera and skin to stimulate vasoconstriction (alpha-adrenergic).
        - Acetylcholine is released onto skeletal muscles, resulting in increased vasodilation to these tissues (cholinergic)

Sympathetic Nerves

- Adrenal epinephrine stimulates beta-adrenergic receptors for vasodilation
- During "flight or fight", blood is diverted to skeletal muscles

Extrinsic Regulation of Blood Flow

- Parasympathetic nerves (cholinergic)
    - Acetylcholine stimulates vasodilation.
    - Limited to digestive tract, external genitalia, and salivary glands
    - Less important in controlling total peripheral resistance due to limited influence

Paracrine Regulation of Blood Flow

- Molecules produced by one tissue control another tissue within the same organ.
    - Example: The tunica interna produces signals to influence smooth muscle activity in the tunica media.
- Smooth muscle relaxation influenced by bradykinin, nitric oxide, and prostaglandin I_2 to produce vasodilation
- Endothelin-1 stimulates smooth muscle contraction to produce vasoconstriction and raise total peripheral resistance.

Intrinsic Regulation of Blood Flow

- Used by some organs (brain and kidneys) to promote constant blood flow when there is fluctuation of blood pressure; also called autoregulation.
- Myogenic control mechanisms: Vascular smooth muscle responds to changes in arterial blood pressure.

Myogenic Reflex

- When the BP increases, it stimulates stretch receptors
- When the stretch receptors stretch, it opens mechanical gated Ca++ channels.
- This causes an AP and smooth muscle contraction

Metabolic Control Mechanisms

- Local vasodilation is controlled by changes in:
    - Decreased oxygen concentrations due to increased metabolism
    - Increased carbon dioxide concentrations
    - Decreased tissue pH (due to CO_2, lactic oxide, etc.)
    - Release of K^+ and paracrine signals

Intrinsic Regulation of Blood Flow

- Reactive hyperemia – constriction causes build-up of metabolic wastes which will then cause vasodilation (reddish skin)
- Active hyperemia – increased blood flow during increased metabolism (reddish skin)

Blood Flow to the Heart and Skeletal Muscles

Aerobic Requirements of the Heart

- The coronary arteries supply blood to a massive number of capillaries (2,500–4,000 per cubic mm tissue).
    - Unlike most organs, blood flow is restricted during systole. Cardiac tissue therefore has myoglobin to store oxygen during diastole to be released in systole.
    - Cardiac tissue also has lots of mitochondria and respiratory enzymes, thus is metabolically very active.
- Large amounts of ATPase are produced from the aerobic respiration of fatty acids, glucose, and lactate.
- During exercise, the coronary arteries increase blood flow from 80 ml to 400 ml/ minute/100 g tissue.

Regulation of Coronary Blood Flow

- Norepinephrine from sympathetic nerve fibers (alpha-adrenergic) stimulates vasoconstriction, raising vascular resistance at rest.
- Adrenal epinephrine (beta-adrenergic) stimulates vasodilation and thus decreases vascular resistance during exercise.
- Vasodilation is enhanced by intrinsic metabolic control mechanisms – increased CO_2, K^+, paracrine regulators

Exercise training

- Increased density of coronary arterioles and capillaries
- Increased production of NO to promote vasodilation
- Decreased compression of coronary arteries during systole due to lower cardiac rate

Regulation of Blood Flow Through Skeletal Muscles

- Arterioles have high vascular resistance at rest due to alpha-adrenergic sympathetic stimulation
    - Even at rest, skeletal muscles still receive 20−25% of the body's blood supply.
- Blood flow does decrease during contraction and can stop completely beyond 70% of maximum contraction.
- Vasodilation is stimulated by both adrenal epinephrine and sympathetic acetylcholine.
- Intrinsic metabolic controls enhance vasodilation during exercise

Circulatory Changes During Dynamic Exercise

- Vascular resistance through skeletal and cardiac muscles decreases due to:
    - Increased cardiac output
    - Metabolic vasodilation
    - Diversion of blood away from viscera and skin
- Blood flow to brain increases a small amount with moderate exercise and decreases a small amount during intense exercise.
- Cardiac output can increase 5X due to increased cardiac rate.
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Circulatory Changes During Dynamic Exercise - continued

- Stroke volume can increase some due to increased venous return from skeletal muscle pumps and respiratory movements
- Ejection fraction increases due to increased contractility

Endurance Training

- Lower resting cardiac rate due to greater inhibition of the SA node
- Increase in stroke volume because of the increase in blood volume
- Improved O_2 delivery

Blood Flow to the Brain and Skin

Cerebral Circulation

- Cerebral flow primarily controlled by intrinsic mechanisms and is relatively constant; the brain cannot tolerate much variation in blood flow.
- Cutaneous flow primarily controlled by extrinsic mechanisms and shows the most variation; can handle low rates of blood flow
- Held constant at about 750 mL/min flow
- Unless mean arterial pressure becomes very high, there is little sympathetic control of blood flow to the brain.
    - At high pressure, vasoconstriction occurs to protect small vessels from damage and stroke.

Myogenic Regulation

- When blood pressure falls, cerebral vessels automatically dilate.
- When blood pressure rises, cerebral vessels automatically constrict.
- Decreased pH of cerebrospinal fluid (buildup of CO_2) causes arteriole dilation.
- Increased pH of cerebrospinal fluid (drop in CO_2) causes constriction of vessels.

Metabolic Regulation

- The most active regions of the brain must receive increased blood flow (hyperemia) due to arteriole sensitivity to metabolic changes.
- Active neurons release K+, adenosine, NO, and other chemical that cause vasodilation
- Astrocytes may play a role

Cutaneous Blood Flow

- The skin can tolerate the greatest fluctuations in blood flow.
- The skin helps control body temperature in a changing environment by regulating blood flow = thermoregulation.
    - Increased blood flow to capillaries in the skin releases heat when body temperature increases.
    - Sweat is also produced to aid in heat loss.
    - Bradykinins in the sweat glands also stimulate vasodilation in the skin.
- Vasoconstriction of arterioles keeps heat in the body when ambient temperatures are low.
- This is aided by arteriovenous anastomoses, which shunt blood from arterioles directly to venules.
    - Cold temperatures activate sympathetic vasoconstriction.
    - This is tolerated due to decreased metabolic activity in the skin.
- At average ambient temperatures, vascular resistance in the skin is high, and blood flow is low.
- Sympathetic stimulation reduces blood flow further.
    - With continuous exercise, the need to regulate body temperature overrides this, and vasodilation occurs.
- Sympathetic Stimulation
    - May result in lowered total peripheral resistance if not for increased cardiac output
    - However, if a person exercises in very hot weather, he or she may experience extreme drops in blood pressure after reduced cardiac output.
    - This condition can be very dangerous.
- Emotions can affect sympathetic activity and cause pallor or blushing