Circulatory System and Disorders

Course 7-8

Regulation of Arterial Blood Pressure I-II

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Nervous Control of the Heart

Nervous Control of the Heart Rate

- Both parts of autonomous nervous system innervate SA node.
  - Sym. stimulation enhances **(+) chronotropy.**
  - Para. stimulation inhibits **(-) chronotropy.**
- Parasympathetic tonus is predominant.
- Atropine vs. Propanolol

Nervous Control of the Heart

Nervous Control of the Contractility

- Sym. stimulation increases contractility. **(+) inotropy**

- Para. stimulation **slightly** decreases contractility*. **(-) inotropy**

** Parasympathetic innervation of ventricles are very weak so the effect on contractility is weak.*

Vagus (Vagal) Escape

- Can vagal stimulation stop the heart?
- The vagal fibers are distributed mainly to the atria and not much to the ventricles.
- **Vagal escape (Vagus escape)**

Nervous Control of the Heart

Nervous Control of the AV node

- Para. stimulation decreases the conduction rate of the **(-) dromotropic effect**.
- If the vagal stimulation is too intense it may block the AV node.
- Sym. stimulation has **(+) dromotropic effect**.

Nervous Control of the Heart

Nervous Control of the Vascularite

- Almost all vessels **except capillaries** innervated by sympathetic nerve fibers.
- Innervation of **small arteries** and **arterioles** allows sympathetic stimulation to increase total peripheral resistance.
- Vasoconstrictor effect is especially powerful in the **kidneys**, **intestines**, **spleen** and **skin**, but it is much less potent in **skeletal muscle** and **brain**.
- Innervation of the **veins** makes is possible to push blood into circulation. Venous return ↑

Vasomotor Center

- Certain important areas in vasomotor center is identified:

1. A ***vasoconstrictor area*** located bilaterally in the anterolateral portions of the upper medulla.
   - They excite the preganglionic vasoconstrictor neurons of the sypmpathetic nervous system.
2. A ***vasodilator area*** located bilaterally in the anterolateral portions of the lower half of the medulla.
   - They inhibit the vasoconstrictor activity of this area, thus causing vasodilation.
3. A ***sensory area*** located bilaterally in the «*nucleus tractus solitarius*» in the posterolateral portions of the medulla and lower pons.
   - The neurons of this area receive sensory nerve signals from the circulatory system mainly through the ***vagus*** and ***glossopharyngeal nerves*.**

Vasomotor Center

- Vasomotor center is controlled by higher centers such as hypothalamus and cerebral cortex.
- Under normal conditions;
  - Vasomotor center transmits signals continuously to the sympathetic vasoconstrictor nerve fibers over the entire body.
  - This continual firing is called ***sympathetic vasoconstrictor tone.***
  - These impulses normally maintain a partial state of contraction in the blood vessels, called ***vasomotor tone.***

*Effect of total spinal anesthesia on the arterial pressure, showing marked decrease in pressure resulting from loss of "**vasomotor tone**."*

Vasomotor Center

Nerve-endings (Almost entirely NE)

- **Norepinephrine (NE)** binds *alpha adrenergic receptors* of the vascular smooth muscle and cause vasoconstriction.

Adrenal Medulla (Mostly Adrenaline)

- Adrenaline is mostly vasoconstrictor but in a few tissues causes vasodilation (β-adrenergic receptors).

Nervous Control of ABP

- One of the most important functions of nervous control of the circulation is its capability to cause rapid increases in arterial pressure.
- Nervous control is the most rapid mechanism.
- To increase blood pressure:
  1. Constriction of arterioles
  2. Constriction of veins
  3. Heart is stimulated

Baroreceptors

- «**Baro**» means pressure. Baroreceptors are sensitive to pressure changes.

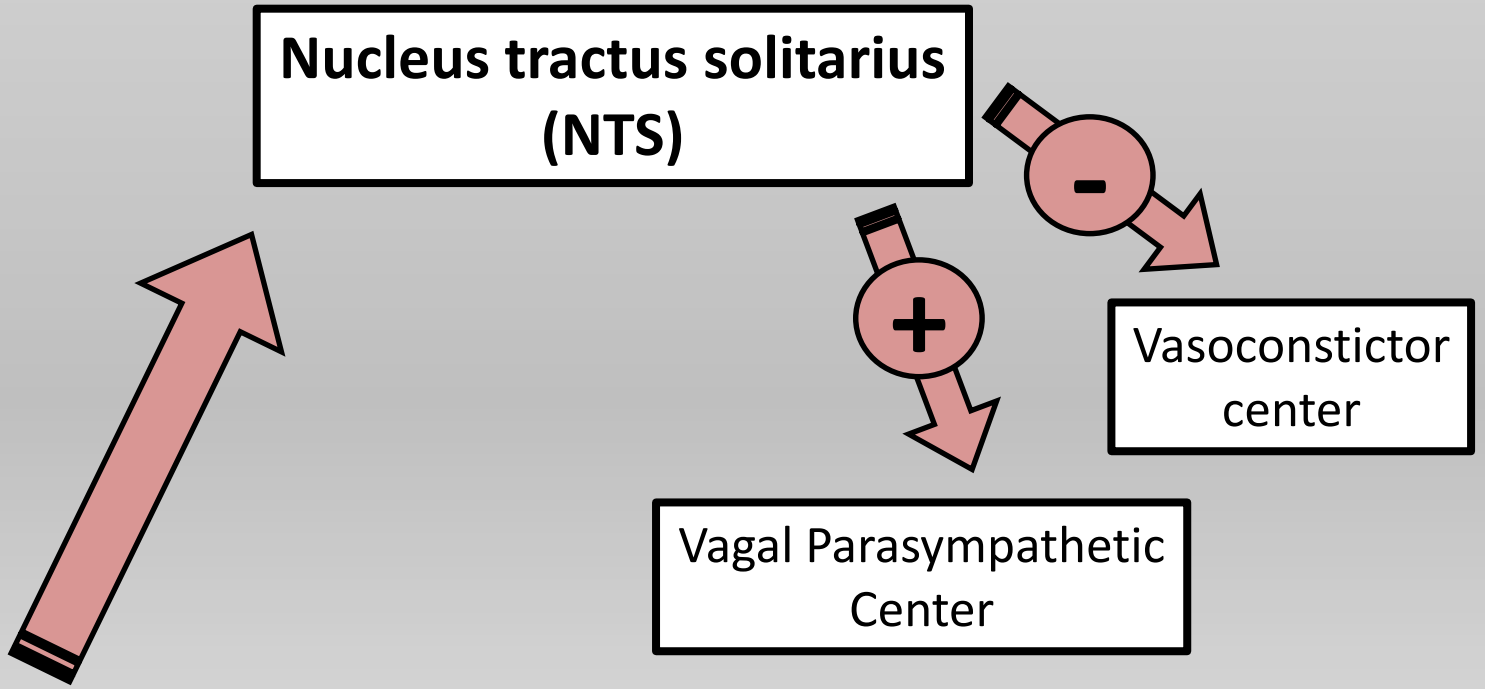
- Baroreceptros are spray-type nerve endings that lie in the walls of the arteries. They are stimulated when stretched.

- Baroreceptors exteremly abundant in:
  1. The wall of each internal carotid artery slightly above carotid bifurcation an area known as **carotid sinus**
  2. The wall of the **aortic arch**

Baroreceptor Reflex

- **«Baroreceptor reflex»** is the best known mechanism for arterial pressure control.
- A rise in arterial pressure stretches the baroreceptors and causes them to transmit signals to CNS. «Feedback signals»
- Signal transduction:
  - Carotid baroreceptors → Hering's nerve → Glossopharyngeus → NTS
  - Aortic baroreceptors → Vagus nerve→ NTS

Baroreceptor Reflex



Blood pressure is **HIGH**
Baroreceptor discharge is **increased**

Net effect:

1. Vasodilation of the veins and arteroles
2. Decreased heart rate and contractility

Baroreceptor Reflex

- The baroreceptors respond **rapidly** to the changes in arterial pressure.
  - They even respond to systole – diastole changes
  - Lying down – standing up changes (posture changes)
- They respond much more to rapidly changing pressure than to a stationary pressure (**Adaptation**)

Pressure **“Buffer”** Function of the Baroreceptor Control System.

Because the baroreceptor system opposes either increases or decreases in arterial pressure, it is called a *pressure buffer system*

Carotid Sinus Massage

The carotid sinus reflex can be activated by rubbing the neck over the carotid sinus.

Baroreceptor Reflex

- Baroreceptors tend to **reset** in 1-2 days to the pressure level to which they are exposed.
- So they are **irrelevant** in long-term control of arterial blood pressure.

Chemoreceptors

- Chemoreceptor = chemo-sensitive cells
- They are sensitive to low O_2 and CO_2 excess and hydrogen ion (pH) excess.
- **Carotid and Aortic bodies** → Hering's nerve → Vagus → Vasomotor Center
- Stimulation of chemoreceptors elevates arterial pressure

Atrial and Pulmonary Artery Reflexes

- Both **atria** and **pulmonary arteries** have in their walls stretch receptors called **«low pressure receptors».**
- They play important role in minimizing arterial pressure changes in response to changes in blood volume
- Sudden, 300 ml blood infusion;
  - All receptors intact pressure rises 15 mmHg
  - Atrerial baroreceptors X pressure rises 40 mmHg
  - Low pressure rec. X pressure rises 100 mmHg

Atrial Reflex Control of the Heart Rate

- Both atria have stretch receptors.
- Atrial stretch causes
  - Increased discharge in SA Node (15%)
  - Bainbridge Reflex (40-60%)
- This reflex helps prevent damming of blood in the veins, atria and pulmonary circulation.

CNS Ischemic Response

- In the event of **cerebral ischemia** blood flow to vasomotor center is lowered and vasomotor center respond directly to the ischemia and become **strongly excited.**
- When this excitation occurs, the systemic arterial pressure often rises to a level as high as the heart can possibly pump.
- The ischemic effect on vasomotor activity can elevate the mean arterial pressure dramatically, sometimes to as high as 250 mm Hg for as long as 10 minutes.
- *The CNS ischemic response is one of the **most powerful** of all the activators of the sympathetic vasoconstrictor system.*

Cushing Reaction

- *Cushing reaction* results from increased pressure of the cerebrospinal fluid around the brain in the cranial vault.
- This action initiates a CNS ischemic response that causes the arterial pressure to rise.
- The Cushing reaction helps protect vital centers of the brain from loss of nutrition if the cerebrospinal fluid pressure ever rises high enough to compress the cerebral arteries

Tissue Blood Flow

- Most tissues have the ability to control their own local blood flow in proportion to their specific metabolic needs.

- Some of the specific needs of the tissues for blood flow include the following:
  1. Delivery of oxygen to the tissues.
  2. Delivery of other nutrients such as glucose, amino acids, and fatty acids.
  3. Removal of carbon dioxide from the tissues.
  4. Removal of hydrogen ions from the tissues.
  5. Maintenance of proper concentrations of ions in the tissues.
  6. Transport of various hormones and other substances to the different tissues.

Blood flow to different organs and tissues under «**basal conditions**»

Control of Tissue Blood Flow

- Continously providing large volumes of blood to every tissue whether they need or not is **IMPOSSIBLE!**
- Such a mechanism would require many times more blood flow than the heart can pump.
- Blood flow to each tissue usually is regulated at the minimal level that will supply the tissue's requirements—**no more, no less**.

Mechanisms for Blood Flow Control

- Local blood flow control can be divided into two phases:
  1. Acute control
  2. Long-term control

- ***Acute control*** is achieved by rapid changes in local vasodilation or vasoconstriction of the arterioles, metarterioles, and precapillary sphincters (seconds to minutes).

- ***Long-term control*** means slow, controlled changes in flow over a period of days, weeks, or even months

Acute Control

- Whenever the availability of oxygen to the tissues **decreases**, the blood flow through the tissues increases markedly.

- Two main theories have been proposed for underlying mechanism:
  - The vasodilator theory
  - The oxygen demand theory

Vasodilator Theory

- Rate of metabolism ↑= Tissue oxygen ↓ **OR** some other nutrients ↓
  - In result, the rate of formation of ***vasodilator substances*** in the tissue cells increases.
  - The vasodilator substances diffuse through the tissues to the precapillary sphincters, metarterioles, and arterioles to cause dilation.
- Some of the different vasodilator substances that have been suggested:
  - *Adenosine, carbon dioxide, adenosine phosphate compounds, histamine, potassium ions,* and *hydrogen ions.*

Vasodilator Theory

- Some vasodilator substances may be released from the tissue in response to oxygen deficiency. **(Adenosine=especially in heart)**

- Some vasodilator substances, tend to increase in when cell metabolism is suddenly increased (carbon dioxide, lactic acid, and potassium ions).

Oxygen Demand Theory

- *Oxygen demand theory* or, more accurately, the ***nutrient demand theory*** (because other nutrients besides oxygen are involved).
- Oxygen is one of the metabolic nutrients required to cause vascular muscle contraction (with other nutrients required as well).
- Therefore, in the absence of adequate oxygen, it is reasonable to believe that the blood vessels would relax and therefore dilate.

Vasomotion

- The precapillary sphincters are normally either completely open or completely closed.
- The number of precapillary sphincters that are open at any given time is roughly proportional to the requirements of the tissue for nutrition.
- The precapillary sphincters and metarterioles open and close cyclically several times per minute, with the duration of the open phases being proportional to the metabolic needs of the tissues for oxygen.
- The cyclical opening and closing is called ***vasomotion.***

Special Tissues

- ***Kidneys***, blood flow control is vested to a great extent in a mechanism called *tubuloglomerular feedback*.

- ***Brain***, in addition to control of blood flow by tissue oxygen concentration, the concentrations of carbon dioxide and hydrogen ions play prominent roles.

- ***Skin***, blood flow control is closely linked to regulation of body temperature.

Endothelial-Derived Factors

- The endothelial cells lining the blood vessels synthesize several substances:
  - *Nitric oxide (NO)*, a lipophilic «**gas**» that is released from healthy endothelial cells.
  - *Endothelin,* a powerful vasoconstrictor released from damaged endothelium.

Nitric Oxide (NO)

- *Endothelial-derived nitric oxide synthase (eNOS) enzymes* synthesize NO.

- NO has a half-life in the blood of only about 6 seconds.

Shear Stress

- The flow of blood through the arteries and arterioles causes *shear stress* on the endothelial cells because of viscous drag of the blood against the vascular walls.
- This stress contorts the endothelial cells in the direction of flow and causes significant increase in NO release.
- NO secretion = healthy endothelium

Endothelin

- *Endothelin*, requires only minute amounts (nanograms) to cause powerful vasoconstriction.
- *Endothelin* greatly increases when the vessels are injured.
- Endothelin induced local vasoconstriction helps to prevent extensive bleeding from arteries as large as 5 millimeters in diameter that might have been torn open by crushing injury.

Long-Term Control

- A key mechanism for long-term local blood flow regulation is to change the amount of **vascularity** of the tissues.
  - If the metabolism in a tissue is increased for a prolonged period, vascularity increases, a process generally called ***angiogenesis***; if the metabolism is decreased, vascularity decreases.

- Oxygen is important for long-term control. Hypoxia induces angiogenesis via **VEGF (vascular endothelial growth factor)**.

Long-Term Control of Arterial Blood Pressure

- **Long-Term** control means weeks or months.
- Long-term control of arterial pressure is closely interwined with homeostasis of body fluid volume.
- The balance between fluid intake and output.

Renal Control

- The renal–body fluid system for arterial pressure control acts slowly but powerfully as follows:

It is the most primitive mechanism:

- If **blood volume** increases and vascular capacitance is not altered, **arterial pressure** will also increase.

- The rising pressure, in turn, causes the kidneys to excrete the excess volume, thus returning the pressure back toward normal.

Renal Control

- An increase in arterial pressure in the human of only a **few mm Hg** can **double** renal output of water, a phenomenon called ***pressure diuresis,*** as well as double the output of salt, which is called ***pressure natriuresis***.

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Intake Parameters

- **Water and salt intake** is added to the graph.
- Long term ABP is determined by:
  (1) Salt-water intake
  (2) Shifting the renal output curve

Chronic Renal Output Curve

Chronic Renal Output Curve is Much Steeper

- Increased pressure
  - Not only has direct hemodynamic effect
  - Also has **indirect effects** mediated by nervous and hormonal system

- When the kidneys are functioning normally, the *chronic renal output curve* is much steeper than the acute curve.

- chronic → acute that create salt sensitivity*

Importance of Salt (NaCl)

- An increase in salt intake is far more likely to elevate the arterial pressure than is an increase in water intake.
- Pure water is normally excreted by kidneys **almost as rapidly as** ingested, but salt cannot be excreted easily.
- As salt accumulates in the body, it also indirectly increases the extracellular fluid volume*
- The amount of salt that accumulates in the body is the main determinant of extracellular fluid volume.

Renin-Angiotensin-Aldosterone System

- **Renin** is synthesized and stored in an inactive form called «**prorenin»** in the **juxtaglomerular cells (JG cells)** of the kidneys.

- When the arterial pressure fall JG cells secrete Renin.
  - Renin itself is an enzyme, not a vasoactive substance.
  - Renin acts enzymatically on ***angiotensinogen***, to release ***angiotensin I*****.**
  - The renin persists in the blood for 30 minutes to 1 hour.

Renin-Angiotensin-Aldosterone System

- Angiotensin I has mild vasoconstrictor properties but not enough to cause significant changes in circulatory function.
- Angiotensin I 

Angiotensin II
- Angiotensin converting enzyme (ACE) converts Angiotensin I to Angiotensin II.
  - This conversion occurs to a great extent in the pulmonary capillaries.

Angiotensin II (AT-II)

- AT-II is an extremely powerful vasoconstrictor.
- Rapidly (1-2 min) inactivated by multiple blood and tissue enzymes **(angiotensinases).**

- AT-II has two principal effects which can elevate arterial pressure:
  1. Vasoconstriction in many areas of the body (rapid) (2 mins*)
  2. Decrease excretion of both salt and water by kidneys (hours-days)

Angiotensin II (AT-II)

- AT II causes the kidneys to retain both salt and water by two major ways:
  1. AT II acts **directly** on the kidneys to cause salt and water retention.
  2. Angiotensin II causes the adrenal glands to secrete **aldosterone**

- Excess amounts of AT II in the circulation set ABP to a point higher than normal.

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First Line of Defense

- Rapidly Acting Pressure Control Mechanisms (seconds – minutes):
  1. The baroreceptor feedback mechanism
  2. the central nervous system ischemic mechanism
  3. the chemoreceptor mechanism

Second Line of Defense

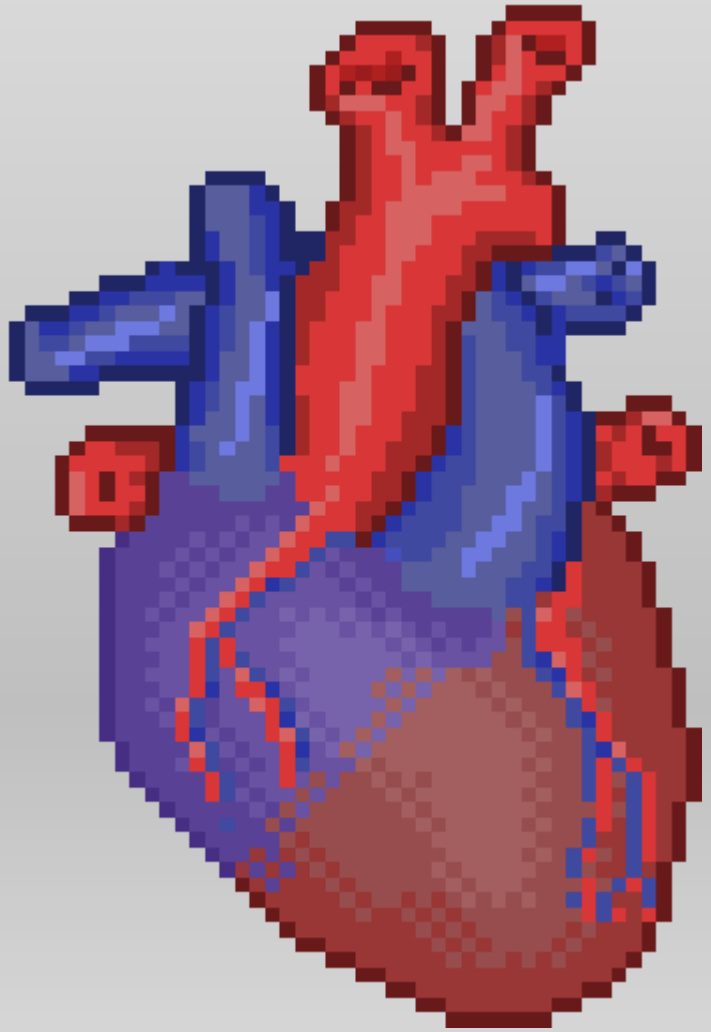
- Pressure Control Mechanisms That Act After Many Minutes:

1. The renin-angiotensin vasoconstrictor mechanism
2. Stress-relaxation mechanism of the vasculature
3. Capillary fluid shift mechanism

Third Line of Defense

- Long-Term Mechanisms for Arterial Pressure Regulation

1. Renal–body fluid pressure control mechanism
2. Renin-Angiotensin-Aldosterone System



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Thank you for your patience!