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Mammalian Physiology II

Lecture Notes

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McGill

McGill Mammalian Physiology II

Lectures (PHGY 210)

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Foreword

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Prerequisites: General Biology I + II, adequate knowledge of general and organic chemistry.

Chapter 1 Pulmonology will cover the all of lectures on respiration spanning from January 8th to 22th, 2024. The topics will revolve about the anatomy and physiology of the lung.

Definition 1.1. The **respiratory system** is a system of organs that perform respiration for an organism. The main organs that mediate this is the *lungs*.

The respiratory system of respiration in general is very important. Its main function is for gas exchange, that is inspire in O_2 into the lung and exchange with CO_2 (produced by oxidative processes of the body) which would be expired out. These 2 molecules are transported in the body through the blood stream hence in this chapter on the respiratory system, there could be some overlap with the cardiovascular system.

1.1 General Anatomy of the Respiratory System

We inspire and expire air through the **nose**. Then air will be filter through the **nasal turbinates** and then move down through pharynx where it can either go to the esophagus or the **larynx** which is where the **vocal cord** is located. After the larynx is the **trachea** that split into the right and left main bronchi. These bronchi the split into smaller bronchi which finally reach the air sac called **alveoli**. These alveolie is covered blood capillary which is where we would be oxygenating blood.

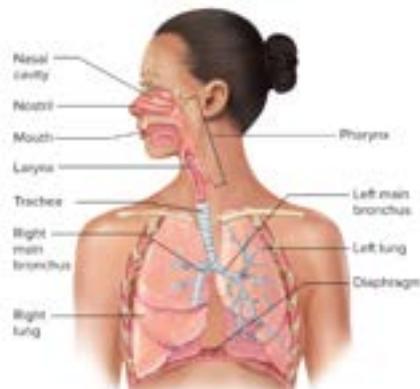


Figure 1.1: Anatomy of the respiratory system.

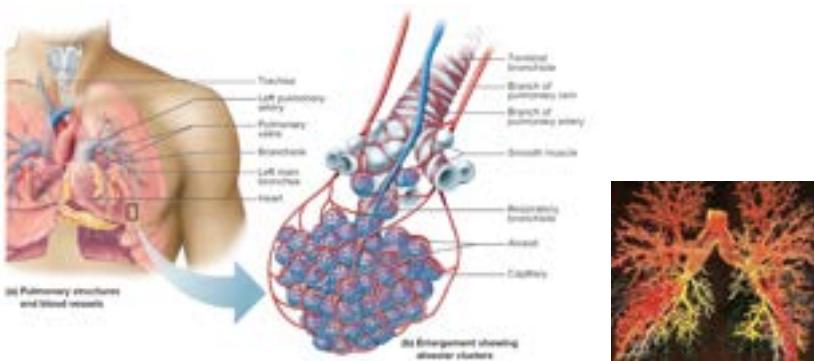


Figure 1.2: Closer look at aveoli and branching of the bronchi "tree".

Upon looking at the entirety of the bronchi's organization, we can see that it has a sort of tree-like pattern as it divides more and more out into smaller branches (see Figure 1.2). This branching effect increases the total surface area for gas exchange.

1.1.1 Pleural Space

The lungs do not inflate on their own but require the diaphragm muscle to enlarge the rib cage. The enlargement of the rib cage will be coupled to the inflation of the lungs via the **pleural space**. The space is made from many layers that is **viseral and parietal pleura**. The layer that attaches to the lung is called the **visceral pleura** while the layer attached to the inner rib is called the **parietal pleura**.

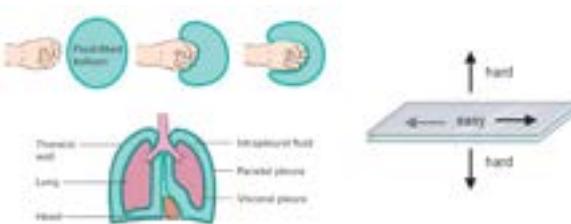


Figure 1.3: Pleural space and glass slide illustration

In the middle of these 2 layers is the intrapleural space filled with **intrapleural fluid** that allow them [the layers] to slide along each other very

easily however when pulling them apart it would be very difficult (think of 2 glass slide with water in the middle).

The typical air pressure at sea level is around 760mmHg and we will call this the reference pressure, for the sake of simplification, it would be $P = 0$. This means under normal condition, the pressure inside the lung would be $P = 0$. Normally, the intrapleural space would have pressure lower than atmospheric i.e. $P < 0$ or specifically $P = -5$. Now the reason why it's negative is hard to understand (for our current level) so we might have to take such number for granted. Although a possible explanation for this is that it helps with lung expansion i.e. because the pressure inside is always negative, it creates an environment that promotes expansion [of the lung] or else the lung would collapse (inherent elastic nature of lung).

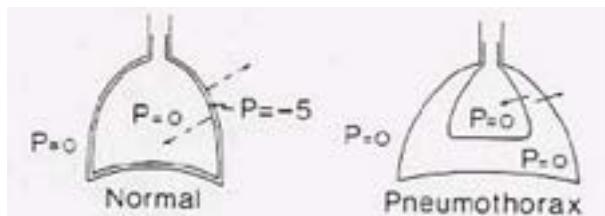


Figure 1.4: Normally, there's a "tug of war" between the elastic nature of lungs to collapse in and its expansion due to low intrapleural pressure. When the intrapleural pressure increases (due to possible puncture), the lung collapses (pneumothorax).

Example 1.1.1. **Pneumothorax** is a condition characterized by the increase of the pleural space's pressure and decrease of lung volume due to possible trauma to the rib cage that allow air come into the pleural space.

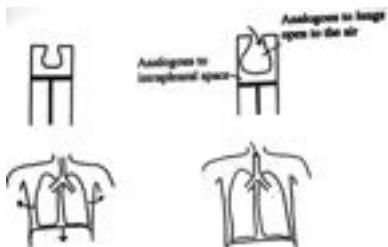


Figure 1.5: Lung expansion analogous to balloon inflating when attached to a syringe. When the plunger (like diaphragm muscle) is pulled down, it creates negative pressure that causes the balloon (like the lungs) to expand.

1.1.2 Conducting and Respiratory Zones

Back to anatomy, the trachea splits into the left and right main bronchi. The right bronchi splits into 3 **lobar bronchi** (indicative for 3 right lobe) while the left splits into 2. They further split into bronchioles until the **terminal bronchioles** where the end of the conducting (airway) zone end and the respiratory zone begins. The main difference between them is that **respiratory zone will begin to have alveoli structure for gas exchange**. The respiratory bronchioles will further split into **alveolar ducts** and finally **alveolar sac**.

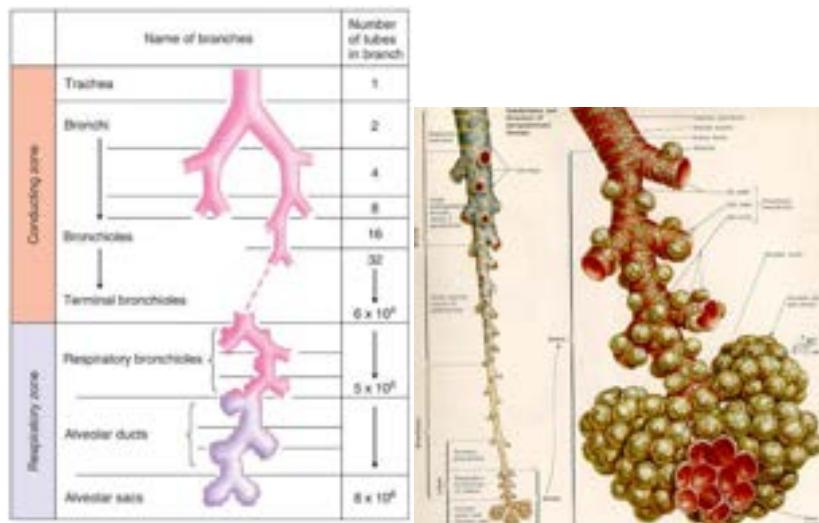


Figure 1.6: Bronchi division and acinus

Upon further inspection, we found that the conducting zone is made from cartilages that are lined with smooth muscle. This smooth muscle isn't there to help with breathing but more to hold the bronchi shape in place. As for the respiratory zone, it is non-cartilage but at the end we can see the alveolar sac bundles together like grapes or berries; and such bundling structure is called **acinus**.

The conducting air ways have many functions:

1. The endothelial lining of the lung release mucus to capture pathogen; and they also have cilia (hair-like projection) that beat upward to

move those mucus to the mouth to either spit out or swallow. This defense mechanism is called **mucociliary defense system**.

Remark 1.1. *These cilia can be temporarily paralyzed because of nicotine. This is also why you tend to see smoker cough up mucus.*

2. It can moisten inhaled air and warm it due to high amount of blood vessel surrounding it.
3. It allows us to produce sounds and talk.
4. Finally its smooth muscle may contract or relax to resist airflow like in the case of asthma.

The respiratory zones on the other hand has its function as a site for gas exchange (oxygenate blood). Furthermore, we have around 300 million alveoli each of which can be associated to nearly 1000 capillaries!

1.1.3 Blood Circulation to the Lung

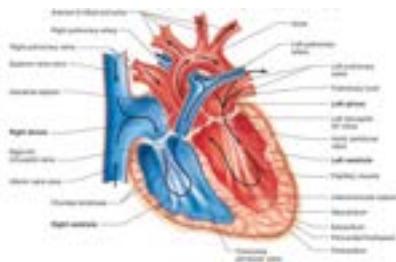


Figure 1.7: Flow of blood through the heart.

then into the ventricles where it will be distributed through the body via the aorta.

To get to the blood circulation of the lung, let's first look at a simple blood circulation from the heart to the lung. First deoxygenated venous blood will flow into the right atrium which then goes to the right ventricle. This deoxygenated blood then flows through the pulmonary artery into the lung where it will be re-oxygenated at the alveoli. Then the oxygenated blood flows back through the pulmonary veins to the right atrium

As for the lung, it has 2 main circulations: **pulmonary and bronchial**. The pulmonary circulation is the typical circulation of deoxygenated blood to the capillaries on the alveoli to the oxygenated then circulate back to the heart. Meanwhile, the bronchial circulation consists of arteries from the aorta to the tracheobronchial tree for oxygenated blood supply.

One thing you may notice is that the **bronchial circulation directly anastomose back to the pulmonary veins** i.e. oxygenated blood from the bronchial circulation becomes deoxygenated blood after supply to the lung is directly poured into the pulmonary veins carrying oxygenated blood ... this is to show our design has imperfection.

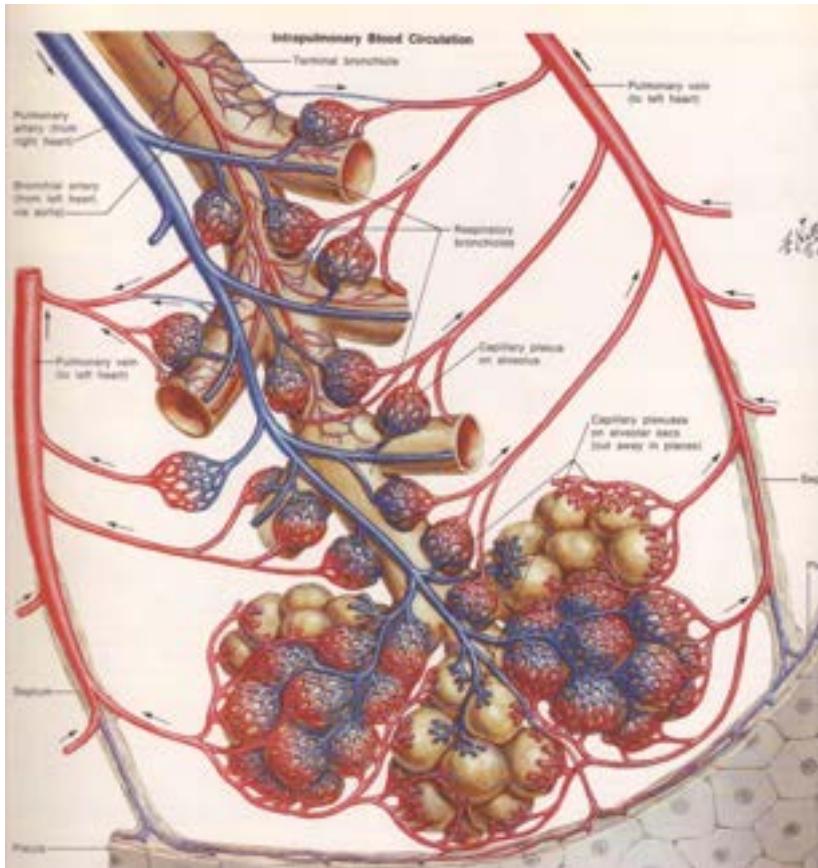


Figure 1.8: Pulmonary and bronchial circulation viewed at the alveolar acinus.

Definition 1.2. **Anastomosis** is the merging or connection of 2 different blood vessels.

1.1.4 Alveolar Cells and Functions

The alveoli is made from 3 types of cells: **epithelial type I and II cells**, **endothelial cells** and **alveolar macrophages**. There are not a lot to be known about epithelial cell type I but we know that type II is important for **surfactant** secretion (will be looked at below). Endothelial cells are the main cells that make up the wall of the pulmonary capillary ($\approx 1\mu m$). Alveolar macrophages are macrophages located in the alveoli that help along with the mucociliary defense system

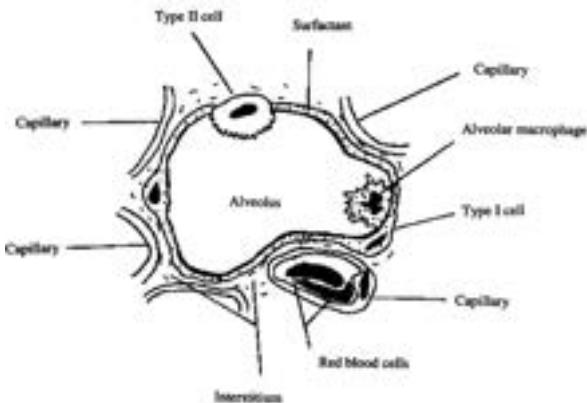


Figure 1.9: Different alveolar cell types.

Surface Tension and Surfactant

Now to talk about surfactant, we need to understand the concept of surface tension.

Definition 1.3. **Surfactant** is the property of the surface of a liquid that allows it to resist an external force, due to the cohesive nature of its molecules

Essentially, surface tension exists at an air-liquid interface due to the strong attraction of water molecule. Surface tension is also the reason a bubble can form: Bubble has an internal environment with air pressure creating an outward force leading to its burst; but the surface tension of the bubble creates an inward force leading to its collapse. The bubble is

thus formed only when the force by the bubble balance out with the internal air pressure.

The reason we need to know about this is because the alveoli are covered with a thin film of liquid (most if not all of the internal environment is like that). The surface tension of this liquid on the alveoli is very strong and their net force lead to a possible collapse of the alveoli. What's worst is that the pressure by surface tension is governed by Laplace's law which tells us that **the smaller the alveolus, the greater the force.**

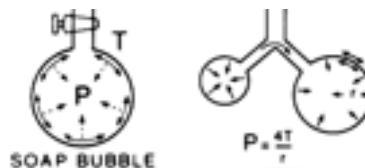


Figure 1.10: Soap bubble illustration and alveolus with Laplace's law,

However fret not since we have type II alveolar cell that secrete surfactant that decreases overall surface tension of this fluid. Pulmonary surfactant prevents the pressure of small alveoli exceeding that of larger alveoli (by having more type II cell in the small alveoli). Not only that, surfactant reduce the surface tension so we can breath or else we won't be able to inflate our lungs.

Remark 1.2. *Babies born prematurely can possibly not produce any surfactant which lead to collapse alveoli hence fatal. But nowadays, we have medication for that before hand.*

1.1.5 Respiratory Muscles

Like we've previously said, the lung are elastic but cannot expand on their own and require the help of muscle and pleural space. We have 2 set of these muscle: **inspiratory and expiratory.**

Principle muscle of inspiration is the **diaphragm**. When the diaphragm contracts, it pull its dome-like shape downward thus increase the area of the rib cage hence allow the lung to expand. There are also **external intercostal muscle** and **parasternal muscle** that when contract pulls up the rib cage and increase its area. Additionally, there are accessory muscles (not

used mainly) for inspiration which is the **sternocleidomastoid muscle** and **scalenus**.

Remark 1.3. *The diaphragm is innervated by the phrenic nerve from cervical segment 3,4 and 5.*

For quiet breathing, the brain simply tell the inspiration muscle to stop contraction for expiration. For heavy breathing, the **abdominal muscle** maybe recruited along with **internal intercostal muscle** that decrease the rib cage area which lead to expiration.

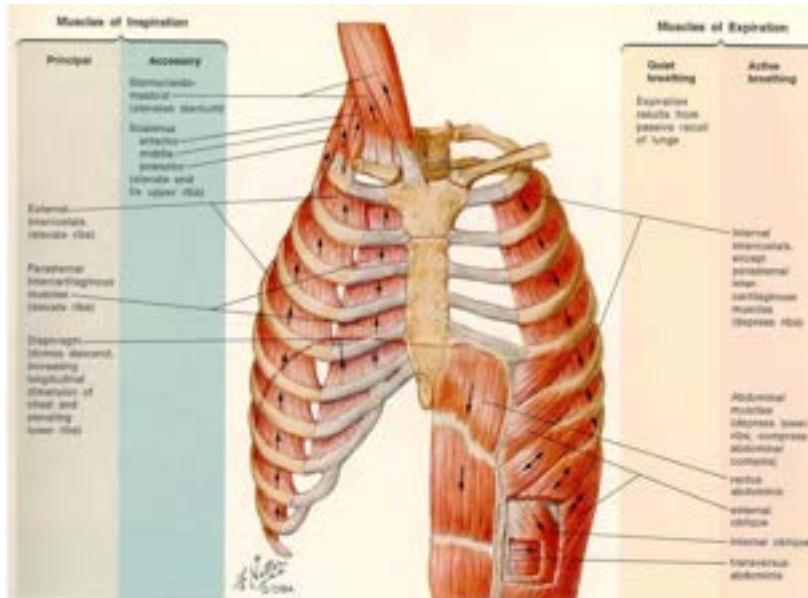


Figure 1.11: Muscles used for respiration.

End of Lecture —

1.2 Lung Mechanics and Alveolar Ventilation

Definition 1.4. **Spirometry** is a common medical test used to measure the lung volumes.

A *spirometer* is simply an upside down canister above water connected to a measuring pen. If the subject breathes out, the air goes up to the canis-

ter which pushes the measuring pend down and the opposite would go up. The volume that a subject breath in or out is called the **tidal volume**.

Remark 1.4. *We do not breath out all of the air of the lung since you need a lot of energy.*

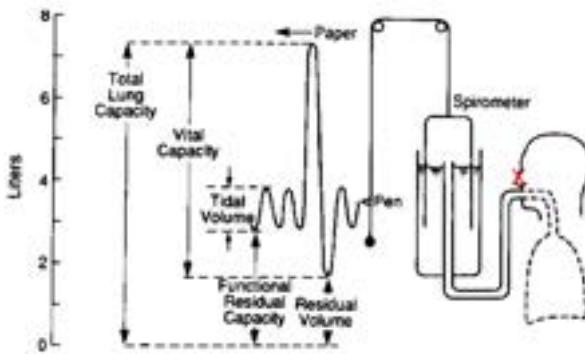


Figure 1.12: Spirometry and different lung volume

The volume of air left after passive exhalation is called **functional residual capacity (FRC)**. If subject takes a deep breath, then the subject will reach **total lung capacity** (the maximum volume that the lung can hold air). If subject exhale as hard as possible, there would still be some air volume left called **residual volume**.

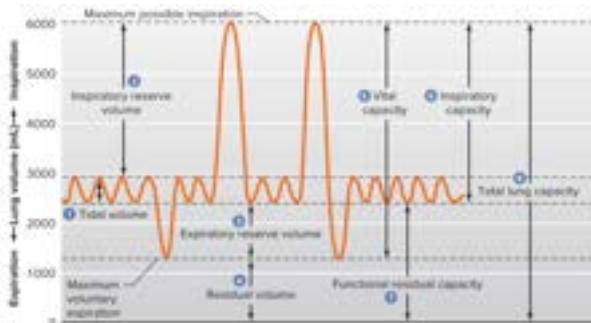


Figure 1.13: More on spirometry

The difference between the total lung volume and residual volume, it

is called the **vital volume**. The difference between the functional residual and residual volume is the **expiratory reserve volume**.

The flaw of spirometer is that it can only measure the breath in and out meaning it cannot measure the total lung capacity, functional residual nor residual capacity.

In order to measure , we us spirometer with helium He dilution. Subject with a nose clip will breath through the spirometer with He with a known concentration C_1 and its volume V_1 in the cannister. The subject will breath out hence reaching FRC then they breath in the He until equilibrium. At this instant, The concentration in of He in the canister changes to C_2 (measurable) and the new volume would be the sum of the canister's volume V_1 and the FRC given as the following equation

$$C_1 V_1 = C_2 (V_1 + \text{FRC}) \quad (1.1)$$

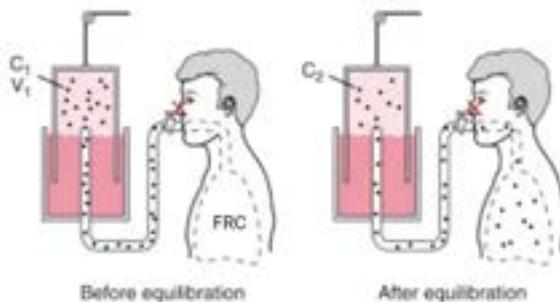


Figure 1.14: Helium diluted spirometry.

Perform some basic algebra and the FRC is given as $\text{FRC} = \frac{C_1 V_1}{C_2} - V_1$.

1.2.1 Ventilation

Sometimes, we need to know how ventilated a person is i.e. how efficient or "good" their breathing is. In order to do this, we measure the **minute ventilation \dot{V}_E** , which is the amount of air inspire every minute. It is calculated as the multiplication of the tidal volume (V_T) and breathing frequency (f , per minute). N.B. The dots represents per min in biology (per sec in physics).

$$\dot{V}_E = V_T \times f \quad (1.2)$$

The number would then allow us to assess whether their breathing properly or not. Nevertheless, need to realize that not all of the air will reach to the respiratory zone for gas exchange. Some of that air is trapped or stay in the conducting airway and they're called **anatomical dead space** and is around 150mL in volume. This dead space is completely normal.

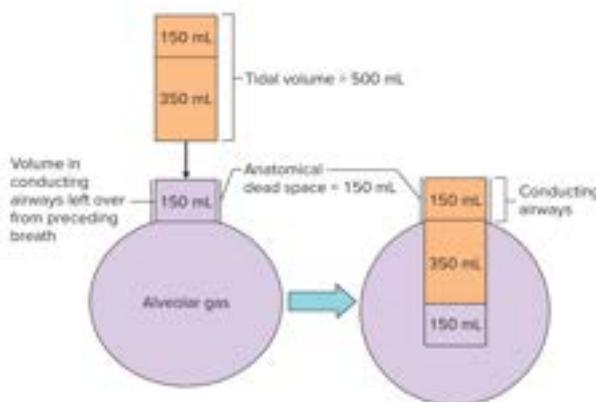


Figure 1.15: Anatomical dead space illustration where 150mL of air will not be used for gas exchange.

The anatomical dead space is hard to measure but in principle, it should be a close magnitude to the person's weight in pound.

Example 1.2.1. A 150lb person will have an anatomical space of roughly 150mL. Which means if they inhale 500mL of air, only 350mL would be used for gas exchange.

Now sometimes, it's best for us to calculate ventilation without the dead space since it does not effect much of physiology. This concept is the the **alveolar ventilation** which is the minute ventilation without the dead-space:

$$\dot{V}_A = (V_T - V_{AD}) \times f \quad (1.3)$$

where \dot{V}_A is the alveolar ventilation and V_{AD} is the anatomical dead space.

Example 1.2.2. A healthy adult male with tidal volume of 500mL, a breathing rate of 12 breaths/min and an anatomical dead space of 150mL, what is his minute and alveolar ventilation?

Answer: Using equation (1.2), the minute ventilation is given as $\dot{V}_E = 6000$ mL/min. The alveolar ventilation can be calculated by equation (1.3) which yield $\dot{V}_A = 4200$ mL/min.

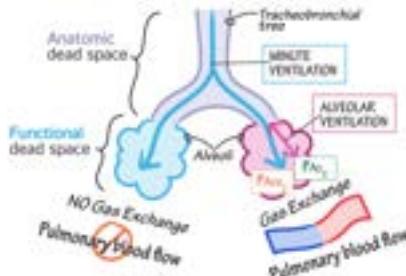


Figure 1.16: Illustration of different dead space type. When there's no gas exchange at an alveolus, then the volume of air in it is called alveolar dead space (which is called functional dead space).

Nevertheless, there are pathological conditions that lead to patient having little to no blood flow through the alveoli. When there's no blood flow through the alveoli then there's no gas exchange hence its air is wasted. Such condition is called **alveolar dead space**.

Finally, to be inclusive of these 2 dead spaces, we call the sum of anatomical and alveolar dead space, **physiological dead space**. Under normal condition (healthy), **physiological dead space is equal to anatomical dead space**.

$$\text{Physiological} = \text{Anatomical} + \text{Alveolar} \quad (1.4)$$

More Terminologies

Before moving on, we need to know that we tend to talk about these gases presence in the body in term of pressure, hence we need to establish some definition on them.

The sum of all pressure in an isolate system (like the air) is the **total pressure**. The **fractional concentration by dry gas x** (F_x) is the fraction in percentage of the gas x in the total gas volume. The **partial pressure of a gas x** (P_x) is the pressure of that gas in the total pressure and is given as

$$P_x = P \cdot F_x \quad P_x = (P - 47\text{mmHg}) \cdot F_x^* \quad (1.5)$$

*Used for a gas with a water vapour pressure of 47mmHg.

Example 1.2.3. the *barometric* pressure is the total pressure of the air we breath and is roughly 760mmHg. The fractional concentration of oxygen in the air is $F_{O_2} = 21\%$ while that of carbon dioxide is $F_{CO_2} = 0.03\%$. The partial pressure of oxygen in the air is thus $P_{O_2} = (760 - 47) \cdot 21\% = 150\text{mmHg}$ while that carbon dioxide is $P_{CO_2} = 0.2\text{mmHg}$.

Remark 1.5. The pressure that we will work with would be higher $P_{O_2} = 160\text{mmHg}$ and $P_{CO_2} = 0.3\text{mmHg}$ but it's almost the same so don't worry.

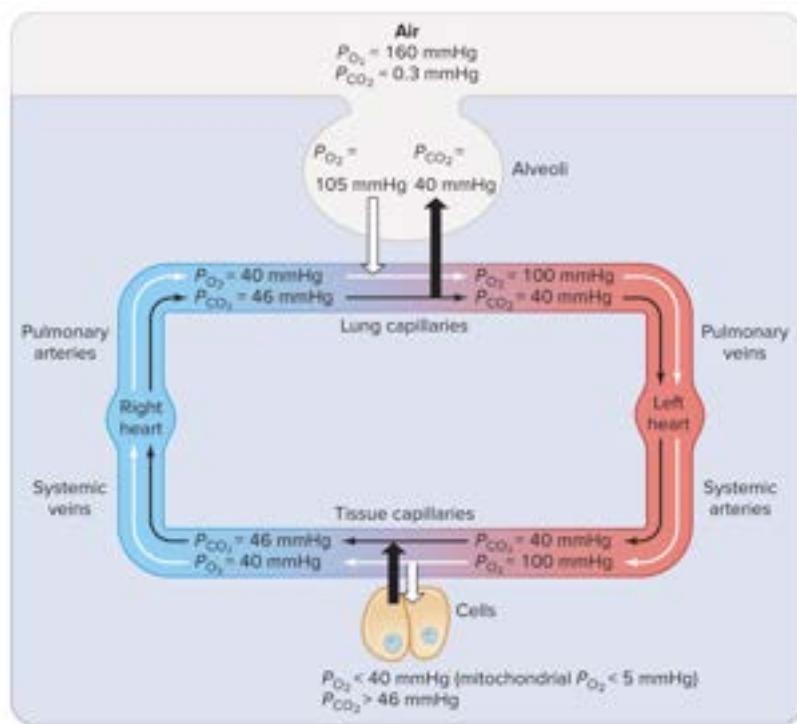


Figure 1.17: Partial pressure of O_2 and CO_2 around the systemic and pulmonary circulation. **THIS FIGURE IS REALLY IMPORTANT!**

Let's look at figure 1.17 and analyze it one by one. We begins with in the alveoli. On average, the P_{O_2} and P_{CO_2} in the lung is 105mmHg and 0.3mmHg respectively. **Why is P_{O_2} less while P_{CO_2} is more?** Well...for O_2 , when you inspire, the air mixed from the previous air and also the new air is instantly used by the pulmonary circulation hence P_{O_2} decreases. For

CO_2 , the pulmonary circulation is constantly removing its CO_2 to the alveoli hence P_{CO_2} increases.

As you breath, O_2 enters while CO_2 leaves your pulmonary circulation. The normal P_{O_2} and P_{CO_2} value in the pulmonary circulation is around 100mmHg and 40mmHg respectively. This blood will be sent to the heart and the system arteries, no change in partial pressure.

Then, the blood reaches the tissues capillaries where the cells are producing lots of CO_2 and consuming lots of O_2 . This causes the partial pressure change in the systemic veins, P_{O_2} and P_{CO_2} are now 40mmHg and 46mmHg respectively. This blood return to the heart and sent back to the pulmonary circulation where gas exchange happens and the cycle restart.

From now you would probably question that wait a minute! **why is that the partial pressure gradient of oxygen is much larger compared to carbon dioxide?** Well...this is what we will see in a few moments but in general, the reason that it happens is because CO_2 is more soluble in blood than O_2 .

Ventilation Types

Now, since we're talking about ventilation, we need to know what is the normal alveolar ventilation. Well, the normal alveolar ventilation level is when you have all the above values or somewhere near it (refers to Figure 1.17). The way our brain keeps this normality is **measuring the arterial CO_2 level**. The alveolar ventilation will keep P_{CO_2} constant at around 40mmHg.

Remark 1.6. *The capital "A" refers to alveolar while a small "a" refers to arterial.*

In **hyperventilation**, there's more O_2 supplied and CO_2 removed than the metabolic requirement. In such situation, P_AO_2 and P_aO_2 would rise while P_ACO_2 and P_aCO_2 would drop.

Remark 1.7. *Hyperventilation does not happen during exercise because during exercise, you're increasing metabolic rate hence you're breathing harder to meet that metabolic requirement.*

During hyperventilation, the level of CO_2 in the body decreases and can lead to the constriction of blood vessels and potentially fainting. This is why we ask hyperventilated individual to breath in a bag so that they can

build back the CO_2 level in the blood.

In **hypoventilation**, the opposite effect is observed. There's now less O_2 supplied and CO_2 removed than the metabolic requirement. In such situation, P_{AO_2} and P_aO_2 would drop while P_{ACO_2} and P_aCO_2 would increase.

Remark 1.8. Hypoventilation can occurs with the following condition: **chronic obstructive lung disease, respiratory muscle damage, rib cage damage and CNS depression.**

TABLE 1.17–6 Effect of Various Conditions on Alveolar Gas Pressures

CONDITION	ALVEOLAR P_{O_2}	ALVEOLAR P_{CO_2}
Breathing air with low P_{O_2}	Decreases	No change*
↓ Alveolar ventilation and unchanged metabolism	Decreases	Decreases
↓ Alveolar ventilation and unchanged metabolism	Decreases	Increases
↑ Metabolism and unchanged alveolar ventilation	Decreases	Increases
↓ Metabolism and unchanged alveolar ventilation	Increases	Decreases
Proportional increases in metabolism and alveolar ventilation	No change	No change

Figure 1.18: Here are some conditions and its effect on the P_{AO_2} and P_{ACO_2} . You can use them as practices.

1.2.2 Gas Diffusion

Definition 1.5. **Diffusion** is the net movement of anything from a higher to a lower concentration (sometimes through a permeable membrane in the context of physiology).

The process of gas exchange occurs due to passive diffusion (by passive meaning no required energy). The diffusion rate D is the speed at which diffusion happens and is governed by Fick's law that is $D \propto$ surface area, partial pressure gradient but inversely proportional to the thickness. Now, the surface area is large ($50 - 100 m^2$) and its alveolar wall is also very thin ($\sim 0.2 nm$) which means that the lung's diffusion rate is high and efficient.

What we realize too is that after reaching through the capillary wall, the gas must diffuse to the plasma of blood, a liquid. To diffuse through a liquid, a gas must be soluble in the liquid and the amount of dissolved gas is dependent on partial pressure.

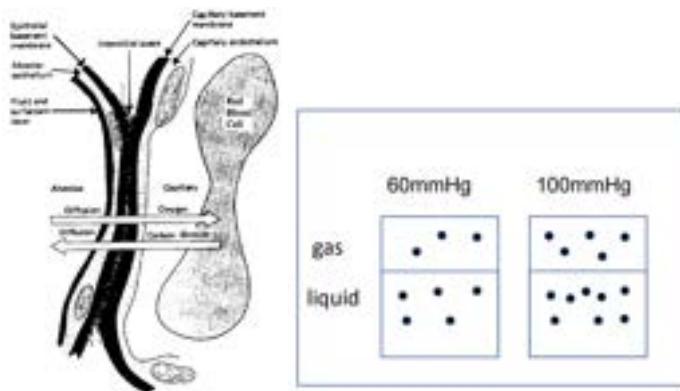


Figure 1.19: Diffusion of O_2 and CO_2 across alveolar-capillary wall (left) and Henry's law (right) which dictates that as partial pressure increase, more gas would be dissolved.

Example 1.2.4. CO_2 is 20 times more soluble in plasma than blood however the pressure gradient of O_2 is 10 times that of CO_2 . So, in the end, their diffusion rate are similar and would reach equilibrium at the same time.

To see that they indeed reaches equilibrium at the same time, we will measure the partial pressure of O_2 and CO_2 of the red blood cell as it passes through the narrow alveolus capillary. At the narrow capillary, the RBC will takes around 0.7s to move across this. Around 0.25, O_2 is completely saturated in the RBC and at the same time CO_2 would be removed. In fact, during exercise, you increase blood and thus the RBC will go through alveolus much faster maybe around 0.3s but that's still enough time to have O_2 fully saturated and CO_2 removed.

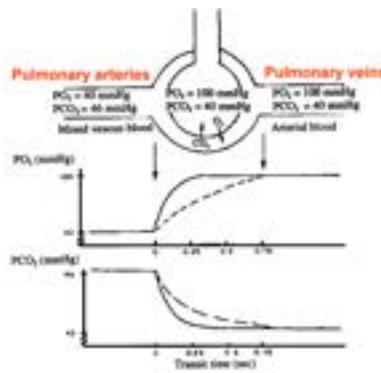


Figure 1.20: The transit time of RBC through the alveolar capillaries and saturation of O_2 and removal of CO_2 .

Interestingly, if you're a patient with edema, your alveolar capillary mem-

brane would be thicker hence diffusion rate would decrease but the saturation of O_2 is still achievable during the 0.7s time frame. However, if they ever exercise, their blood won't get enough O_2 since the RBC won't have enough time to be saturated.

1.3 Pulmonary Circulation

Like we've discussed in the first lecture, in order to understand the pulmonary system, we sort of have to understand the heart circulation hence we'll briefly go through it again.

In short, deoxygenated blood travel from the venous circulation will end up in the right atrium which would contract and push the blood to the right ventricle. The right ventricle also contracts creating a pressure that forces blood to flow to the pulmonary arteries which begins the **pulmonary circulation**. As the blood reaches the alveoli via at the capillaries, it will be oxygenated and send back to the heart via the pulmonary veins. This blood will end up at the left atrium which then go to the left ventricle. The left ventricle produces a great pressure that pushes the blood to the aorta which begins the **systemic circulation**.

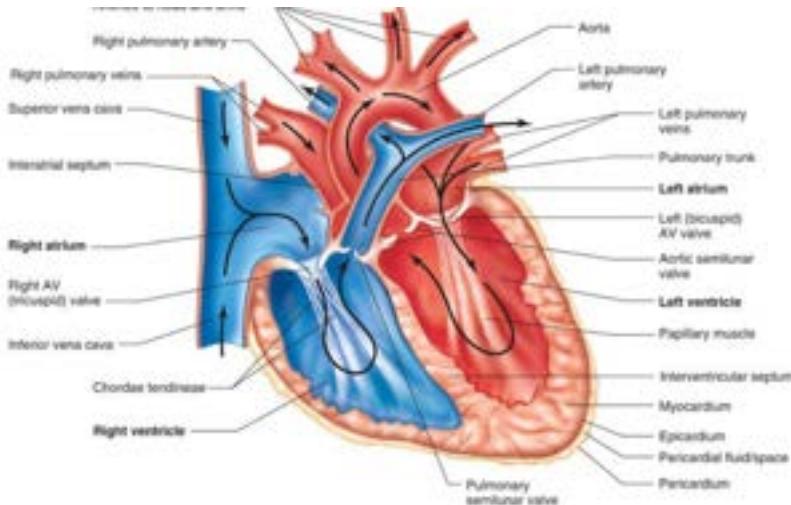


Figure 1.21: Circulation of blood in the heart

Now although they share some similarities, the pulmonary and systemic circulation has differences as well. To begin with, the pressure of the right ventricle $P_{RV} = 25\text{mmHg}$ is much smaller than that of the left ventricle $P_{LV} = 120\text{mmHg}$.

$$P_{RV} \ll P_{LV}$$

Why is that the case? Well...because the heart is the same level as the lung so it does not need to push as much (right ventricle) as the one that move blood to the entire body (left ventricle).

Another difference you would see is that the blood pressure in pulmonary circulation is also much lower than the systemic's, **why is that the case?** Well...When we have high pressure in the lung, we could have leakage to the alveoli which is dangerous since it increases alveolar-capillary membrane thickness hence gas exchange would be more difficult.

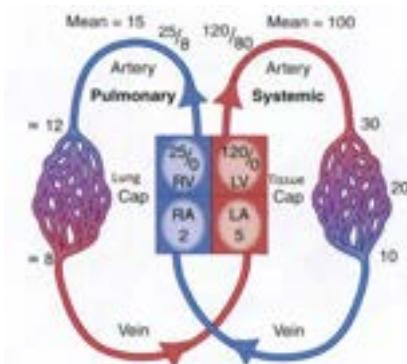


Figure 1.22: On the pulmonary circulation side, the mean pressure is 15mmHg at the pulmonary artery. As we go toward the alveoli-capillary membrane, it drops to 12 then 8 at the venous return. On the systemic side, the mean pressure is 100mmHg at the aorta and as it travels through it drops to 30 and then 10 at the venous return.

As you can see from the image, there's the 2 number written **25/8** and **120/8**. These 2 number in order X/Y are the **systolic pressure** (pressure when the heart contracts) and **diastolic pressure** (pressure when the heart relaxes) respectively. However, we can simplify this by taking the average of the 2. Nevertheless, as the image suggested and its caption, we can clearly see that **systemic circulation's pressure is lower than that of pulmonary's**.

Even so, when your heart pump, it's best to pump the same amount of blood i.e. same volume thereby same flow (cardiac output); but we have 2 different pressures on the system, so **how do we do so?** Well...to answer this, we need to look at flow of fluid through a pipe. For fluid to flow through a pipe, it needs to have a difference in pressure of the inlet and

outlet. But also we need to remember that certain properties of the pipe we can change to make the flow rate. Putting them together and you get

$$\text{Flow} = \frac{\text{pressure}}{\text{resistance}} \quad (1.6)$$

Example 1.3.1. If 2 pipe have the same pressure but 1 have a smaller diameter, that one would have a higher resistance since it takes more time for fluid to flow through in a smaller cross-sectional area v.v. So to make them equal, you increase the pressure of that pipe.

So back to the question, if we want to have equal flow for systemic and pulmonary, we have to either **reduce the resistance of the pulmonary circulation** or increase resistance of the systemic's. In this instance, we reduce pulmonary resistance. To do so, the wall of the blood vessels will be thinner and has less smooth muscle than the systemic circulation. This allows pulmonary vessels to be flexible and thus change to a larger size reducing resistance and increase flow.

Using the above understanding, we found that the drop from pulmonary artery to left atrium is about 10mmHg hence the **pulmonary resistance have to be 1/10 that of systemic**. The low vascular resistance and high compliance of pulmonary circulation allows lung to accept cardiac output at all time.

1.3.1 Vascular Resistance and Accommodation

Supposed that you want to exercise thus the cardiac output will increase. If cardiac output increases then the pressure would increase to so

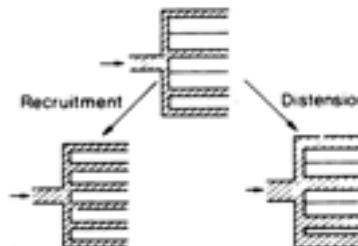


Figure 1.23: Recruitment and distension

how would we maintain a constant flow and pressure through the pulmonary circulation? Well...We can either do **recruitment or distension**.

In recruitment, the pulmonary circuit will recruit more blood vessel to ease the increased pressure. In distension, the pulmonary circuit will expand in size to reduce resistance and increase flow.

Drugs and their effects

There are drugs that can change blood vessel diameter hence change the pulmonary vascular resistance.

- Serotonin, dopamine and norepinephrine can cause pulmonary smooth muscle contraction hence increases vascular resistance.
- Acetylcholine and isoproterenol does the opposite by relaxing the pulmonary smooth muscle and decrease vascular resistance.
- Nitric oxide is a chemical produced by endothelial cells which cause vasodilation.

Remark 1.9. *There's also a vasoconstriction reflex that redirect blood flow to a well-oxygenated region of the lung.*

1.3.2 Gravity Effect on Blood Flow and Ventilation

When we're standing, blood flow is more preferably to go down the toe due to gravity. Similarly, we would expect blood flow to be more at the bottom of the lung than the top. To do so, we measure the flow rate at the top and bottom of the lung using radioactive Xenon (Xe) injection.

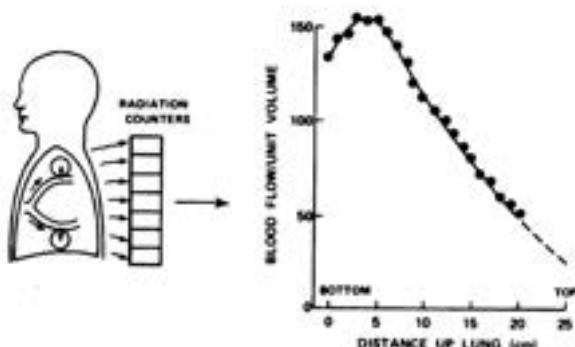


Figure 1.24: Radioactive Xenon injection and pulmonary blood flow.

After the Xe is distributed, the radioactive level at different region of the lung is measured and indeed the bottom is more radioactive hence more blood flow.

Starling's Resistor Concept

Another way to look at the above phenomenon is through the starling resistor concept. We can make a simple illustration like so.

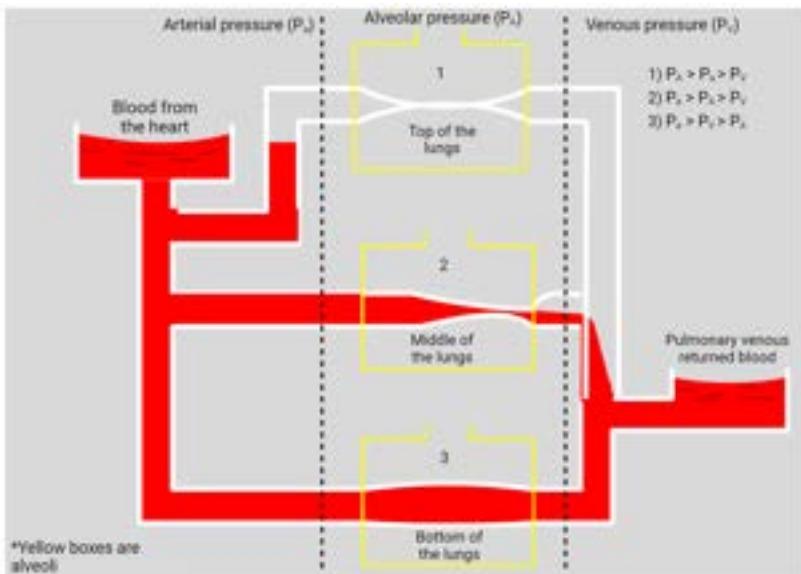


Figure 1.25: Starling's resistor concept illustration. At the top of the lung, blood cannot reach plus P_A is much higher than P_a or P_V thus no blood flow. At the middle layer, P_A is in the middle but less than P_a so blood can still flow through due to P_a . At the bottom layer, P_a and P_V are higher than P_A hence capillaries won't be blocked. Note that P_a must always be higher than P_V to have a flow.

As the illustration demonstrated, at the top of the lung, there are almost no blood flow since the blood cannot reach it due to gravity but also since alveolar pressure is higher (as compared to arterial and venous pressure), it would close down the vessel. At the middle portion, the blood can reach it but alveolar is still slightly high yet enough for some blood flow. Finally, at the bottom, alveolar pressure is low and blood can reach it thus has a highest flow

Remark 1.10. *The capillaries are not going through the alveoli but is going around it. Nevertheless its pressure still has an effect.*

Gravity also has an effect on ventilation. The top alveoli are more opened than the bottom alveoli since the lung is elastic (compliance) and is pulled down by gravity. Think of holding a slinky! At the top where you hold it the slinky is stretched but as it reached the bottom it closes in. Because of this fact, during air inspiration, the change in volume at the top of the lung is less since it's already opened while at the bottom it would be a larger change since it started nearly close to maximally open.

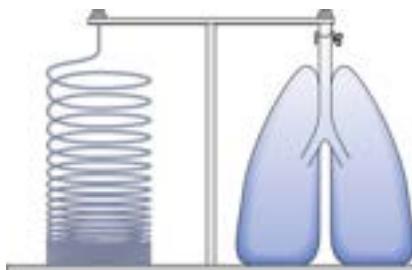


Figure 1.26: Lung and slinky illustration. The lung has elastic properties like that of a slinky. When the lungs suspend in our body, it has similar stretch like the slinky where the top is stretched while the bottom is compacted together. This causes top alveoli to be more open while the bottom to be close at rest.

What does this means? Well...This means the amount of air inspire at the top is less than at the bottom. This is further proven by letting subject inhale radioactive Xe and check for radiation level. Indeed, at the top would be less compared to the bottom.

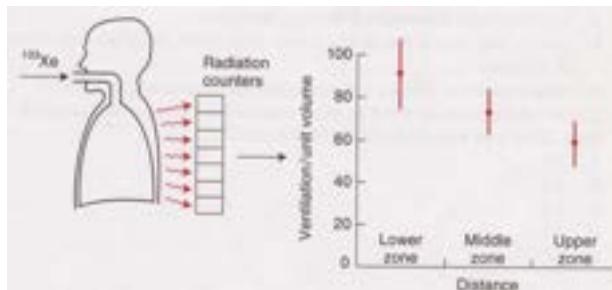


Figure 1.27: Radioactive xenon inhalation. This test shows us that the distribution and intake of gases is uneven between the top and the bottom of the lung during inspiration.

With all of this into consideration, we would expect that the pulmonary ventilation rate and circulation rate would be the same with gravity. Well....not

really, there are still differences in the blood flow between the top and bottom as well as the ventilation between the top and the bottom i.e. **blood flow changes more rapidly as you go up the lung as compared to the changes in ventilation.** We can combine the 2 graph by dividing the ventilation rate over the circulation rate at every particular length increase. By dividing we would obtain the **ventilation perfusion ratio** in normal gravity. As we move up toward the top, the ratio changes more rapidly showing that the ventilation is reaching near 0 before perfusion.

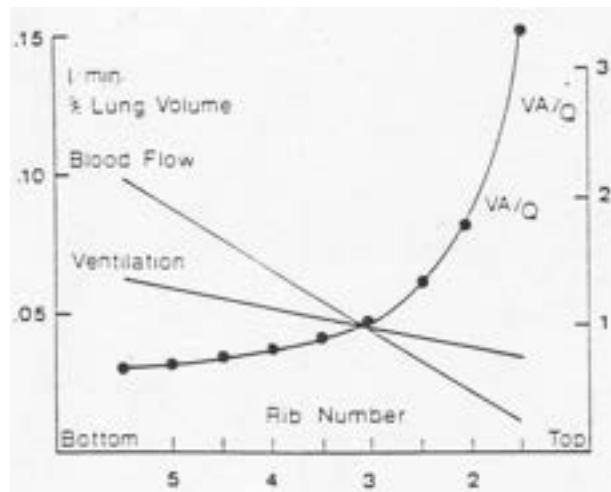


Figure 1.28: Ventilation and perfusion graph and their ratio.

1.3.3 Fick's Principle

Finally we want to talk about **Fick's Principle**. In general, the O_2 consumption per min is equal to the O_2 by the blood in the lungs in 1 min. **How do we use this to calculate the blood flow?** Well we would use this equation

$$\dot{V}_{O_2} = \dot{Q}(C_a O_2 - C_V O_2) \quad (1.7)$$

which we can rewrite as

$$\dot{Q} = \frac{\dot{V}_{O_2}}{(C_a O_2 - C_V O_2)} \quad (1.8)$$

Where \dot{V}_{O_2} is measured by comparing the $[O_2]$ in the expired and inspired air, \dot{Q} is the pulmonary blood flow, $C_V O_2$ is the $[O_2]$ in the systemic veins while $C_a O_2$ is the $[O_2]$ in the pulmonary artery.

Remark 1.11. To measure the arterial concentration of a gas, we can measure it either in the systemic artery OR pulmonary veins. Same with systemic circulation, we can measure systemic veins or pulmonary artery.

1.4 Transport of O_2 and CO_2

In this lecture, we will look at the transportation of these gases in our body. As we know, the amount of dissolved gas in fluid is dictated by its partial pressure (Henry's law) i.e. $\text{diffusion} \propto \text{pressure gradient}$.

1.4.1 Transport and Dissociation of O_2

We will begin by looking at O_2 , what you recall from previous lectures is that O_2 is not very soluble in plasma i.e. the amount of dissolved O_2 in it is very low, also is $\propto P_{O_2}$.

Example 1.4.1. In a sample of 100mL, only 0.3mL is O_2 dissolved at $P_{O_2} = 100\text{mmHg}$.

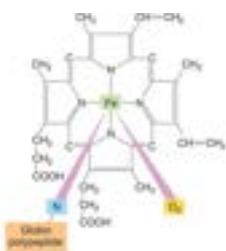
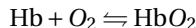


Figure 1.29: 1 heme group and its iron ion.

But this is contradictory since our body cells require an oxygen supply of 300mL/min so **how is that it's insoluble but still meet the demand?** Well...It must have another way to transport O_2 . Indeed it does and this is through an iron-containing protein called **hemoglobin (Hb)** and they take up **65× as much O_2 as plasma would**. An Hb is made up of 4 smaller subunit called **heme group** and each of this group has a center Fe^{2+} ion that can bind to 1 O_2 .

Hb is also essential since it can bind and release O_2 at a very quick pace. This allows it to quickly uptake O_2 in the lung and release it to cells. The

general mechanistic "reaction" of it is given as the following



Knowing this, we can return to example 1.4.1 to see that the amount of O_2 dissolved in plasma is 0.3vol.% but the total O_2 bound in Hb is given 19.5vol.% which means the total arterial O_2 is roughly 20vol.% (20mL O_2 in every 100mL of plasma/blood).

Remark 1.12. O_2 bound to Hb does not contribute to P_{O_2} , only plasma dissolved O_2 is responsible. However, it P_{O_2} determines the amount of O_2 bound to Hb.

Dissociation Curve of Oxygen

If we can plot the % Hb saturation against the partial pressure, we would get a **sigmoidal shape** graph where initially, there is a rapid increase in % Hb as the partial pressure increase but then it begins to plateau. **How do we interpret such graph?** Well...let's begin at the lower partial pressure 40mmHg.

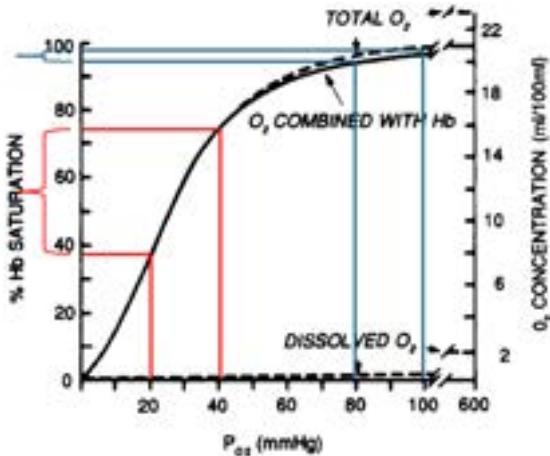


Figure 1.30: Dissociation curve of O_2

At 40mmHg, we can think of it as the P_{O_2} in the peripheral tissues. There, % Hb is at around 75 which to show that Hb dissociate its O_2 to the tissues. Supposedly, the metabolic activity increase and the tissues require

more O_2 which means P_{O_2} drop further, let's say, 20mmHg. We can see at that point, % Hb drops to 38 i.e. Hb dissociate/let go more of its O_2 to supply to the cell. To make this short this portion of the graph shows that **Hb provides an automatic mechanism that matches O_2 supply and demand.**

On the other hand, if we look at $P_{O_2} = 100\text{mmHg}$, % Hb is roughly 100 and we can think of it as Hb at the alveoli taking up O_2 and not letting go of it. As it goes through the pulmonary veins, P_{O_2} may drop a bit to supposedly 80mmHg but the oxygen saturation level doesn't change that much since it's 96% Hb.

To summarize what we've analyzed, the HbO_2 dissociate curve tells us the amount of O_2 carried at different P_{O_2} . At low P_{O_2} , it represents Hb in the periphery and is letting go of its O_2 while at high P_{O_2} , Hb is in the alveoli and is taking up O_2 .

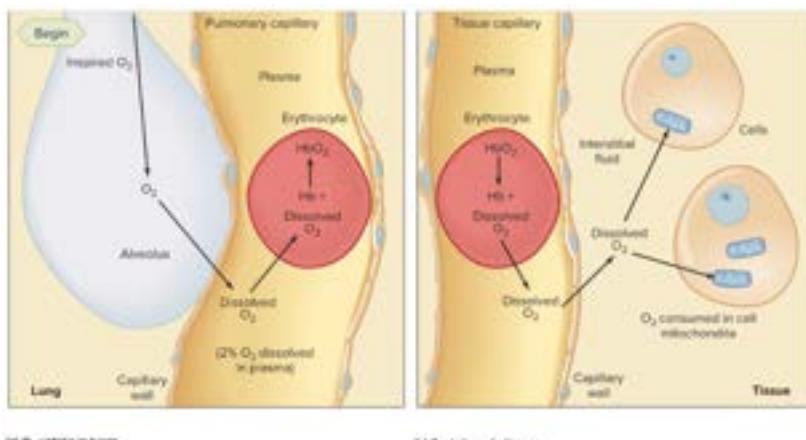


Figure 1.31: Illustration of O_2 dissolving and transporting.

The above figure provide a brief illustration of what we've said above. At the alveoli where the P_{O_2} is high, O_2 moves and dissolves in the plasma, small amount would stay in the plasma while the rest dissolves further to RBC and the bound to Hb. When it reaches to peripheral tissues, P_{O_2} drops and O_2 dissociate from Hb, become dissolved in the RBC then dissolved in plasma to finally move to the cell.

Before moving on further, you might ask **well why is the dissociation**

curve a sigmoidal? Well...It has something to do with the quaternary structure of the Hb (4 heme groups) and its affinity to O_2 . When the first heme group is bounded with O_2 it would increase the O_2 affinity of the second and etc. This effect is called **cooperative binding**.

However, a similar protein found in muscle that perform a similar function as Hb called **myoglobin** does not have the sigmoidal shape but a hyperbolic!

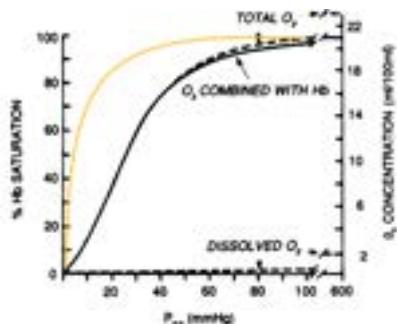


Figure 1.32: Myoglobin % saturation curve in yellow. The curve follow a hyperbolic shape which shows us that myoglobin only release when P_{O_2} is very low. This makes sense since muscle have different energy pathway before reaching oxidative phosphorylation that do use O_2 .

Because Hb is the main vehicle to carry O_2 (dissolving is too low), we would expect that **the amount of Hb affect O_2 content in blood**. And surely, this is the case, as your Hb count decreases, your O_2 content also decreases with it even with high saturation. A lowering of Hb count could signify that you're having anemia but having too high Hb count is also dangerous since it's possible for polycythemia vera. The best is the balance between which is **14g/100mL**.

1.4.2 Bohr Effect

The Bohr effect describes a phenomenon whereby the HbO_2 dissociation graph shift to the right due to an increase in CO_2 , temperature and an decrease in blood pH.

Example 1.4.2. When we exercise, we increase the CO_2 , lactic acid and heat. This drives the graph toward the right i.e. now for every drop of P_{O_2} we would require additional O_2 for the tissues. When you're not exercising, at 40mmHg, the % Hb is at 75 but drops to 60 when you're exercising hence require more O_2 .

Remark 1.13. These factors has little effect beyond 80mmHg as we're in the alveolar "zone" where gas exchange occurs.

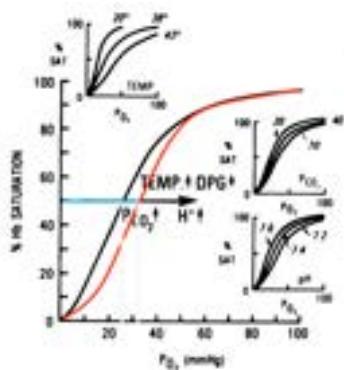


Figure 1.33: Bohr effect shift HbO_2 graph toward the right. As CO_2 , temperature increase and pH decreases, the cell requires additional O_2 (to maintain basic need + metabolic function) and thereby drives graph to the left so every drop of pressure result in even lower saturation.

Carbon Monoxide Poisoning

Carbon monoxide (CO) is a dangerous colourless and odorless gas but is also used at very low amount by your nervous system for signalling. CO is dangerous since it has $210\times$ the affinity to Hb's binding site than O_2 . Because of this, exposure to CO would lead to a decrease O_2 bound to Hb therefore it shifts the HbO_2 dissociation graph to the left since there's no O_2 to dissociate to the tissue so saturation increases for whichever O_2 is on the Hb.

In CO poisoning there's very little stimulation to increase ventilation because our body does not detect CO but most importantly, **it does not detect O_2 bound to Hb but only P_aO_2** . Typically, P_aO_2 is normal in our body even in the presence of CO since it's comprise only of dissolved O_2 .

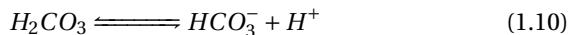
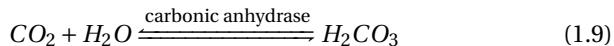
1.4.3 Transportation of CO_2

Carbon dioxide (CO_2) is a common waste product of oxidative processes and is removed by the blood and exhalation. CO_2 is transported in blood by 3 ways: **dissolve in blood (10%), combine with Hb (11%) and turning into bicarbonate (79%).**

We've already discussed that CO_2 can dissolve better than O_2 in blood so we need not get into it. CO_2 can also bind to the globin part of Hb to (instead of heme like O_2). Now, what we really focus on is the bicarbonate form of CO_2 as its the ways that majority of it is transported.

In general, CO_2 can react with H_2O with the help of *carbonic anhydrase* to

form **carbonic acid** (H_2CO_3) that instantly ionizes to **bicarbonate** HCO_3^- and H^+ ions.



Remark 1.14. *The arrows show that the process can be backward or forward i.e. reversible.*

We will now look at how it is transported. Let's begin at the peripheral tissue where CO_2 is released to the blood stream as waste. Some of the CO_2 will dissolve directly to the plasma, while the rest move to the RBC. At the RBC some would bind to the globin of Hb forming $HbCO_2$ while the rest will become carbonic acid which instantly turns into bicarbonate and protons to be released in the plasma from the RBC. At the same time, Cl^- will move into the RBC to neutralize the entire process.

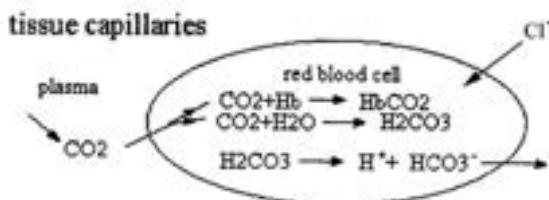


Figure 1.34: Tissue's CO_2 transportation.

Additional to what we've said above that reaction (1.9) and (1.10) is reversible, they also go in either direction depend upon the condition.

Example 1.4.3. If CO_2 production at the tissue increases, more H_2CO_3 , HCO_3^- and H^+ . On the other hand, if P_{CO_2} lowers, HCO_3^- will be reconverted back to H_2CO_3 and even back to H_2O and CO_2 . Not only that but also CO_2 will unbind from Hb.



The example above happens at the venous flow toward lung capillaries. Because P_{CO_2} of blood is higher than the alveoli's, the net diffusion of gases will go to alveoli thus lowering P_{CO_2} of blood and example 1.4.3 will occur. At the end, CO_2 will be generated from HCO_3^- and H_2CO_3 and will be released to the air via expiration.

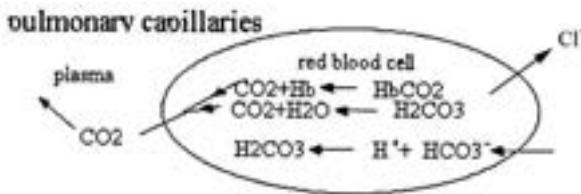


Figure 1.35: Pulmonary capillaries' CO_2 transprtation.

The 2 events above is summarize as the follow figure

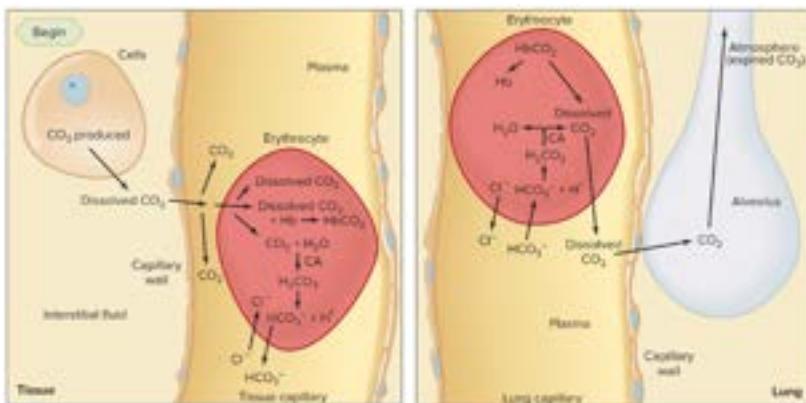


Figure 1.36: CO_2 Transportation.

1.4.4 Haldane Effect

You can think of *Haldane effect* similar to that of Bohr effect but for CO_2 . In short, when Hb is free from O_2 at the periphery tissues, it may combine with H^+ because reduced (deoxygenated) Hb is less acidic than HbO_2 so it acts like a buffers against H^+ .



This reduced Hb, which stabilizes the released H^+ , also help with increase blood capacity to carry CO_2 by pushing equation (1.9) and (1.10) toward the right (by Le Chatelier's principle); this pushing is called **Haldane**

effect. The results we get from this effect is that at any given P_{CO_2} , the deoxy

Looking at CO_2 dissociation curve, we find a striking difference compared to the O_2 dissociation curve is that it does not have steep or plateau but only a linear curve. This means that as P_{CO_2} increases CO_2 content also increases with it.

1.5 Nervous System and Respiration

We'll begin this lecture with some terminologies.

Definition 1.6. **Respirator failure** is an event when the respiratory system is unable to do its job properly.

This could be due to a failure in gas exchange, neural control of ventilation and problems with the neuromuscular apparatus (e.g. muscular dystrophy).

Definition 1.7. **Hypoxia** is low P_{O_2} in the air you're breathing. **Hypoxemia** on the other hand is a low P_{O_2} in blood.

Hypoxia and hypoxemia can be caused by inhalation of low PO₂ air, hyperventilation, ventilation/perfusion imbalance and O_2 diffusion impairment

Example 1.5.1. As you go up the mountain, P_{O_2} decreases and you become hypoxic due to low P_{O_2} air you're breathing which subsequently lead to hypoxemia.

Example 1.5.2. As you're breathing rapidly (hyperventilate), you don't get enough O_2 which is hypoxia and thus decreases P_{O_2} in your blood (hypoxemia).

Example 1.5.3. **Asthma** (ventilation imbalance) causes the bronchi to constrict thus reducing air intake hence hypoxia which subsequently lead to hypoxemia.

Additionally there is a condition called **patent foramen ovale (PFO)** shunting blood flow to the lungs and cause hypoxemia. Babies *in utero* has a connection in their left and right heart called *foramen ovale*, such hole exist because babies do not need to oxygenate their blood *in utero*. As they grow, this hole eventually closes off but in PFO, it stays opened which causes deoxygenated blood to mix with oxygenated blood thus causing hypoxemia.

Example 1.5.4. When alveolar-capillary membrane thickens, it will cause O_2 to diffuse slower and less efficient hence hypoxia and thus hypoxemia.

Now that we're clear of it, we'll focus on breath control.

Breathing is both voluntary and involuntary control. The CNS controls ventilation by integrating information, coming from receptors of peripheries, then send out a signal that give *adequate depth and frequency of breathing*.

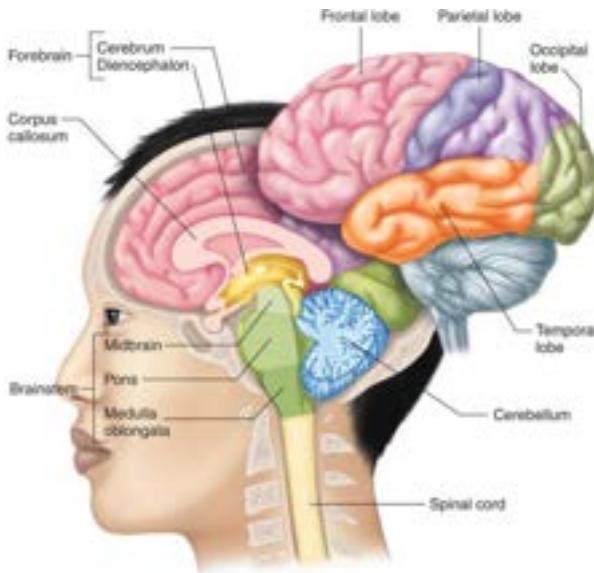


Figure 1.37: Illustration of the brain.

There are 2 different parts of the brain that control breathing: **cerebral hemisphere for voluntary** and **brainstem for involuntary**. These 2 parts can interact with each other.

Example 1.5.5. When you try to hold your breath as long as possible you would breath out eventually. This is because your P_aCO_2 is now 50mmHg while your P_aO_2 is 70mmHg and these can be detected. At this point, your voluntary control is overridden by your involuntary's, forcing you to breath again. This is called the **breaking point**.

Now, there are 3 components to the control of ventilation: **sensors, controller and effectors**. Sensors will gather information about your gas level

and they can be chemoreceptors that sense pH, P_{O_2} and P_{CO_2} as well as mechanoreceptors that sense lung volume. These sensors send these infos to the central controller in the pons and medulla that integrate these messages and send an output to the effectors. Effectors, respiratory muscles, will contract according to the efferent they received.

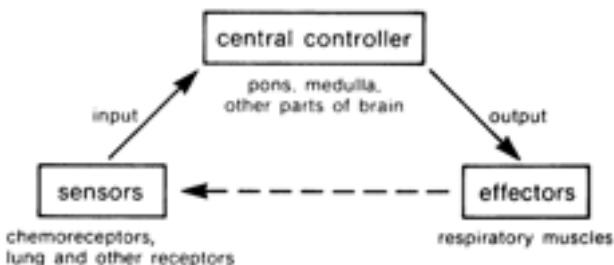


Figure 1.38: Control of respiration illustration.

1.5.1 Controller

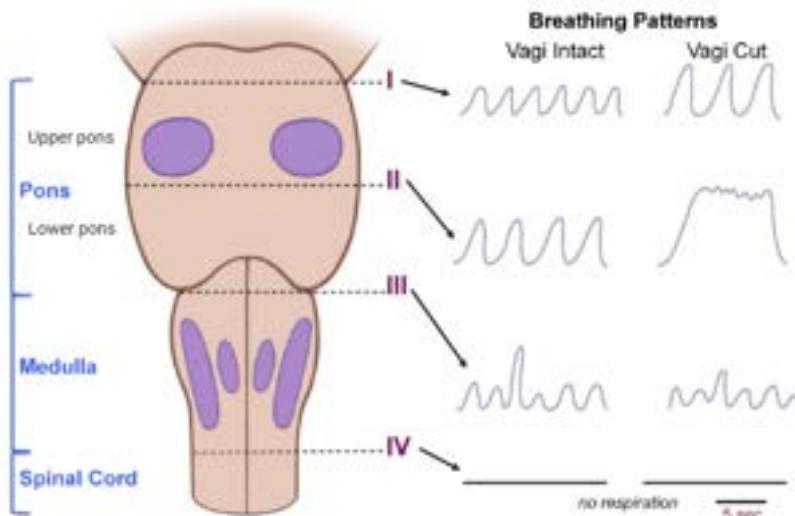


Figure 1.39: Changes of breathing pattern according to cut made at the brainstem.

We'll do an imaginary experiment involving cutting and removing part of the CNS involved in breathing and see how it affects the breathing rate (see Figure 1.39)

Cut The Cerebral Hemisphere

Cutting the cerebral hemisphere result in no changes since it is used in voluntary control but majority of breathing is through automation in the brainstem. The only thing we would lose is the ability to consciously want to breath. (See Figure 1.39, I Vagi intact)

If we also cut the vagus nerve, we would remove all incoming sensory input thus our breathing reset to default that is **deep breath in and deep breath out.** (See Figure 1.39, I Vagi cut)

Cut The Medulla

If we make a cut below the medulla, obviously we get no breathing because we removed the brainstem from sending any output to the lung. (See Figure 1.39, Level IV Vagi intact and cut)

If we cut above the medulla, we would still have a sort of rhythmic breathing but no control in volume and this is the same if you have or have no vagus nerve (See Figure 1.39, Level III Vagi intact and cut).

Interpretation: The neurons of medulla is located and divided into 2 main groups: **ventral and dorsal respiratory group.** The **ventral respiratory group** contains pacemaker cells that are essential to generate rhythm in breathing. The **dorsal respiratory group** are important to receive sensory input and integrate it along with the ventral. All in all, **medullar respiratory neurons are important for breathing rhythmicity.**

Cut The Pons

If we cut at the upper pons (the *pneumotaxic center*) [above the lower pons], we would get slow and deep breath. If the vagus nerve is also cut we would have **apneustic breathing** where patient would take deep breath to maximum lung capacity, hold it and then respire. (See Figure 1.39, Level II Vagi intact and cut).

Interpretation: Cells located in the upper pons turn off inspiration. In normal condition, these cells lead to smaller tidal volume but higher breathing frequency. In the case of cutting them, we return to default breathing. In

apneustic breathing, the brainstem isn't receiving any information about the tidal volume so it will keep inspiring and since you cannot turn off inspiration, it will keep going till maximum lung capacity.

Finally, from these 2 we can deduce that cells in the lower pons (the *apneustic center*) would send excitatory input to medullar respiratory groups hence promote inspiration. In general, **upper pons' cells turn off inspiration while lower pons' cells promote inspiration.**

We can return to the figure 1.39 and update it to the following illustration.

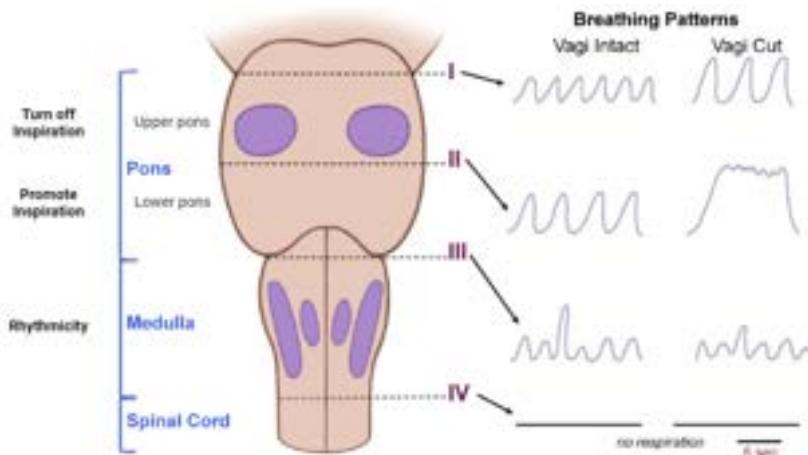


Figure 1.40: Changes of breathing pattern according to cut made at the brainstem. Illustration also included the role of cells located in the medulla, lower and upper pons.

1.5.2 Sensors

We begin with chemoreceptors. They detect P_{O_2} , P_{CO_2} and pH of the arterial blood. If these values change then ventilation also changes.

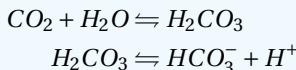
Example 1.5.6. Ventilation will increase if $P_aO_2 < 60\text{mmHg}$ and $P_aCO_2 > 40\text{mmHg}$. On the other hand, ventilation will decrease if $P_aO_2 > 100\text{mmHg}$ and $P_aCO_2 < 40\text{mmHg}$.

We can further classify chemoreceptors into 2 types: **peripheral and central chemoreceptors.**

Central Chemoreceptors

Central chemoreceptors are located on the ventral surface of medulla. These chemoreceptors are very sensitive and can detect pH changes in the CSF (Not arterial blood!). They also give rise to the main drive to breath under normal condition.

Mechanism of Action (Central chemoreceptors): CO_2 in the blood vessel of the brain can easily cross it as well as the ECF environment surrounding it, but not the same for H^+ or HCO_3^- . When CO_2 reaches the CSF, it would undergo rapid change to H^+ by equation (1.9) and (1.10)



Due to the presence of H^+ , pH of CSF will decrease which would be detected by the central chemoreceptors.

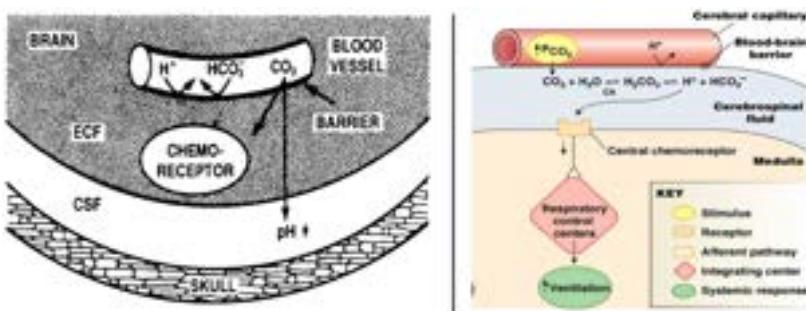


Figure 1.41: Illustrations of the central chemoreceptors in class (left figure). I also found some better illustrations (right figure) although please note that it does not mention pH value.

We can test the sensitivity of central chemoreceptors by doing the CO_2 breathing test. In this test, subject will be breathing air with increasing P_{CO_2} . By doing so, we've conditioned the subject's body into **hypercapnia** (elevated CO_2 in blood). As a result, we found there's a linear relationship between the minute ventilation and P_{CO_2} of the air inspired. We can think of this receptors as sensitive at all time.

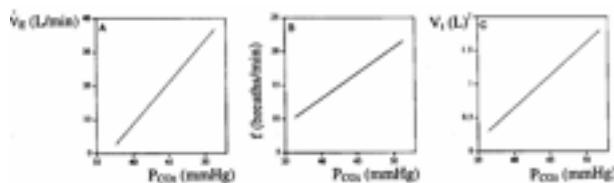


Figure 1.42: Ventilatory response to hypercapnia in subject is through increasing minute ventilation.

Peripheral Chemoreceptors

Peripheral Chemoreceptors are sensitive in changes in arterial P_{CO_2} and pH. They're excited when there's an increased in P_{CO_2} and decreases in pH. Peripheral chemoreceptors can be found on the aortic bodies and carotid body. They are innervated directly to the vagus nerve (if they're on the aortic bodies) and the glossopharyngeal (if they're on the carotid bodies)

Remark 1.15. We also call vagus and glossopharyngeal nerve: cranial nerve X and IX respectively.

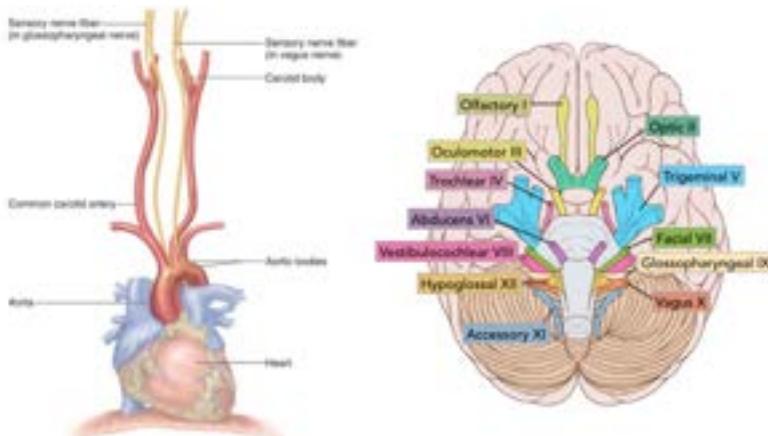


Figure 1.43: Peripheral chemoreceptors are innervated by vagus and glossopharyngeal nerve (left). These 2 nerves are part of the cranial nerves and will send afferents back to the respiratory group of the medulla (right).

To check for peripheral chemoreceptor sensitivity, we can let subject inspire air with decreased P_{O_2} . At **normocapnia** (normal CO_2 level), P_{AO_2}

can be reduced down to 60mmHg before any rapid changes in ventilation would be induced. This means that these receptors are sensitive at any point below 60mmHg. We can do 1 more thing is which is increase the P_{ACO_2} which would lead to a large change in ventilation regardless of P_{AO_2} due to highly sensitive central chemoreceptors.

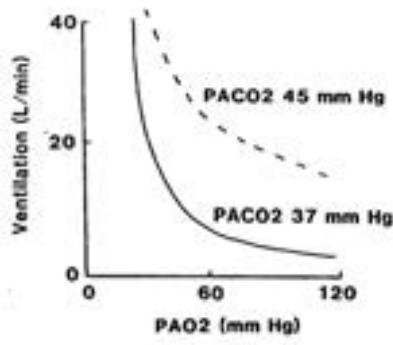


Figure 1.44: Decreasing the P_{AO_2} by letting subject breath air with decreasing P_{O_2} will lead to an increased in subject's ventilation. The rapid increase of ventilation really manifest below 60mmHg which is the sensitivity of peripheral chemoreceptors. Additionally, by increasing P_{ACO_2} , we would activate central chemoreceptors and shift the graph upward, thus increasing ventilation regardless of P_{AO_2} .

Now that we've talked about chemoreceptors, we will look at **mechanoreceptors** which are receptors that can detect mechanical changes/deformation. Mechanoreceptors for the lung volume has a special name and it is called **pulmonary vagal receptors**. There are 3 types of them: stretch, irritant and juxta-capillary receptors.

Remark 1.16. *Afferent fibers of these receptors are the vagus nerve so if we cut it, we won't have information about the lung thus back to default deep and slow breathing.*

Pulmonary Stretch Receptors

Pulmonary stretch receptors are located in smooth muscles of the trachea to the bronchioles. When you breath, the lung expand in size and caused stretch receptors to be activated and will afferent through myelinated fibres to the brain. They will remain activated as long as the lung is stretched.

There's an important reflex that are associated to these receptors and it is called **Hering-Breuer inflation reflex**. In such reflex, there's a decrease respiratory frequency due to a prolongation of expiratory time i.e. If you breath in a large volume, you'd need time to breath out.

Remark 1.17. *This reflex is not very important as it's very well observed with normal individual. The reason we talked about it is because it was the first feedback system.*

Irritant Receptors

The **irritant receptors** are located between the airway epithelial cells. They're stimulated by noxious gases, smokes, histamine, cold air and dust. They're innervated by myelinated fibers and once stimulated it would lead to bronchoconstriction and **hyperpnea** (increase breathing depth). Irritant receptors are also important by bronchoconstriction stimulated by histamine released during an allergic reaction.

Juxtagapillary Receptors

The **juxtagapillary receptors** originate in the alveolar walls close to the capillaries. They are innervated by non-myelinated fibers and have short lasting activity. They're stimulated by an increase in pulmonary interstitial fluid (maybe due to pulmonary congestion and edema). These receptors also cause a reflex that is characterized by rapid and shallow respiration, and even apnea.

These receptors also have a role in **dyspnea** (sensation of breathing difficulty) which is associated with heart failure, lung edema and congestion. In heart failure, the heart has a hard time pumping blood out of the pulmonary circulation which means there would be a build up in fluid in the lungs and thus activate juxtagapillary receptors.

1.5.3 Control of Ventilation during Exercise

From what we've said above, CO_2 stimulates central chemoreceptors by decreasing the pH in the CSF. So this would be tempting to relate the exact mechanism during exercise where we would release a lot of CO_2 in the muscle which leads to increased ventilation. Well...turns out this is not how we control breathing, in fact, we don't really know what controls ventilation during exercise.

We can look at trained and untrained subjects and their ventilation. We realize that the minute ventilation \dot{V}_E increases linearly with metabolic rate of around 50 to 65% of V_{O_2} max. **Beyond this point, \dot{V}_E changes much more significantly as V_{O_2} max increases.** We can see this *inflection point* is presented for both trained and untrained persons, the only difference is the inflection of the trained person is at a higher V_{O_2} max due to high endurance.

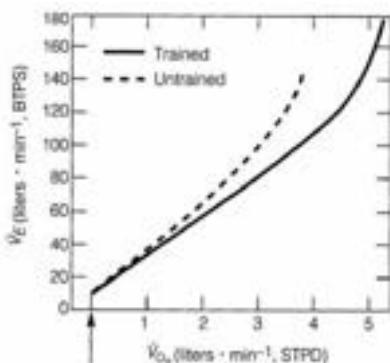


Figure 1.45: Graph represents the linear relationship between \dot{V}_E and V_{O_2} max of untrained and trained individuals. As metabolic rate increases more due to exercise, both are observed to have a spike (inflection point) where the \dot{V}_E changes more disproportionately to V_{O_2} max. The main differences between them is the inflection point occur at higher V_{O_2} max for trained individual, since they have higher endurance.

Why would there be an inflection point like so?

We can look at more information about the individual P_{O_2} and P_{CO_2} to understand what happened.

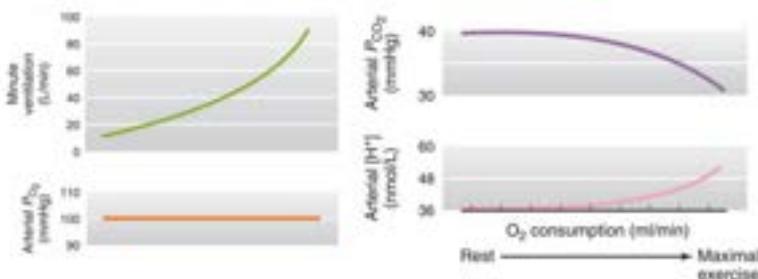


Figure 1.46: Enter Caption

As you can see from the arterial P_{O_2} , it has no changes so it cannot activate the peripheral chemoreceptors to cause the inflection. For P_aCO_2 , we can actually see it decreases which would generate an **alkalytic response** that decreases ventilatory response. **What about lactic acid?** Well...lactic acid is produced in muscle which can go through the blood stream thus decrease its pH. But remember, H^+ cannot cross arteries in the brain so it has no effect. This also shows that **central chemoreceptors are important during rest but not exercises.**

What researchers theorize is that it is the combination of increased lactic

acid (decrease pH) and very subtle change of P_{O_2} during exercise that lead to changes in the peripheral chemoreceptors' sensitivity.

We also look at peripheral mechanoceptors such as pulmonary mechanoceptors, the muscle spindles, the Golgi tendons, and the skeletal joint receptors. Through stimulation we can see a very minor increase in \dot{V}_E but it is insignificant.

The final theorization is that the initiation and ending of exercises is much more "neurological" i.e. it's through the CNS that our body has a spike in ventilation at the beginning (onset) as well as decrease in ventilation after exercises (recovery). During exercises, the increase in ventilation is caused due to humoral response in the blood.

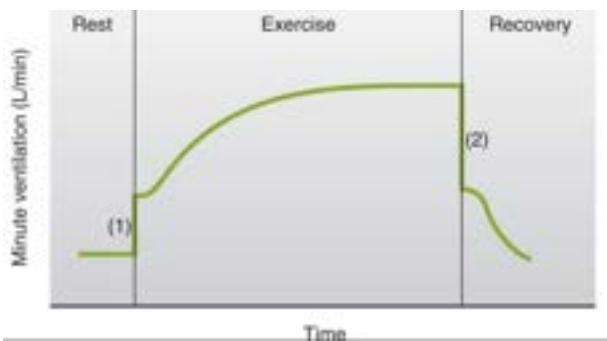


Figure 1.47: The onset and recovery of ventilation of exercising is thought to be controlled by neural pathway while the increase ventilation during exercising is controlled by humoral response in blood

1.6 Static Properties of Respiratory System

In this lecture, we will look at some static properties of the respiratory system. Going back from previous lectures, we introduce the notion of a *pleural space* which is the space between the lung and the rib cage (chest wall). This space is made by the *visceral pleura* that connects to the lung and the *parietal pleura* that connect to the chest wall. Between them is a thin layer of fluid that allows sliding but hard to pull apart.

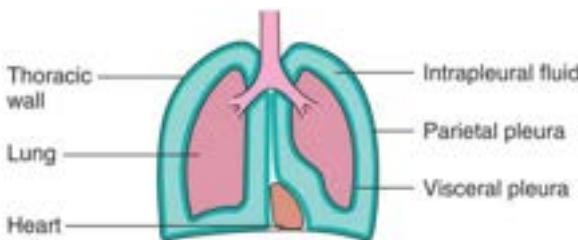


Figure 1.48: Exaggerated view of the pleural space.

When we inspire air, our diaphragm contracts and pulls down the parietal pleura thus increasing the volume of the chest. Because of the pleural space, it would pull the lung with it thus increasing the volume of the lung and allow air to flow in. When we expire air, the opposite effect happens where relaxation of diaphragm and lower lung volume force air out.

We also said the **pleural space has negative pressure**. This is a hard concept to grasp but essentially, the pressure inside of your lung is equal to the outside air when you open your mouth/nose. We reference this pressure as 0 and compared to this pressure, the pressure in the pleural space is less therefore it is negative.

The reason it is less is because the lung wants to collapse due to its elasticity but the rib cage wants to "expand" (stay at its constant size instead of collapsing in). It just so happens that the lung's collapsing force is slightly higher than the rib cage thus creating that negative environment. Nevertheless, there are also other factors such as protein content and fluid that we won't get into.

This is best understood when looking at pneumothorax condition where there's a puncture to rib cage. When this happens, the pleural space pres-

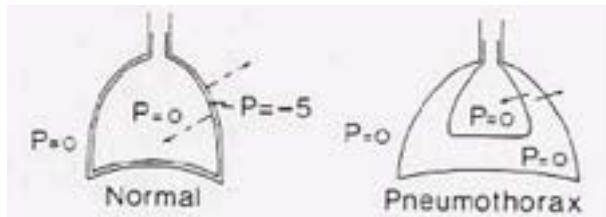


Figure 1.49: Lung under normal condition with negative pressure in pleural space (left) and lung with pneumothorax.

sure equalize with the outside to 0, which means the lung will collapse and the rib cage expand back out.

1.6.1 Elasticity of the Respiratory System

We mentioned lots of time about the elasticity of the lung we've never truly define what it is, so we will do just that.

Supposed you're at a balloon party and they asked you to inflate 2 balloons made from 2 different materials. The first balloon, you inflate it by putting some effort in to reach a certain volume but in the second balloon you found that with the same effort, the volume is much larger! This is due to the elastic properties of the balloon.

So from the imaginary experiment above, we can sort of put a rough definition that the **elasticity** of material is a relationship between **the force applied on to that material and its change in volume**. Similarly, we can use this definition for the measure the elastic properties of the respiratory system by simply measuring the **recoil pressure** for a given change in lung volume.

Definition 1.8. Recoil pressure is the pressure difference between the inside and outside of an elastic structure (in this case, the lung).

We know that to measure the lung volumes, we will use a spirometer. For the lung pressure, we will measure it using a **manometer** or **pressure transducers**. The manometer is simply U-tube column filled with a certain liquid (in this instance, it's water) with a ruler so we can measure the change

Mechanism of Action: The lung is connected to the manometer. When we push air into the lung, it also forces some of the air to the manometer which then increase the water column in the U-tube that we can measure.

What this system failed to mention is that the outside of the lung is not 0 but negative. To create a better system to that of human, we will attach a balloon to a jar that is open to the atmosphere. The jar also have another connection to a vacuum pump that removes its air. If you reduce the jar pressure down to, supposedly 10cmH₂O (water), we would see that the balloon begins to expand. To know the elastic property of the balloon, we would measure the pressure across the balloon and the jar which is 10cmH₂O.

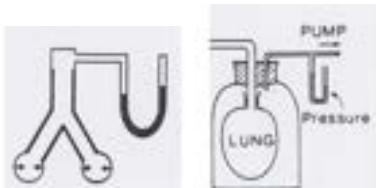


Figure 1.50: Simple lung connected to manometer model (left) and realistic model of balloon in vacuum jar (right)

But then **How do you actually do this in human subject?** Well...you actually measure the pressure inside the esophagus, the reason for this is because **the esophagus has similar pressure to the pleural space**. The way this is done is by inserting a catheter with a balloon attached at the end inside of which pressure is reference as 0. As it goes into the esophagus, the pressure transducer connected to the catheter can measure the changes of pressure.

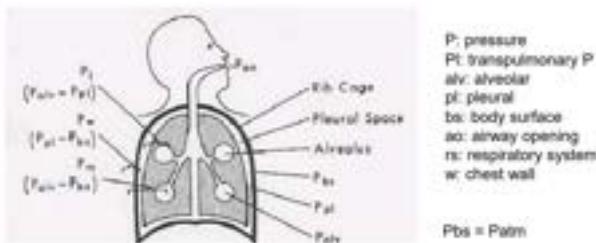


Figure 1.51: Different types of measured pressure.

To summarize, if we want to measure elastic property of the lung, we

need its recoil pressure which in this case would be the pressure between the pleural space and the alveoli called **transpulmonary pressure**. You'll later see that we'll be using other pressure too such as **chest wall pressure** which is the pressure between pleural space and the atmosphere. There's also **respiratory system pressure** which is the pressure between the alveoli and the atmosphere.

1.6.2 Compliance of the Lung

This elasticity we've been eluded to is called **compliance** (of the lung) which is defined as

$$C = \frac{\Delta V}{\Delta P} \quad (1.13)$$

where C is the compliance, ΔV is the change in volume and ΔP is the change in pressure. This equation describes the "ease" at which the structure would stretch/distend. Using this equation for compliance, we can graph out a **static pressure-volume** curve and to see the relationship they have with each other.

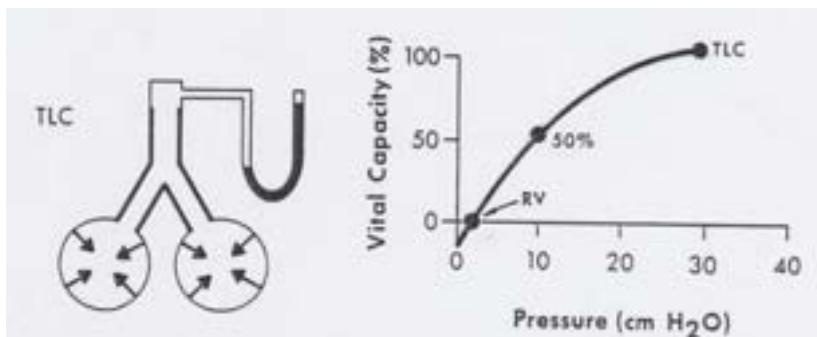


Figure 1.52: The compliance in this case is the curve produced. To make this curve, the lung is inflate to total lung capacity (TLC), where the pressure would roughly be around 30cmH₂O. Then slowly deflate till 50% vital capacity and so on and so forth. We can see that as lung reach TLC, compliance is less steep i.e. compliance decreases a bit. You will see that as you go pass TLC, compliance will drop (beyond this course).

The compliance curve is useful as it can changes through patient of different conditions.

Example 1.6.1. Looking at compliance curve of patients suffer from either **fibrosis** or **emphysema**, we can see 2 different shifts.

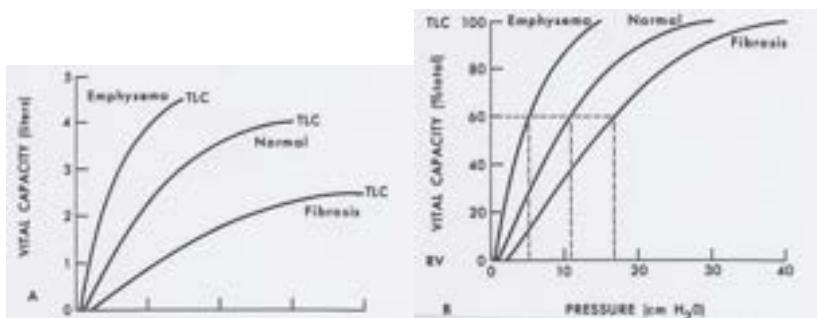


Figure 1.53: Compliance of normal, fibrosis and emphysemic subjects.

In fibrosis, there is deposition of fibers to the lung making it less compliant which means that the lung cannot inflate to normal volume. On the curve, the fibrosis compliance is below the normal one's. In emphysema, there's a breakage of the alveolar wall making the lung easy to inflate hence higher compliance. On the curve, the emphysema compliance sits above the normal one's

Like before, the equation above is not so complete since we also need to include the outside pressure (pleural space's) for it to be applicable to human. This new compliance is thus given as

$$C_l = \frac{\Delta V}{\Delta P_{alv} - \Delta P_{pl}} \quad (1.14)$$

where C_l is the pulmonary compliance, ΔP_{alv} is the pressure of the alveoli and ΔP_{pl} is the pleural space's pressure.

Remark 1.18. Sometimes, people also use elastance instead of compliance but it simply mean 1/compliance.

1.6.3 Compliance of the Chest Wall

The chest wall has compliances since it has some elasticity that allow it to recoil inward or outward. To calculate its compliance we also need to know how to measure its pressure. Well...From figure 1.51 above, it defined that the chest wall pressure is the differences between pleural space and the atmosphere.

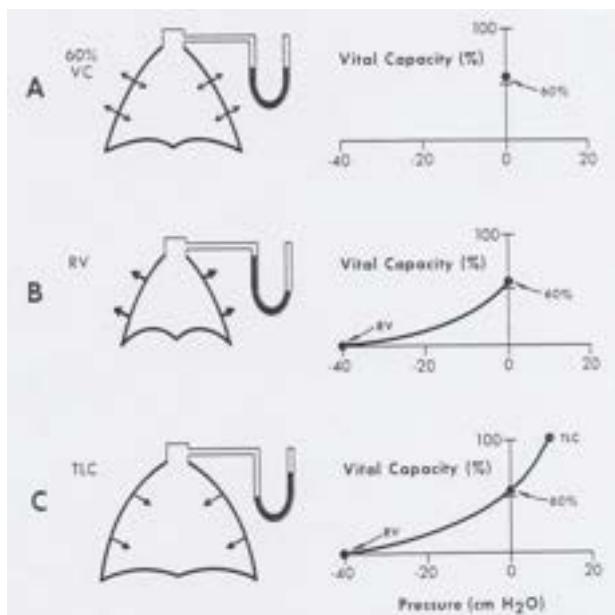


Figure 1.54: Pressure-volume curve of chest wall.

We can also come up with a pressure-volume curve for the chest wall. We begin with the chest wall at TLC which is normal of pressure roughly $10\text{cmH}_2\text{O}$. We can then slowly decrease the volume of the chest wall. At 60% vital capacity, we found that it does not generate any pressure, this is also its **resting position**. If we further force the chest wall below 60% vital capacity, the graph reaches negative pressure and the reason for this is because it wants to spring back out to its resting position.

The compliance is thus defined as the change in volume of the thorax over the change in pressure across the chest wall

$$C_w = \frac{\Delta V}{\Delta P_{pl}} \quad (1.15)$$

since $\Delta P_w = \Delta P_{bs} - \Delta P_{pl}$ but ΔP_{bs} is 0 (we reference atmospheric to be 0) thus $\Delta P_w = \Delta P_{pl}$.

1.6.4 Compliance of the Respiratory System

To measure the compliance of the entire respiratory system, we would need to see again what is the pressure across it. Using simple math and definition of pressures from figure 1.51 we would get the respiratory system pressure as

$$\begin{aligned}
 P_{rs} &= P_{alv} - P_{bs} \\
 &= P_l + P_{pl} - P_{pl} - P_w \\
 &= P_l + P_w \\
 \implies P_{rs} &= P_l + P_w
 \end{aligned} \tag{1.16}$$

We can interpret this equation as: for a given volume, the pressure across the respiratory system is the sum of pressure that'd take the lung and the rib cage to such volume. And the compliance would simply be

$$C_{rs} = \frac{\Delta V}{\Delta(P_l + P_w)} \tag{1.17}$$

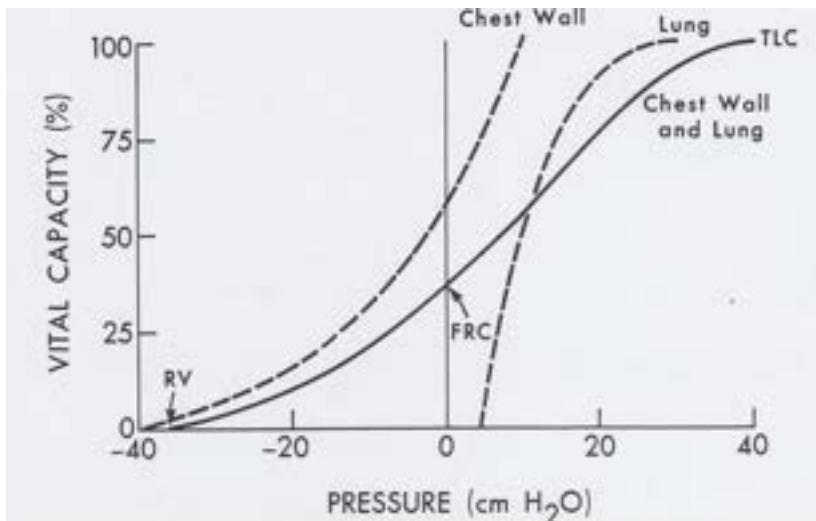


Figure 1.55: Volume-pressure curve of chest wall and lung combined to become that of the respiratory system.

We can also graph it out like before. On the graph, you will see the curve of the lung is always positive since it wants to recoil inward. The chest wall's

curve is either positive or negative as it can recoil outward or inward. We can also see at 60% vital capacity, the lung would have to generate its own pressure since the rib cage is at equilibrium. 1 point that is important on the graph is where the respiratory system's curve reach 0cmH₂O and it is called the **functional residual capacity** where everything is in equilibrium with each other.

At FRC, the volume left when we expire normally, the inward recoil of the lung of 5cmH₂O is balanced by the outward recoil of the rib cage of -5cmH₂O i.e. the lungs is above the resting volume and the chest wall is below its resting volume.

We can use this understanding to once again describe pneumothorax. When there's a puncture to the rib cage, air will rush into the pleural space since $P_{pl} < P_{bs}$ naturally. This allow the lung to fully collapse to its resting volume of 0% while the rib cage expand back to 60%. This is dangerous because without the coupling of the pleural space between the lung and chest wall, you cannot breath.

1.7 Dynamic Properties of Respiratory System

In this lecture, we will look at the flow of air in and out of the airway. Just to summarize about the dynamics of a single breath: At rest, your lungs are at FRC while P_{pl} is negative. When you inspire, you contract your diaphragm and the chest wall is pulled open which also decreases P_{pl} more and thus increases the volume of the lung driving air in, and that is 1 breath. The expire, it's the opposite action.

Now, we want to have a more scientific way of defining air getting into and out of the lung. To do so, we introduce the notion of flow, which as previous lectures already state, is the change pressure divided by the resistance and is given as the following equation

$$F = \frac{P_{alv} - P_{atm}}{R} \quad (1.18)$$

where P_{alv} and P_{atm} is the alveolar and atmospheric pressure respectively, R is the resistance.

As we can see, In the case of **inspiration**, the flow of air is said to be negative ($F < 0$). This is because lung volume increases which decreases its pressure to $P_{alv} < P_{atm}$ and by equation (1.18) $F < 0$.

On the other hand, during **expiration**, the flow of air is positive ($F > 0$); since lung volume decrease hence its pressure increases to $P_{alv} > P_{atm}$ and by equation (1.18), $F > 0$.

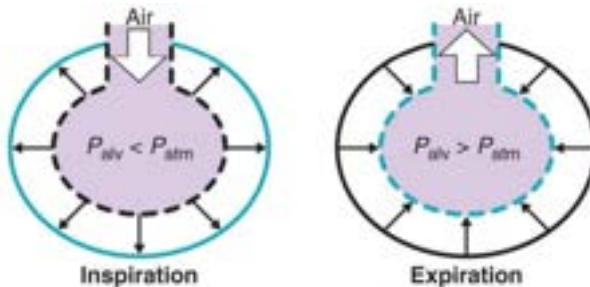


Figure 1.56: Flow of air illustration.

We will look at some parameters that we can measure to describe the dynamics of a breath. Everything will be described in the figure below

Remark 1.19. For most of these model, we set $P_{atm} = 0$ and use it as a reference e.g. at rest, $P_{alv} = P_{atm} = 0$.

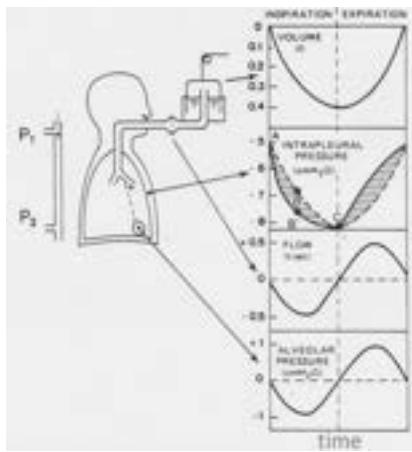


Figure 1.57: During inspiration, the volume of the lung increases in size and this is caused by the diaphragm contraction thus decreasing in P_{pl} that pull onto the lung and expand it. Because of this, P_{alv} decreases and thus F also decreases and allow air to flow in. Eventually, P_{alv} will start increasing to 0 since the air coming in has filled up the alveoli. Similarly, because air is filling up, the F increases to 0 i.e. flow inward is decreasing. During expiration, volume decreases because P_{pl} increases. P_{alv} increases and thus F increases and allow air to flow out, and then so on.

1 thing you should know is that the time of changes in P_{pl} during inspiration and expiration depends on the contraction of respiratory muscles and air way resistance. This ties up with the observation that there are these dashed line running across the graph of P_{pl} , P_{alv} and flow. **What is its meaning?** Well...it represents the amount of pleural pressure needed to overcome the airway resistance.

When there are no airway resistance, then we would follow the dashed line on the graph of P_{pl} ; the P_{alv} would be constant because the air rushing in would balance out the decreasing P_{alv} instantaneously, same with air flow. Now, because you're having resistance, **the P_{pl} must decreases more (to solid line) so that P_{alv} can decreases even further to get the air in and overcoming the airway resistance.**

1.7.1 Airway Resistance

The airway resistance we've talked about can be caused by many way: diameter of the airway, types of air, etc. Even so, the airway resistance is given as

$$R_{aw} = \frac{P_{alv} - P_{ao}}{F} \quad (1.19)$$

where R_{aw} is the airway resistance, P_{alv} and P_{ao} is the alveolar and outside air pressure and F is flow.

For the sake of simplicity we can think of airway resistance in term of its diameter. With a larger diameter, the airway can carry a larger flow for a given pressure than that of a smaller diameter airway hence it has a lower resistance.

Example 1.7.1. In the case of **asthma**, allergens comes in and interact with mast cell which then release histamine can cause bronchoconstriction and reduce the diameter of the airway therefore increase its resistance. Additionally, certain condition of asthma would also increase mucus released which also decrease cross-sectional area of airway and further increase resistance.

To treat this, patient will inhale bronchodilator that have medication and substances to either relieve the allergens or increase the airway diameter.

We will now examine the **dynamic airway compression test** which is a test that look at the flow in the airway as a function of expiratory volume.

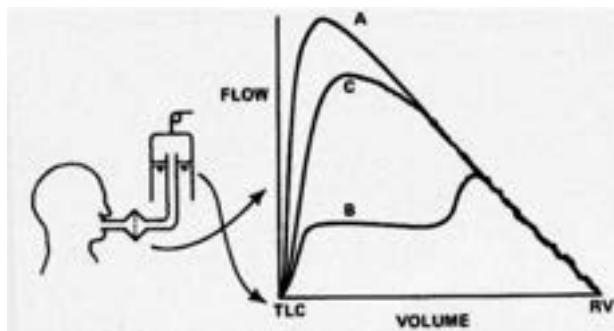


Figure 1.58: Dynamic airway compression test graph. In A, subject breath to TLC; in C, subject breaths to lower than A; and in B, subject breaths normally.

To do so, the subject is asked to first breath in to their TLC then breath out as hard as they can (forced expiration). What you'll see is a spontaneous increase in flow to the airway and then during forced expiration, the flow gradually decreases. The subject then asked to do the same but now at a point lower than TLC and still the forced expiration is similar to before. Now subject is breathing normally with maximum expiration and once again, the forced expiration drop is still similar to the previous 2!

We can thus conclude that **the descending portion of the flow-volume curve is independent of effort**. **Why is that it is independent?** Well...It's due to the airway compression during forced expiration.

To begin with, we defined a new pressure called **transmural pressure (P_{tm})** which is the differences between P_{aw} and P_{pl} (meaning that at rest $P_{tm} = 5\text{cmH}_2\text{O}$). **The only way $P_{tm} < 0$ is if the airway collapse since $P_{aw} < P_{pl}$.** So during pre-inspiration (A), $P_{aw} = 0$ and $P_{pl} = -5\text{cmH}_2\text{O}$ [$P_{tm} = 5\text{cmH}_2\text{O}$]. Then during inspiration (B), P_{aw} and P_{pl} drops like usual allowing air to flow in [$P_{tm} = 6\text{cmH}_2\text{O}$]. During post-inspiration (C), P_{aw} go back to 0 since the air balance the decreased pressure and P_{pl} decreases and stabilize at $-8\text{cmH}_2\text{O}$ [$P_{tm} = 9\text{cmH}_2\text{O}$].

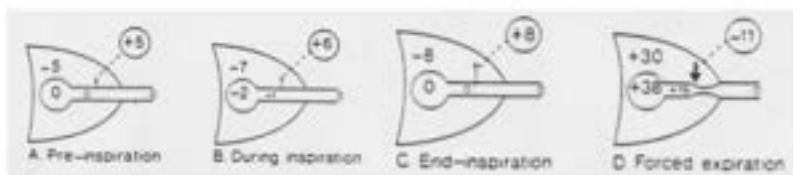


Figure 1.59: Normal expiration vs forced expiration illustration.

What's interesting is during forced expiration (D), $P_{pl} = 30\text{cmH}_2\text{O}$, wait... but isn't P_{pl} always negative? Well...during forced expiration, the chest wall is forced to close down beyond its resting position hence making P_{pl} become positive. Because $P_{pl} > 0$ and $P_{aw} = 0$, $P_{tm} < 0$ which means that the airway collapses and hinders the flow of air to the outside. As you increase effort, you would force more air out but at the same time, your airway closes more. This is why during forced expiration, regardless of effort, the flow of air to the outside is always constant for an individual.

Looking at Figure 1.59 D, you will see that the air pressure is dropping toward the point of collapse, **why is that?** Well...This is due to the airway resistance. As you move through the airway, there would be friction along the way hence decreasing its pressure, creating a sort of pressure gradient.

Flow-Volume Curve Disease Variation

The flow-volume curve can vary by disease that the patient is suffering from.

Example 1.7.2. In restrictive diseases, like fibrosis , the lung has too low compliance which causes TLC decreases (to around 4.4L). The maximum air flow in also decreases. The residual volume though is a bit lower than that of a normal person. The 1 thing the notice is that the descending portion is a higher than normal. The reason for this is because the lung is so stiff that it wants to recoil as much as possible hence it forces air more.

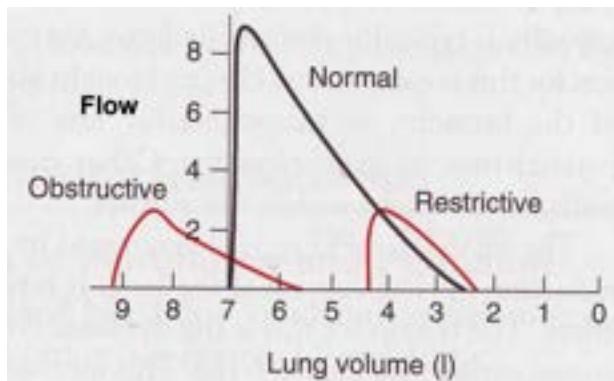


Figure 1.60: Flow-volume curve and its variations.

Example 1.7.3. In obstructive diseases, like emphysema, the lung has too high compliance which means airway is floppy. Because it's floppy, TLC also increases (to around 9.2L) however its flow is much lower but also slower. Its residual volume increases because due to high compliance lung, they can't fully respire out the air. What you will notice also is that there's a small drop during respiration, **why is that?** Well...it's because the lung is so floppy that the airway will collapse instantly when forced expiration begins.

1.7.2 Summary of Respiration Event

We'll now go briefly through all of the events occurred when you take a breath and breath out.

During **inspiration (breath in)**, the following will occur in order:

- I. Diaphragm and intercostal muscles contract.
- II. Thoracic cage expands.

- III. Intrapleural pressure becomes more negative.
- IV. Transpulmonary pressure increases.
- V. Lungs expands.
- VI. Alveolar pressure becomes subatmospheric.
- VII. Air flows into alveoli

During **expiration (breath out)**, the following will occur in order:

- I. Diaphragm and external intercostal muscles stop contracting.
- II. Chest wall moves inwards.
- III. Intrapleural pressure goes back towards preinspiratory value.
- IV. Transpulmonary pressure goes back towards preinspiratory value.
- V. Lung recoil towards preinspiratory volume.
- VI. Air in lungs is compressed.
- VII. Alveolar pressure becomes greater than atmospheric pressure.
- VIII. Air flows out of the lungs.

1.7.3 Ventilation During Exercise

For this last part of the lecture, we will discuss ventilation during exercise. As we know, minute ventilation increases linearly as the level of exercise/activity increases. Then at some point, minute ventilation rapidly rises non-linearly which looks like hyperventilation.

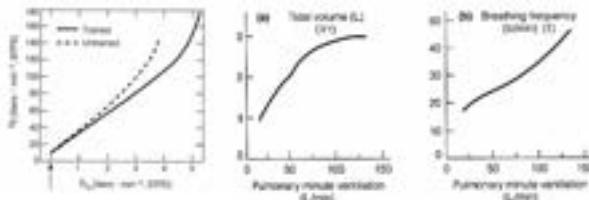


Figure 1.61: Minute ventilation, tidal volume and breathing frequency during increasing exercise level.

We can look at other parameters during exercising: we can see that tidal volume and breathing frequency both increases linearly as exercise level increase (pulmonary minute ventilation increases with higher exercise level). However, for the tidal volume, it eventually reaches a plateau, **why is that?** Well...the lung is a definite object and it cannot keep stretching forever. We can also realize from this that **high ventilation rate is caused by increasing in breathing frequency.**

Because you're increasing breathing frequency, the inspiratory and expiratory rate would decreases to fit the frequency.

Remark 1.20. *We've seen that inspiratory and expiratory rate are equal but in fact that's just an idealization, typically inspiratory is faster and expiratory rate.*

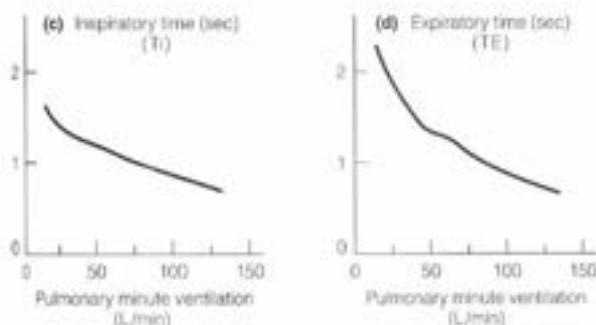


Figure 1.62: Differences in inspiratory and expiratory rate with expiratory rate decreases much more during increasing exercise level.

Because of this remark, the decrease of expiratory rate is higher than the inspiratory rate. This also means that the **flow rate during expiration is faster than during inspiration.**

Is ventilation a limiting factor in aerobic performance at sea level?

Turns out, no and we will see that it's in fact that cardiac output that is a limiting factor.

First of all, during exercise, minute ventilation can increase to $35 \times$ its original value i.e. a fit individual with \dot{V}_E of 5L/min can go up to 190L/min.

However looking at cardiac output, it only increases to $5 - 6 \times$ its original value i.e. a fit individual with CO of 5L/min can go up to only 25-30L/min. For this individual, their ventilation perfusion ratio \dot{V}_E/\dot{Q} at rest is ≈ 1 . However as they exercises, **this ratio increases to be > 1 since \dot{V}_E increases significantly more than \dot{Q}** . This shows that ventilation is not limiting aerobic activity at all. Theoretically, if the ratio is < 1 then ventilation is a limiting factors since its the blood flow that's contributing to activity.

Remark 1.21. *For a less fit individual, the value of ventilation and perfusion alone would be less however their ratio would be relatively the same to everyone.*

Another thing we can say ventilation is not the limiting factor is that the alveolar surface is very large ($50m^2$ or 1/2 tennis court) as compared to the average total blood volume of 5L only. Additionally, **only 4% of the 5L would flow into the pulmonary system during intense exercise**. This shows that even though we have a large capacity for gas exchange yet not much blood from the cardiovascular system flow through showing that cardiovascular system is the one limiting aerobic performance and not pulmonary's.

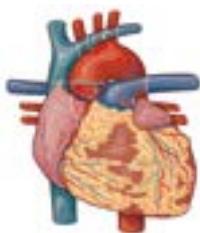
Just to end the lecture on pulmonary system, we want to say again that as exercise increases to $50 - 65\% V_{O_2} \text{max}$, both the trained and untrained subject's \dot{V}_E increases linearly. Beyond this point \dot{V}_E increases disproportionately greater than the increasing exercise level (V_{O_2}) max . This point is called the **ventilatory inflection point T_{vent}** and there's not much literature about the reason for this point to exist.

Chapter 2 Cardiology will cover the all of lectures on cardiovascular system spanning from January 24th to February 14th, 2024. The topics will revolve about the anatomy and physiology of the heart.

In this lecture, we will look at components and their functions of the CVS, the exchanges of nutrients and waste and CVS variation on living organisms.

2.1 Basics of Cardiovascular System

Definition 2.1. The **cardiovascular system (CVS)** is organ system to transport molecules and other substances rapidly over the long distances between cells, tissues and organs



The main organ in the CVS is the **heart** which pump **blood** around the body via **vasculatures**. Essentially, it's a pump that ensure irrigation of blood to other organsm and system. A closer look at the heart, we can see 4 pair of cavities: **2 ventricles and 2 atria**. A pair of ventricle and atrium is used for deoxygenated blood while the other pair is for oxygenated blood transportation. To be more specific, contraction of the right ventricle will pump deoxygenated blood to the lung while contraction of the left ventricle will pump oxygenated blood to the rest of the body.

Figure 2.1: Simple heart illustration

Another important organ of CVS is **vasculatures or blood vessels** which is designed to carry blood. If we think of the heart as a pump, we can think of blood vessels as pipes. There are 2 types of blood vessels: **arteries and veins**. Arteries are blood vessels that carry blood away from the

heart while veins are blood vessels that carry blood toward the heart. They can change their size and structure. This ability allow them to have **conductance** which is its changing in morphology to best fit the flow of blood according to diastolic and systolic pressure. These blood vessels can split into smaller arterioles and venules at capillaries and this is vital for **microcirculation**, which is the exchange of materials between the blood and extracellular fluid (ECF).

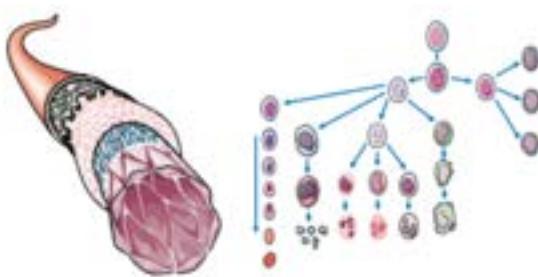


Figure 2.2: Simple blood vessel and blood cell illustration.

Blood is the medium where nutrients, O_2 and wastes are located. In it, there are **red blood cells or erythrocytes (RBCs)**, **white blood cells or leukocytes (WBCs)** and **platelets or thrombocytes**. RBCs are the main cells that carry O_2 toward the peripheral tissues, WBCs are responsible to provide us protection and immunity and platelets are for coagulation of blood vessels if there was a vascular injury.

What is the function of the CVS and why do we need it?

Well...It has loads of functions: bring nutrients to the rest of the organ, bring fuels to the cells, bring O_2 to the cells, remove waste products (e.g. CO_2 and urea), circulate hormones (e.g. adrenaline and aldosterone), circulate immune cells and antibodies, regulate water balance, pH and body temperature.

Truly, the CVS has all of these important function, but do we really need it? Well...Yes, because we need lots of energy due to us being a complex organism. To get these energy, the body need to fuel up via the CVS through a process called *diffusion*.

Definition 2.2. **Diffusion** is the net movement of matter from high concentration to low concentration.

Remark 2.1. Certain organism can exists without the CVS thanks to their simplicity morphology.

Example 2.1.1. **Amoeba**, a unicellular organism, can exist without the CVS since O_2 can easily diffuse through its cell membrane. Inside it, $[O_2]$ is low while $[O_2]$ outside is high which allow a diffusion of O_2 across the amoeba hence having CVS is sort of useless.

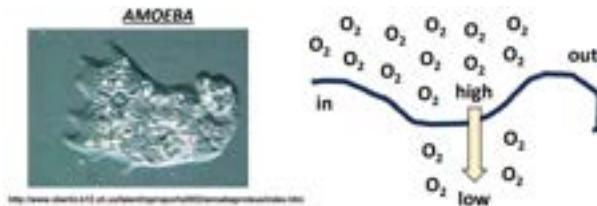


Figure 2.3: Amoeba and diffusion of O_2 across its body.

Knowing that amoeba can diffuse easily but us we need CVS to help so...what's the different? Essentially, we're asking...

What factors can allow/regulate the process of diffusion?

Well...there are many factors, we begin with the simplest that is distance.

Example 2.1.2. **Cardiomyocytes** are individual heart contractile cells and they can group together to form the heart muscle. You need to have blood vessel to irrigate these cardiomyocytes and feed nutrients for them because they cover a large area.

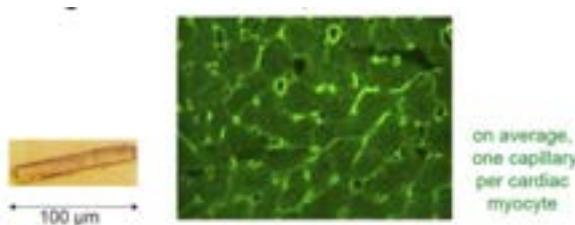


Figure 2.4: Cardiomyocytes and green fluorescent tagged O_2 .

We can fluorescent tag O_2 and see that there are these green mass which are oxygen and its capillaries and they're tightly compacted around the car-

diomyocytes. On average ≥ 1 capillary would surround 1 cardiomyocytes. This is important as it **decreases the distance which promotes diffusion.**

There are other factors as well that affect diffusion too such as: **temperature, solvent, molecule and barrier characteristic.** When temperature is high, it promotes more movement thus promotes diffusion. Denser solvent that the molecule is suspending in would lead to higher diffusion rate too. If the molecule is too heavy and bulky, it takes more times and energy to move hence lower diffusion. Increasing cell barrier thickness decreases diffusion but increasing its surface area increase diffusion.

2.1.1 Fick's Law of Diffusion

Flux of gas (Φ) (amount of gas passes through a given area) in diffusion is equal to membrane diffusing capillaries times pressure gradient, this is also known as **Fick's law of diffusion** and is given as the following equation

$$\Phi = \frac{A}{T} \times \frac{K}{\sqrt{MW}} \times (P_1 - P_2) \quad (2.1)$$

where A and T is the barrier's area and thickness respectively, K is the solubility, MW is the molecular weight of the molecule and $(P_1 - P_2)$ is the pressure gradient.

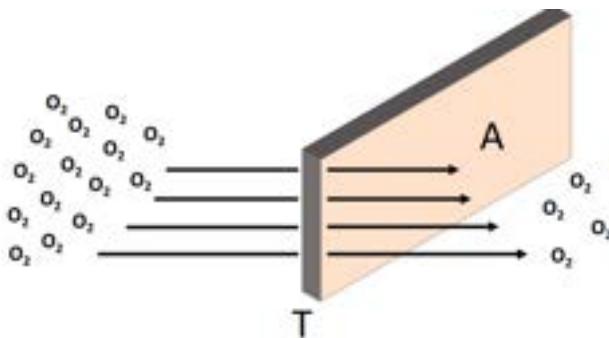
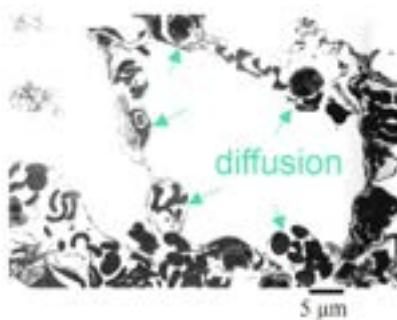


Figure 2.5: Illustration of Fick's law.

From this equation, we can learn a lot about the diffusion. First, when the A of the barrier increase Φ increases. When T of the barrier increases, Φ decreases. When K increases, Φ increases. When MW of the molecule decreases, Φ increases. Finally, if $(P_1 - P_2)$ is high meaning a high pressure gradient, Φ would also increase.

Example 2.1.3. Looking at the follow figure of alveoli and pulmonary capillary, describe what are the essential things that promotes gas exchange between them.



Answer: Well, the main driving force for this gas exchange is of course diffusion. We can see that the alveoli has a very big pocket of air meaning it has a large surface area hence facilitate diffusion. Additionally, the thin membrane between them also make it easier for gases to pass through.

What would happen to this process during fibrosis?

Answer: Well, during fibrosis, there is an overproduction of the extracellular matrix in the alveoli and thus making it thicker, and because we're increasing the thickness of the barrier, diffusion and thus gas exchange would decrease.

2.2 Comparative Physiology and Haemodynamics I

Today, we will look at CVS of different organisms. We will also look at different hemodynamics factors that influence blood circulation in the CVS as well as how flow is an important player in circulation.

2.2.1 Comparative Physiology

Definition 2.3. Comparative physiology physiology that studies and exploits the diversity of functional characteristics of various kinds of organisms.

We will inspect the CVS of the following organism: insects, fish, amphibians (+most reptilian), crocodiles and human (+avians).

Circulation of Insects

Insects have a very simple CVS and this is because it has an open circulation i.e. it's not a closed loop. They don't have blood but rather **hemolymph**. They do not have hemoglobin which means that O_2 is carried into the body by another way (tracheal system). The hemolymph will move from the posterior end through the dorsal vessels which consists of dorsal and thoracic bulbs. These bulbs can contract and push fluid forwards, they also have **ostioles** which are valves separating each bulb. The hemolymph will then move to the **dorsal aorta** that lead to the anterior opening.

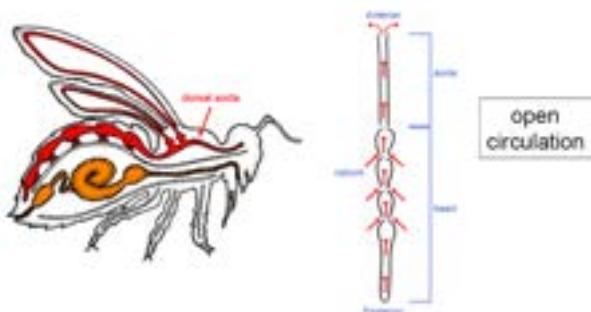


Figure 2.6: Circulatory system of Insects

Notice how the anterior opening does not loop back to the posterior, hence this is an **open system** for circulation.

CVS of Fish

Fish has a **closed circulation** that is it forms a loop. And here we see the separation between oxygenated and deoxygenated blood as well as a similar CVS structure as us.

Circulation: deoxygenated blood from the systemic capillaries enters the atrium. From here, it moves to the ventricle and is sent to the gill capillaries. Then it goes back directly to the systemic capillaries.

Characteristics: 1 loop circulation with 2 chambers-heart.

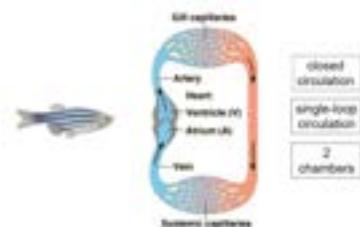


Figure 2.7: CVS of fish illustration.

CVS of Amphibian and Most Reptilians

Amphibians and most reptilian is a bit more complex than fish as it has 2 loop for circulation: 1 loop feeds the organs while the other loop is for oxygenating of blood.

Circulation: Beginning at the central ventricle, it pumps oxygenated blood out to the body. Then blood passes through the peripheral tissues and become deoxygenated blood which goes back to the atrium via the veins. The atrium pour the deoxygenated blood to the same central ventricles then pump it to the lung for oxygenation.

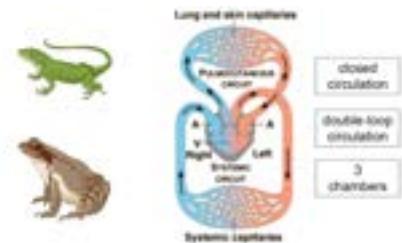


Figure 2.8: CVS of amphibian and most reptilian.

Characteristics: 2 loops circulation with 3 chambers-heart.

What's interesting here is that there's only 1 ventricle to pump oxygenated and deoxygenated blood. Does that means the deO₂ and O₂ blood is get-

ting mixed? Well...No, they don't because the pressure and structure of the heart is so well balanced for amphibian and most reptilian that it does not require a **septum** to separate them into 2 ventricles. Obviously, there will be small mixture here and there but it's not significant.

Remark 2.2. *Structure and pressure of the heart will become important later when we look at haemodynamics.*

CVS of Alligator and Crocodile

The CVS of alligator is similar to that of mammalian. That is it has 4 chambers-heart with 2 loops circulation. The only difference is that they have a 2 second aorta connecting to the right ventricle and this is essential for their ability to be underwater for a prolonged period.



Figure 2.9: CVS of crocodile and alligator.

Circulation: It has the exact circulation as us (described below) so we won't look into it here. When alligator/crocodile dive underwater, the valve between right ventricle and pulmonary artery will close. This causes deoxygenated blood to enter left aorta. At the same time, right aorta's valve will close off too. This means the only blood circulating is poorly oxygenated blood. Additionally, they will typically lower metabolic rate and their heart beats much slower too.

Characteristics: 2 loops circulation with 4 chambers-heart and 2 aorta.

CVS of Mammalian and Avian

For us and birds, our CVS consists of 2 loops circulation and 4 chambers-heart. 1 loop is for periphery the other is for the lung. The main advantage

we have is the we don't mix deoxygenated blood with oxygenated which means we can supply O_2 better to the cell hence we're also considered as **warm-blooded** animal (there are a whole host of reason why but we'll stick to the simple one.)

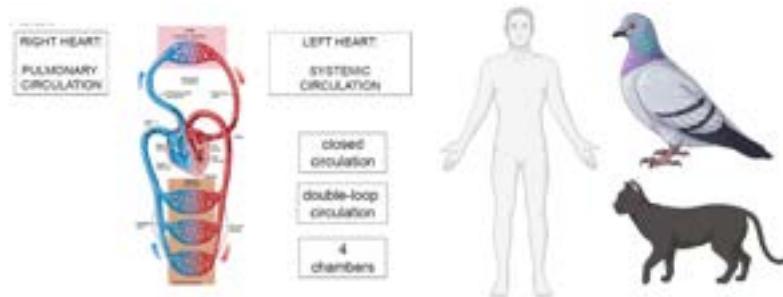


Figure 2.10: CVS of mammalian and avian.

Circulation: Deoxygenated blood travelling toward the right atrium via the **vena cava**. It's then dumped into the right ventricle which would pump it to the pulmonary circulation for oxygenation (1st loop). Then the oxygenated blood travel back to the left atrium and enter the left ventricle which would be sent to the systemic circulation via the **aorta** (2nd loop).

Characteristics: 2 loops circulation with 4 chambers-heart.

2.2.2 Haemodynamics

Definition 2.4. Haemodynamics is the study of circulation and movement in the body and forces involved.

To begin with, we need establish some common ground. First, our **blood volume** is around 5L, a **unit of blood** is defined as 450mL and a **stroke volume** is 70mL. **Where does the 450mL come from?** Well...it's around a container of blood in hospital used for blood transfusion.

Majority of the blood volume is found in the veins or venous system and the reason for this is that **the veins is like a big chamber (61% of total volume)**. It is compliant meaning it can change its size according to the changes in volume. The arterial system on the other hand has only 18% of the total volume. **Why so little?** Well...Because it is more resistant meaning it resists to the change of blood volume. By doing so, it ensures that there

is enough of the pumping force for blood to flow properly. You can think of 1 as a reservoir while the other is pipes and pumping.

Now comes to stroke volume...**How do we calculate that?** Well...we use the following equation.

$$\text{Stroke volume} = \text{End-diastolic V} - \text{End-systolic V} \quad (2.2)$$

where V is volume. But **what does diastole and systole even mean?** Well... Diastole is when you ventricles relaxes and allow blood flow into it. **systole** is when your ventricles contracts and force blood out. So, with that analogy, end-diastolic volume is the volume of blood pumped or received at the end of diastole and similarly with end-systolic volume.

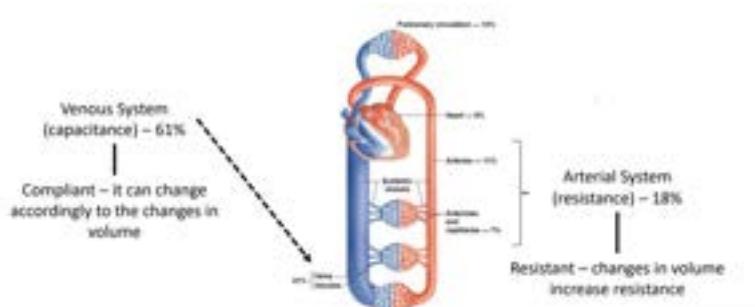


Figure 2.11: Haemodynamics and important volumes.

Once blood is fed to the organs, it will come back to the right heart and then oxygenated it in the lung. Notice that if 5L of blood must pump in and 5L will come out i.e. the pumping machine has to be ideal that the volume coming out has to be the same as coming back in. We called amount of blood pumped out to the body *cardiac output* while amount of blood pumped in is *venous return* and they have a more formal definition as follow.

Definition 2.5. **Cardiac output (CO)** is the amount of blood the heart will pump in 1 minute. Similarly, **venous return** is the amount of blood the heart receive back in 1 minute and it is equal to cardiac output, which is given as the following equation:

$$CO = HR \times V_{stk} \quad (2.3)$$

where CO is cardiac output, HR is heart rate and V_{stk} is the stroke volume. On average CO is 5L/min given that the average HR is 70 bpm .

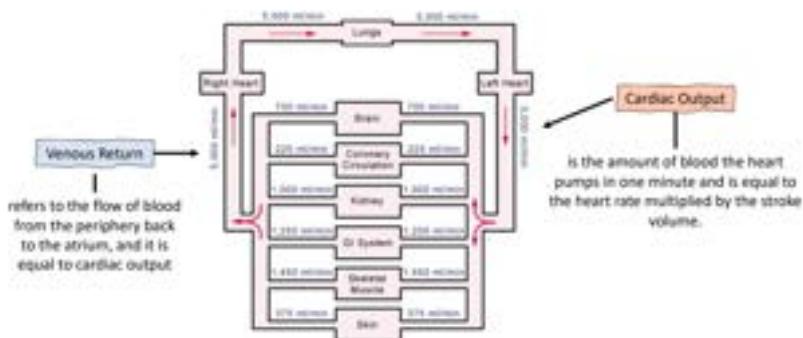


Figure 2.12: Cardiac output and venous return.

Notice on figure, the distribution of blood looks constant but in reality it can varies according to the metabolic needs e.g. exercises, sleeping, eating, etc.

How do we measure flow?

Well...flow is defined as the following equation

$$\text{Flow} = \frac{V}{t} \quad (2.4)$$

where V is the volume and t is the time. Different organs will get different amount of flow as well as depending on the condition it is in. Knowing this, we can know our blood flow during donation as around 45mL/min (450mL of blood in 10 mins).

Factors Affecting Flow

Blood flow is affected by the area and velocity of blood flow.

The **lumen** is the open area of the blood vessels where the blood will flow through. So, the area we mentioned above is the cross-sectional area of the lumen. If you increase this area, we increase flow since flow is also defined as

$$\text{Flow} = \text{Area} \times \text{mean velocity} \quad (2.5)$$

Similar with velocity where its increase also increase flow. Now, **velocity of blood** also changes through out the cross-sectional area, to be more specific, the **center of the lumen has higher blood flow than its side** because it has less resistance (the only resistance is the blood around them) while the side has higher resistance (the vessel wall). This is also why we take the mean velocity which is the average velocity across the entire area.

Different Vessels in the CVS

We have different sub-classification of the typical veins and arteries.

At the beginning, blood coming to the periphery has high pressure and is carried by the aorta. From the aorta, the pressure is dissipated by large **artery**. Then the large artery split into smaller arteries that are highly resistant (keeping constant pressure) which then split into **arterioles**. These smaller arteries and arterioles are ideal for maintaining the pumping action. After the arterioles is the **capillaries** which has **high area and is very thin**, **why is that?** Well..because of better diffusion!

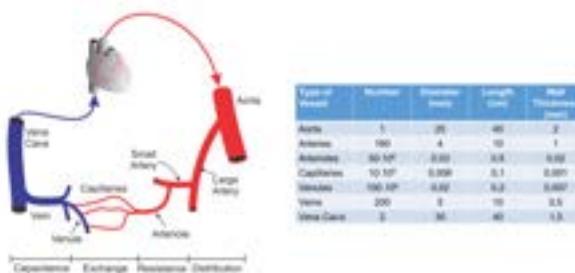


Figure 2.13: Different vessels type in the CVS.

Additionally, the capillaries also slow blood down to maximize the time for blood exchange nutrient with the tissues and organs. Then from the cap goes to the **venules** then the **veins** and finally the **vena cava**.

The structure of the blood vessel is important because it allows it to work properly. Arteries has more smooth muscle but veins has valves. **Why do veins have valves?** Well...because when there's less muscle, they can't

pump as much and as strong; so to recompensate, they have valves to hinder the back flow of blood. Veins also have larger diameter to accommodate more blood.

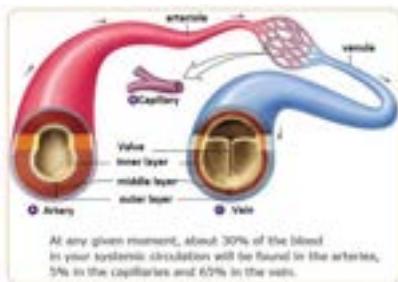


Figure 2.14: Structure of arteries vs veins.

Going back to the capillaries, another reason the blood slows down is because the total capillaries cross sectional area is much larger and if we rearrange equation (2.5), we can clearly see that **area is inversely proportional to mean velocity**. This means an increase in area lead to a decrease in mean velocity.

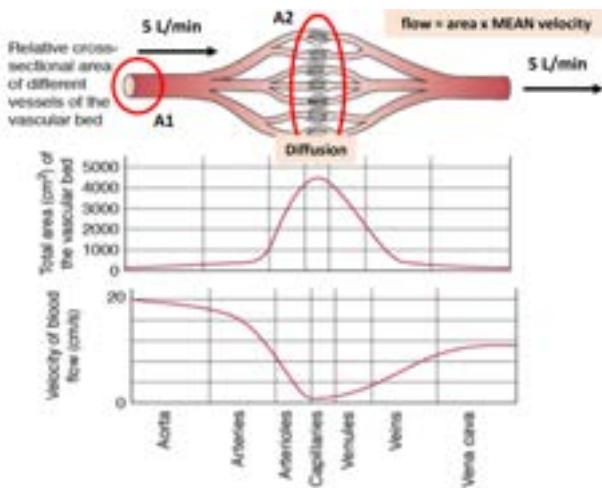


Figure 2.15: Capillaries' cross sectional area and decrease of blood flow.

2.3 Haemodynamics II

From last time, we begin at the aorta and then slowly work our ways down to capillaries where nutrients are exchanged. Essentially we're trying to find the best way to diffuse nutrient through the blood vessels so we increase the total cross-sectional area by branching the aorta into smaller vessels. This not only increases the diffusion by area but also slows the velocity of blood hence allowing more time for diffusion.

Now let's recapitulate everything from last time before moving on to newer topics. All in all, you have around 5L of blood, your heart will pump blood to the systemic circulation which is then picked up by the veins going back to the heart, which is then sent to the pulmonary circulation and then travel back to the heart to be pumped out again.

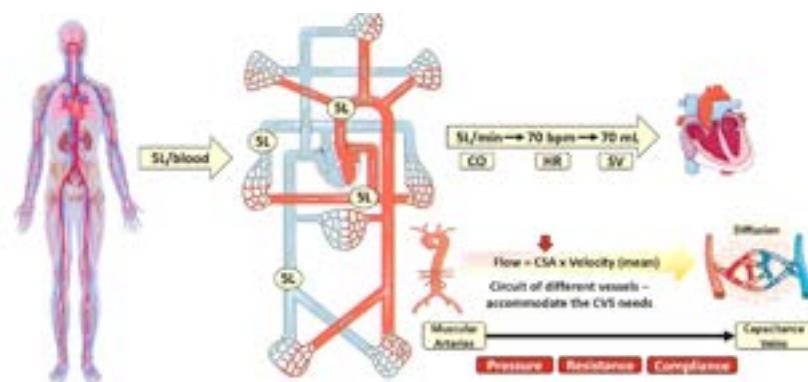


Figure 2.16: All of last lecture.

The amount of blood that the heart pumps in a minute is called cardiac output (CO) and is calculated as 5L/min. We know that the average HR is 70bpm which means the stroke volume (V_{stk} or SV) is approximately 70mL. We also learned about flow rate and its relation to cross-sectional area and mean velocity. This concept of flow and cross-sectional area links directly to how the large aorta can produce high *pressure* that branches down to smaller arteries and arterioles with high *resistance* and then finally ends up in the veins with large *compliance*.

2.3.1 Blood Pressure

Blood pressure is defined as the pressure of blood exerted on the vessels' wall. The typical systemic blood pressure (systolic/diastolic) is roughly 120/80mmHg mean while the **central venous pressure** (pressure of the vena cava) is roughly 6-12mmHg. The thing about blood pressure is that there must be a pressure difference between the inlet and the outlet of a vessel to have a blood flow. Pressure is given as the following

$$\text{Pressure} = \frac{\text{Force}}{\text{Area}} \quad (2.6)$$

Remark 2.3. When the heart stops beating, there's no pumping action and no force generated thus the pressure across the blood vessel is constant which means no blood flow.

Example 2.3.1. To see this in action, we have a tube of saline where both end is closed off. As we apply the force on 1 side of the tube, because it's closed off on the other side as well, an opposing equal force is created thus generate equal pressure across the tube therefore no flow.

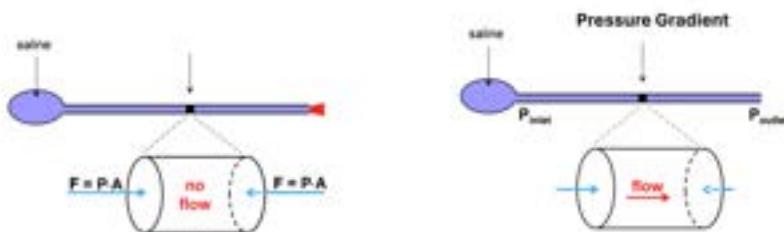


Figure 2.17: Saline tube experiment showing pressure difference generate flow.

On the other hand, if we run this same experiment with 1 opening, the force exerted generate a pressure that is greater than the outside air pressure. Because of this pressure difference or *pressure gradient*, the saline will begin to flow to the lower pressure environment.

This simple concept is important as it allows our body to have appropriate blood flow. Looking at the pressure as you're moving through the blood vessels starting at the aorta, you will see a decrease in pressure. This makes sense because you would guarantee diffusion. **What do we mean by that?** Well...under pathological condition, if the pressure is too high, it could push materials in the blood into the interstitial space which is not

good. Hence pressure is important for proper diffusion.

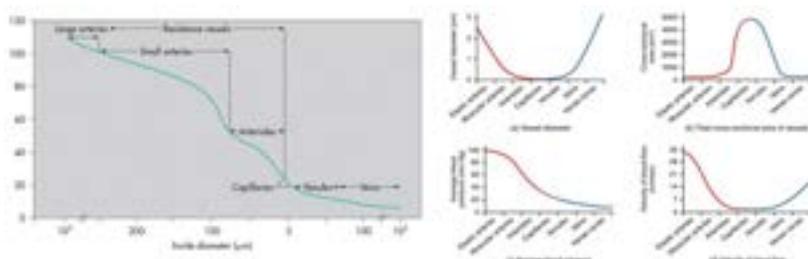


Figure 2.18: Measurement of blood pressure and other values. Figure (d) shows a drop in blood velocity as it reaches the capillaries for diffusion same for figure (a) but for the vessel's diameter. Figure (c) shows a gradual decrease in pressure and figure (b) shows a peak in area at the capillaries

The blood vessels that can "deal" or regulate the high pressure is called **resistance arteries**. These resistance arteries are the small arteries and arterioles. Therefore, we say that smaller arteries and arterioles have higher resistance than that of capillaries, venules and veins.

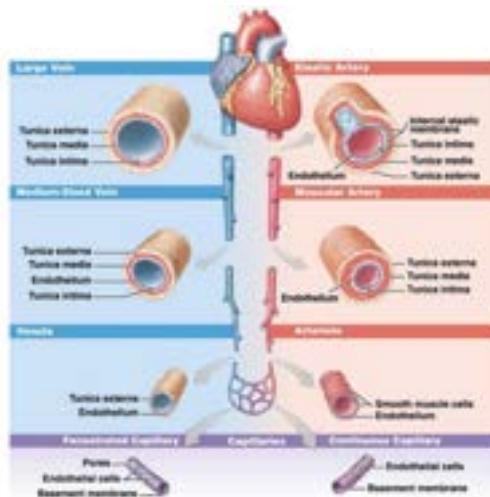


Figure 2.19: Structural differences between veins and arteries

Why can resistance arteries control pressure better than other vessels? Well...because it all comes down to **structure**. The arteries has more smooth muscle ergo contract more efficiently. Veins can still contract but they have less smooth muscle. (see Figure 2.19)

Is the pressure in pulmonary circulation same as systemics's?

No, it will not be the same. The reason is quite obvious as the circuitry of the pulmonary circulation is small while that of the systemic circulation is much larger. This means the systemic circulation requires higher pressure to push the blood out to the body.

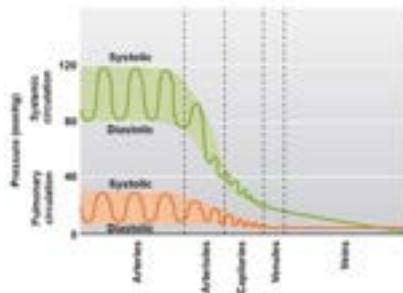
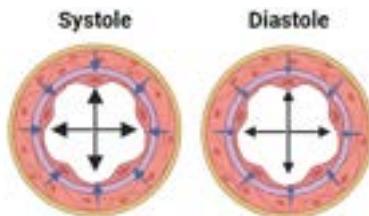


Figure 2.20: Pressure differences between systemic and pulmonary circulation.

Another thing you will notice is the oscillation of pressure between diastole and systole at the arterial level but as you reach the veins, there won't be much oscillation anymore.



During systole, higher pressure is generated in the lumen causes arteries vasoconstrict more. Meanwhile, in diastole, lower pressure allow arteries to vasoconstrict less. This creates the oscillation of pressure.

Figure 2.21: Cross section of arteries during systole and diastole showing pressure (black arrow) and vasoconstriction (blue arrow). Bigger the arrow head the bigger the effect.

The reason for this is when there's a change in pressure, **the resistance**

of the arteries changes with it through varying its vasoconstriction. In the veins however, such process is not so important as well as pressure is low.

Perfusion Pressure

Definition 2.6. **Perfusion pressure (ΔP)** is the pressure that keeps the blood flowing in your body as well as properly feed your organs. It is defined as

$$\Delta P = P_{\text{in}} - P_{\text{out}} \quad (2.7)$$

where P_{in} and P_{out} is the inlet and outlet pressure respectively.



Figure 2.22: Perfusion pressure through organ illustration.

For an organ, we typically define the inlet as the arteries while the outlet as the veins; so really, equation (2.7) can be written as

$$\Delta P = P_a - P_V \quad (2.8)$$

where P_a and P_V are arterial and venous pressure respectively.

Remark 2.4. *Because in most case, arterial pressure is so much higher than venous', we make an approximation that $\Delta P \approx P_a$*

Once again, to drive the point home, if the perfusion pressure is 0 then there would be no flow since there's no difference between the inlet and outlet pressure.



Figure 2.23: Equal inlet and outlet pressure means no perfusion pressure ($\Delta P = 0$). This also means no flow through that system.

Supposedly, you are measuring the perfusion pressure across an tube where the inlet is $P_{in} = 100\text{mmHg}$ while $P_{out} = 10\text{mmHg}$, which means $\Delta P = 90\text{mmHg}$. Now, you pick another tube and perform the measurement, however $P_{in} = 500\text{mmHg}$ while $P_{out} = 410\text{mmHg}$. This means ΔP is also 90mmHg .



What this shows to us is that **the flow in both tube would be the same if they have the same ΔP regardless of P_{in} and P_{out}** . We can see this through the following equation

$$\text{Flow} = \frac{\text{Perfusion Pressure}}{\text{Resistance}} \quad (2.9)$$

Basically, flow is proportional to perfusion pressure but is inversely proportional to resistance.

Remark 2.5. *Knowing that flow is proportional to perfusion pressure, that is approximately arterial pressure hence the main vessel controlling flow is the arteries.*

2.3.2 Resistance

The concept of resistance is important for pathological condition such as **hypertension** where an increase in resistance in the blood vessel lead to an increase in blood pressure.

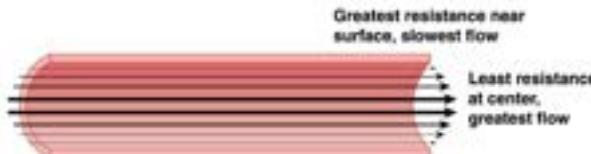


Figure 2.24: Resistance increases as we move toward the blood vessel's wall.

Resistance can be simply thought of as a force that is opposed to a movement. We can think of resistance as the **friction between the vessel**

wall and blood. This is why previously, we said blood velocity in the vessel's side is lower than the center due to resistance. Interestingly, if you increase the length of the blood vessel, resistance increases with it. This is because increasing the length also increase the internal area which means blood makes more contact with the wall ergo drives up resistance.

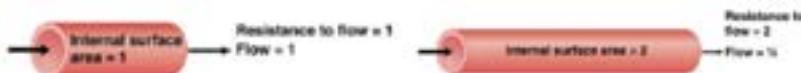


Figure 2.25: Resistance increases as the blood vessel length increases.

Generally, the above is applicable if the blood is said to be a **laminar flow**, that is the entire fluid flow in the same direction. However, if there was obstruction (such as a plaque), it would create swirling and we end up with **turbulent flow**.

Not only does friction with the wall can affect flow but also the friction between blood "particles" also affect its flow and it is called **viscosity**. These particles we said is simply RBC but also other proteins and materials in the body. But fundamentally, the more RBC there are (high hematocrit) the more viscous the blood is and thus the more resistance it would be.

Remark 2.6. *Generally, variation of Ht is low hence viscosity is constant and blood vessel length is constant in an organism.*

What do we mean by "constant in an organisms"? Well...it's basically comparing the blood vessel length to a standard 70-kg male model. When this comparison is made for everyone, there seems to be very little variation hence it is constant.

The concept of cross-sectional area, resistance, viscosity and length is summed up in **Poiseuille's law** which states the resistance is directly proportional to viscosity and length but is indirectly proportional to its radius (or cross-sectional area). This is given as the following equation

$$R = \frac{8vL}{\pi r^4} \quad (2.10)$$

where v , L and r are the viscosity, length and radius of the blood vessel respectively. We know from Remark 2.6 that v and L would be constant which means **the main determinant of blood vessel variation is cross-sectional area.**

Remark 2.7. *Blood vessel's length is NOT the same as radius/cross-sectional area, they're 2 different measurement.*

So how can the cross-sectional area be regulated?

Well...we can regulate the change in cross-sectional area through contraction and relaxation of the vessel's smooth muscle. These 2 biochemical processes is controlled by local metabolites, hormones, neurotransmitters and chemicals released by endothelial cells.

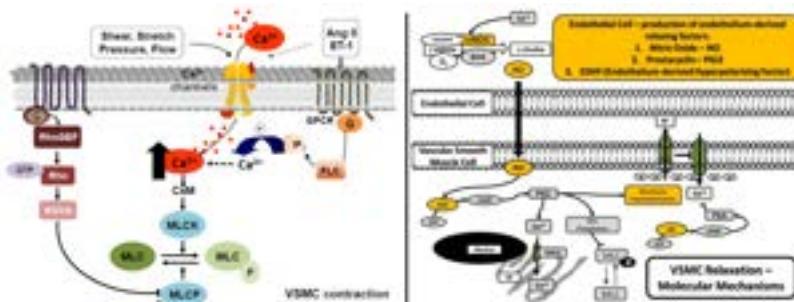


Figure 2.26: Biochemical process that lead to vasculature contraction (left) or relaxation (right).

In short, changing the concentration of Ca^{2+} in vascular muscles can lead to its contraction that lead to higher resistance. While a Ca^{2+} influx in vascular muscles lead to its relaxation that leads to lower resistance.

This leads us to the graph below. As you can see, we plotted resistance as function of radius (or cross-sectional area). What we found is an increased in radius lead to a decrease in resistance which means sense since there's more space for blood to flow through. Similarly yet opposite for a decreased in radius that leads to an increased in resistance.

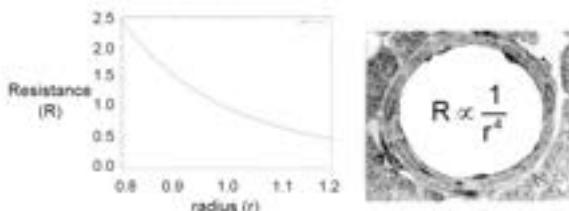
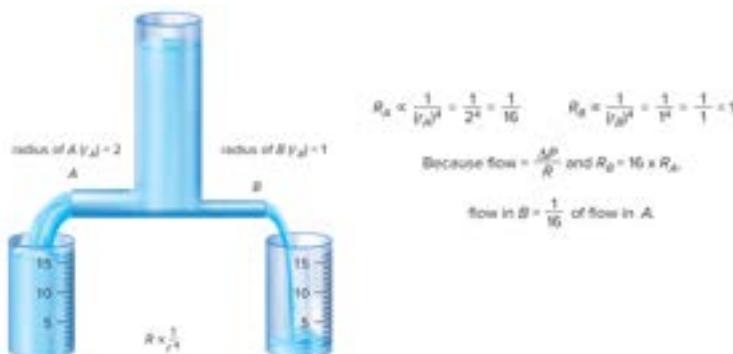


Figure 2.27: Resistance as a function of time.

Example 2.3.2. The effect of resistance and cross-sectional area is illustrated with this example. Taking 2 tubes of different radius and pour water through them.



We found that the water will flow through tube A much faster since the cross-sectional area is higher thus lower resistance hence increased in flow. In tube B however, water flow through slower since it has lower cross-sectional area thus higher resistance.

In term of systemic circulation, you would need both tube A and B. Tube A is good to deliver a high volume of blood into the periphery while tube B is good to slow down blood flow thus help with diffusion at the periphery.

Series and Parallel Circulation

The systemic circulation in the body branches in a way that everything is in parallel with each other. **but why would we favour parallel over in-series circulation?** Well...it all comes down to the total resistance through the circuit.

Supposedly, we have circuitry that is connected in series, they would have equal flow through them this means that

$$\Delta P = \Delta P_1 + \Delta P_2 = (\text{flow} \times R_1) + (\text{flow} \times R_2)$$

$$= \text{flow}(R_1 + R_2)$$

$$\text{flow} \times R = \text{flow}(R_1 + R_2)$$

$$\Rightarrow R = R_1 + R_2$$

where R is the total resistance and R_1 and R_2 are the resistance in vessel 1 and 2 respectively. What the equation shows us is that there as there are more blood vessels, the resistance will increase and eventually the systemic circulation fail.



Figure 2.28: Vasculature in series.

Now, if the circuitry is in parallel, they would have equal perfusion pressure for each of the branch meaning

$$\begin{aligned} \text{flow} &= \text{flow}_1 + \text{flow}_2 = \frac{\Delta P}{R_1} + \frac{\Delta P}{R_2} \\ &= \Delta P \left(\frac{1}{R_1} + \frac{1}{R_2} \right) \\ \frac{\Delta P}{R} &= \Delta P \left(\frac{1}{R_1} + \frac{1}{R_2} \right) \\ \Rightarrow \frac{1}{R} &= \frac{1}{R_1} + \frac{1}{R_2} \end{aligned}$$

This shows us that the total resistance will be less than the branches' resistance. This makes sense since the branching leads to capillaries and diffusion meaning that the vessel has to increase its resistance to slow down the flow. But as it reaches to other side, the resistance is less allowing blood to pick up speed again and return back to the heart.

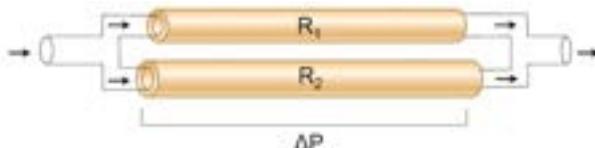


Figure 2.29: Vasculature in parallel.

All in all, the branching of blood vessels allow us to have a better control of the vessel's resistance and thus control of circulation.

2.3.3 Compliance

Unlike that arteries that have high resistance (which is why only 18% of blood total volume is found in it), veins have high compliance. **Compliance** is the ability of blood vessel to stretch and is defined as the following equation

$$\text{Compliance} = \frac{\Delta V}{\Delta P} \quad (2.11)$$

where ΔV is the change in volume and ΔP is the change in transmural pressure. While arteries can contract very well (resistance), the veins can relax very well (compliance) thus accommodate more volume. The reason that it can hold more volume is, once again, thanks to its structure.

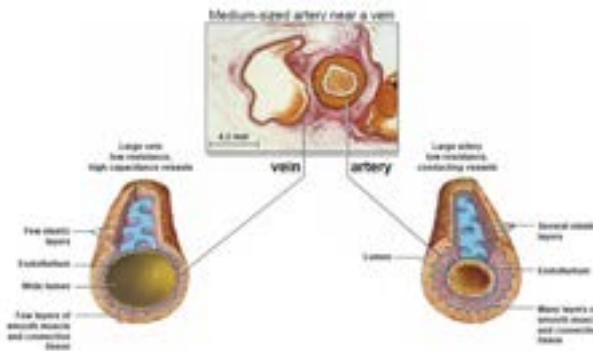


Figure 2.30: Structural differences between veins and arteries

We can see that in veins, it has less smooth muscle and fewer elastic layer. This allows it to stretch out when pressure is applied when blood enter it.

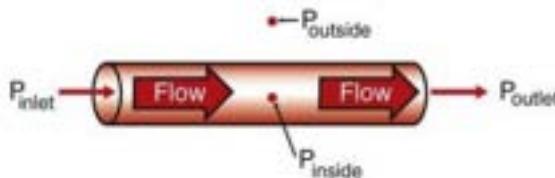


Figure 2.31: A little reminder that **transmural pressure** is the pressure between the outside and the inside of the tube while **perfusion pressure** is the pressure between the inlet and outlet.

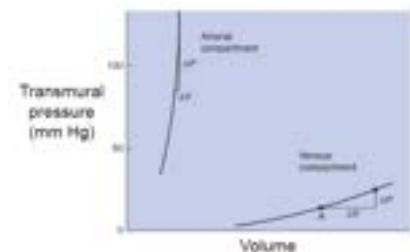


Figure 2.32: Transmural pressure vs volume curve for arteries and veins. Compliance is 1/the slope of each curve. Arteries has a smaller ΔV for a large ΔP hence lower compliance while veins has a large ΔV for a smaller ΔP hence higher compliance

Compliance still exists in arteries but it's at a very minimal level that it's insignificant to that of the veins. We can see from the transmural pressure vs volume curve for veins an arteries, in order to make a minuscule change in volume of an artery, we need to increase transmural pressure very high. However, for veins, a small transmural pressure is enough to cause a big change in volume. This shows, like we've said, **venous compliance is more important than arterial's.**

How is the pressure controlled in the venous system?

We know that the pressure in the venous system is very low so body came up with ways to maintain this flow of blood against gravity to reach the heart. 1 way is to have valves, the valves allow blood to not "drop" back down as it gets pushed upward to the heart. The other way to get blood up is through contraction of skeletal muscles. Because veins can change its shape easily, as we contract our muscle, the veins sitting in between will get squeezed and thus pushes blood upward.

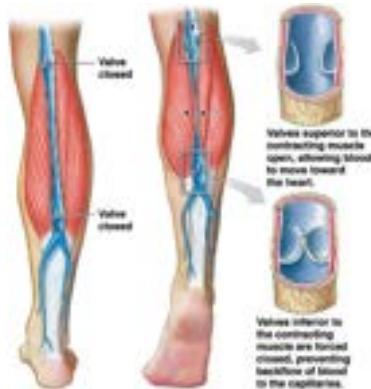


Figure 2.33: Veins' valve and effects by skeletal muscles.

2.4 Cardiac Anatomy and Conduction System

In today's lecture, we will talk about the anatomy of the heart and its conduction system that enable its contraction. Beginning with the cardiac anatomy, we will divide into 5 subsections: **4 chambers of the heart, great vessels, valves, heart wall and coronary circulation.**

2.4.1 4 Chambers of the Heart

Before getting started, we need to remember that when talking about the position/direction in anatomy, we always reference as if we're looking at the patient. e.g. An object might be to our right but it is on the anatomical left.

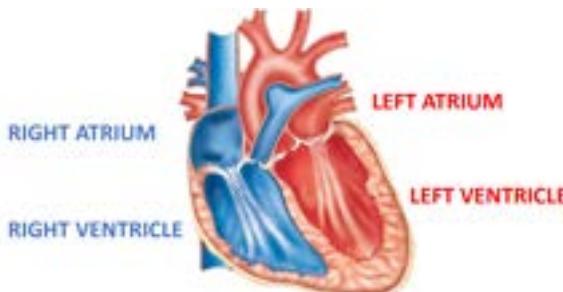


Figure 2.34: 4 chambers of the heart.

So we have a total of 4 chambers: 2 atrium and 2 ventricles. The right ventricle and atrium deal with the pulmonary circulation while the left ones' deal with systemic circulation. It's a simple circuit of right atrium receive deoxygenated (deoxy) blood and push it to the right ventricle which will pump it to the pulmonary circulation for oxygenation. The oxygenated blood travel back to the left atrium which is pushed to the left ventricle which is then pumped to the systemic circulation and the cycle repeat.

2.4.2 Great Vessels

There are 2 types of blood vessels: arteries and veins. Typically arteries carry oxygenated blood while veins carry deoxy blood in systemic circulation. In pulmonary circulation, the opposite would be true.

Remark 2.8. Personally, I think this definition is problematic, so a better way to see this is: arteries carry blood away from the heart while veins carry blood back to the heart.

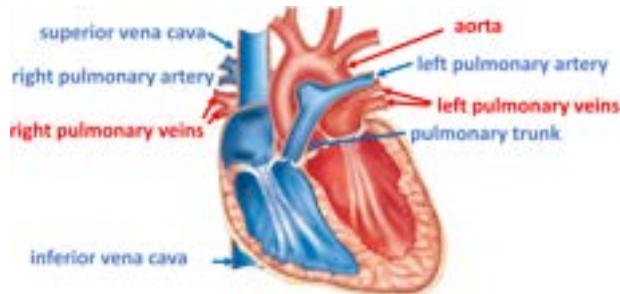


Figure 2.35: Great vessels in the CVS

When we say great vessels, we mean these large veins and arteries that branches out from the heart. First, we have the **superior vena cava** and **inferior vena cava** that drains deoxy blood into the right atrium of the heart. The deoxy blood will be pumped from the right ventricle to the **pulmonary trunk**, which is a junction connecting the left and right **pulmonary arteries**. The pulmonary arteries goes into the lung for oxygenation of blood after which it will leave and travel back to the left atrium via the left and right **pulmonary veins**. This oxygenated blood is pumped to the systemic circulation via the **aorta**.

We can take a closer look at the actual heart anatomy, so here is then vertical cross-section and cross-section through the ventricle of the real heart



Figure 2.36: Different cross-section of a real heart

wheat you'll probably notice right away is the large size of the left vs the right ventricle. The reason is quite simple, the right ventricle only need to pump deoxy blood toward the lung but the left must pump blood to the entire body. Therefore it needs more muscle power to generate the necessary pressure to push blood around. Another structure you can see here is the **septum** which is a wall separating the left and right ventricles (from not mixing deoxy and oxygenated blood).

2.4.3 Coronary Circulation

Now every organ in the body requires blood supply and the heart is no exception, which is why it has its own blood supply from the **coronary circulation** that doesn't go through the aorta. It has 2 **coronary arteries** starting right above the valve to the aorta and they will feed the entire heart with oxygenated blood. The deoxy blood will return via the **coronary veins** merging to the **coronary sinus** that feed back to the right atrium.

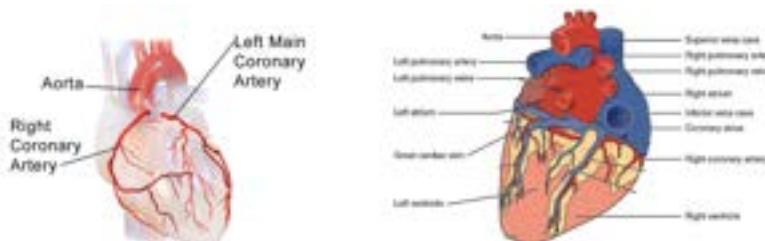


Figure 2.37: Illustration of the coronary circulation.

You've probably noticed that almost every diagram of the heart include these small fat layers. These are interesting as they're where neurons that interact with the heart is located.

Remark 2.9. *When there's a plaque build up in the coronary arteries, the heart muscle will be starved of oxygenated blood and begin to die which causes a **myocardial infarction** aka a heart attack.*

2.4.4 The Cardiac Valves

The heart have valves to maintain proper directional flow of blood. The heart has valves that separate its left and right ventricle from the left and right atrium respectively called the left and right **atrioventricular (AV) valve**. The right AV valve is also called the **tricuspid valve** while the left AV valve

is also called the **bicuspid valve** (or even **mitral valve**). It is called that way because of its structure: the bicuspid valve has 2 cusps structure (projection of an arc) while the tricuspid has three.

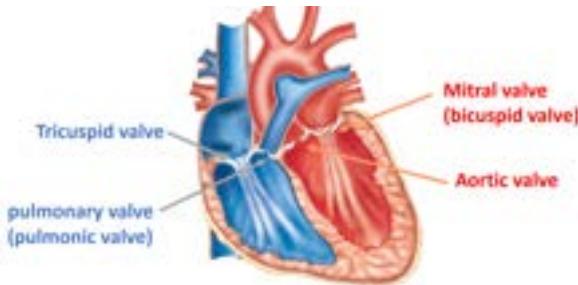


Figure 2.38: Valves of the heart.

There are a few things we should notice from these 2 valves. First off, they're made of thick connective tissues and 1 of the reason is to electrically insulate the atrium from the ventricle. Second, the AV valves are connected to **papillary muscles** via the **chordae tendinae**. The papillary muscle helps to prevent the prolapse (almost like bulging out) of the AV valve due to high pressure generated when the ventricle contract. (see Figure 2.40 below)

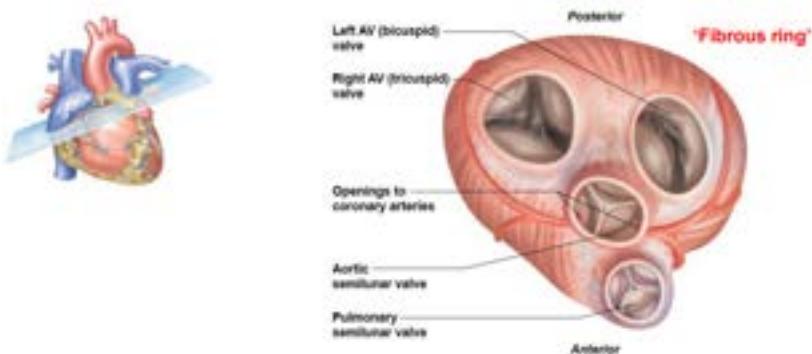


Figure 2.39: Cross section of the heart revealing the valve.

The heart also has valve separating its great arteries that are the pulmonary and aortic valve (see Figure 2.38). The **pulmonary valve** or **pulmonary semilunar valve** separates the right ventricle from the pulmonary trunk, while the **aortic valve** or **aortic semilunar valve** separates the left

ventricle from the aorta. Like the AV valve, it has the "semilunar" in its name is because the valve structure looks like half of a crescent moon.

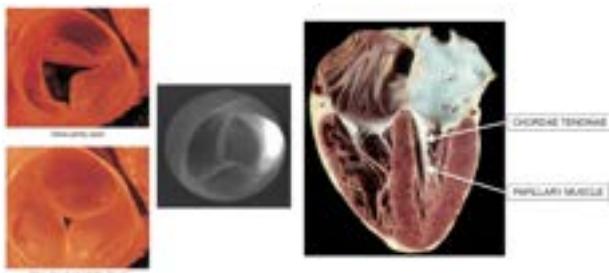


Figure 2.40: Real dissected heart valve

2.4.5 The Heart Walls

The heart is composed of mostly contractile cells (muscle) called **myocardial cells**. Look from the outside in, we can see different layer of the heart wall which are: the **pericardium**, **epicardium**, **myocardium** (cardiac muscle layer) and **endocardium**.

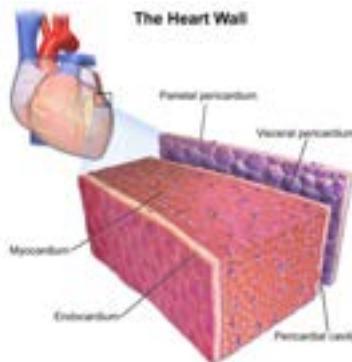


Figure 2.41: Layers of the heart wall.

The pericardium forms a thin sac surrounding the heart. This sac is non-expandable so that the heart do not overfill and it also protect the heart. On the inner wall of the pericardium are specialized cell that secrete roughly 70mL of **pericardial fluid**, which help with lubricating the heart

during contraction. The epicardium is made up of epithelial cells and is the outer layer of the heart. Then comes that myocardium which is the layer of the cardiac muscle. Finally is the endocardium that is made up of endothelial cell and is the innermost layer of the heart (in contact with the blood).

2.4.6 Summary of Cardiac Circulation

With all of what we know above, we now have a somewhat complete picture of cardiac circulation

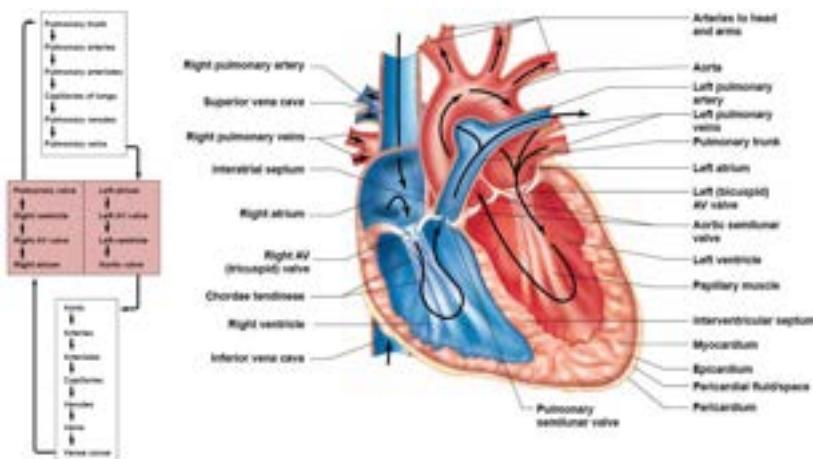


Figure 2.42: Summary of cardiac circulation.

Let's say we begin with oxygenated blood in the left atrium. From here, blood is sent to the left ventricle through the left AV valve. Blood from the left ventricle will enter the aorta through the aortic valve. The aorta will branch out into around 40 different systemic arteries. These arteries then branch into arterioles and then reach the capillaries where gas exchange happens. This exchange makes oxygenated blood become deoxy blood. The deoxy blood moves out of the capillaries to the venules which drain into veins and finally merge back into the vena cava. Deoxy blood in the vena cava drains into the right atrium which is projected into the right ventricle through the right AV valve. The right ventricle pumps the deoxy blood to the pulmonary trunk which splits into the left and right pulmonary arteries. The pulmonary arteries

becomes pulmonary arterioles, and then to the capillaries where gas exchange happens again between the pulmonary circulation and the alveoli. This changes deoxy blood into oxygenated blood. The oxygenated blood exits the capillaries via the pulmonary venules, then the left and right pulmonary veins. Both pulmonary veins drain into the left atrium and the cycle repeats.

2.4.7 Cardiac Conduction System

The heart has a conduction (electrical) system that allows it to coordinate the excitation of the heart so it will pump blood. In the right atrium lies a cluster of specialized cells called **sinoatrial (SA) node** (AKA sinus node) that can "beat" (fire electrical signal) at a rate of 1 beat per second. The atrium walls are made from cardiac muscle which are connected together hence when 1 cell fires, the adjacent cell fires with it thus **the electrical signal propagates through the atrium wall**.

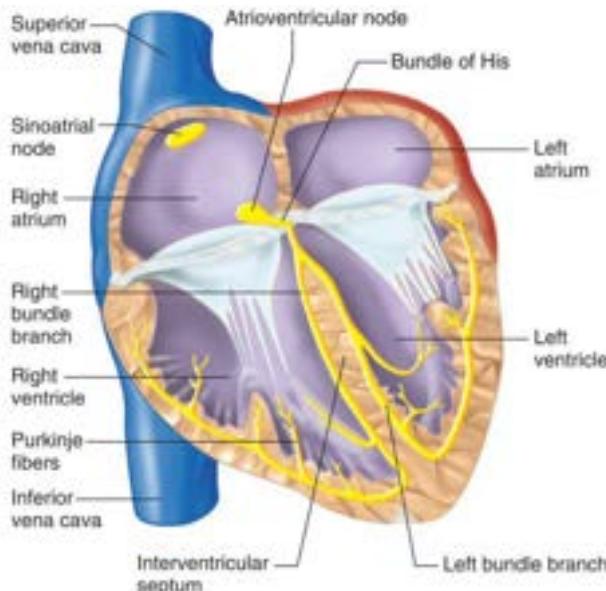


Figure 2.43: Cardiac conduction system

Now, the electrical signal can propagate toward the left atrium and half way through, it hits another cluster near the right AV valve (blocking the

signal from travelling down to the ventricle) called the **atrioventricular (AV) node**. The AV node is special as it can delay the conducting signal and this is because the atrium requires time to fully contract before the ventricles. The AV node then send the signal down to another conducting structure called the **bundle of His** and it can conduct signal very quickly.

The bundle of His splits into the **left and right bundle branches** which both travel down the interventricular septum of the heart. The left bundle branch will feed toward the left ventricle while the right will feed to the right one's. Interestingly, the left bundle branch is a bit "leaky" i.e. it allows some of the conducting signals to propagate through the septum leading to its activation and contraction. Signals from the left and right bundle of his will reach the apex of the heart and move to the ventricles via the **Purkinje fibers**.

The Purkinje fibers connect to all of the myocytes in the left and right ventricles thus leading to the synchronous contraction of the ventricles. The signal from the purkinje fibers to the ventricles' myocytes will travel from endo to epi i.e. it propagates from the inside to the outside.

Synonyms

Sometimes, certain terms are used interchangeably:

- SA node = sinoatrial node = sinus node.
- Av node = atrioventricular node.
- Bundle of His = His bundle = AV bundle = atrioventricular bundle.
- Purkinje fibers = Purkyne fibers.
- His-Purkinje System = Bundle of His + left and right bundle branch + Purkinje fibers.

Pacemaker Activity

Remark 2.10. *There's a misconception that the nervous system activate the beating of the heart. The heart can beat by itself but the nervous system can modulate it.*

The SA node is considered the pacemaker of the heart i.e. it sets the rhythm of the heart. SA node isn't the only structure that can beat by itself,

we can see this happens in patient has defective SA node. In such case, the AV node will take over as the pacemaker but with a slower rate of beating. Similarly, if the AV node is removed, the His-Purkinje system takes over but at an even slower magnitude.

We will now look at some real anatomy of these nodes. First is the AV node which is located near the AV valve opening.

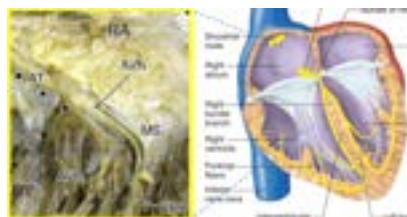


Figure 2.44: anatomical location of the AV node (AVN)

We can also look at the bundle branches. What we see is that they're specialized myocardial cells that can propagate signals very fast. They can still contract but not too much. Additionally, they are connected next to the septum, unlike the right bundle which is insulated, which means the propagating signals can get into the septum. This propagation is characterized by signals moving from left to right and top to bottom.

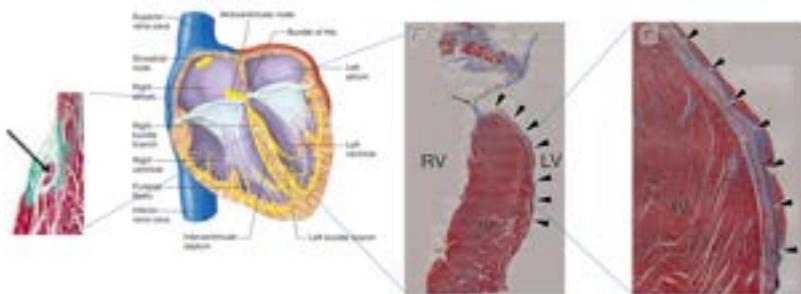


Figure 2.45: Left and right bundle branch anatomy

We can also look at the Purkinje fibers to see it forms a giant tree-like network all through out the ventricles.

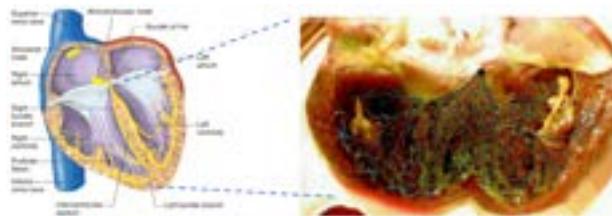


Figure 2.46: Purkinje fibers anatomy.

2.4.8 Signal Pathway Between Myocytes

Now, the specialized conduction system makes up only 10% of the entire heart myocardium so then **how do signals travel between myocytes?** Well...it's all due to the their structure. A very striking feature of these cardiac cells is that their connective structure looks like a brick wall. At the end of these myocytes are specialized structure that permit such propagation.

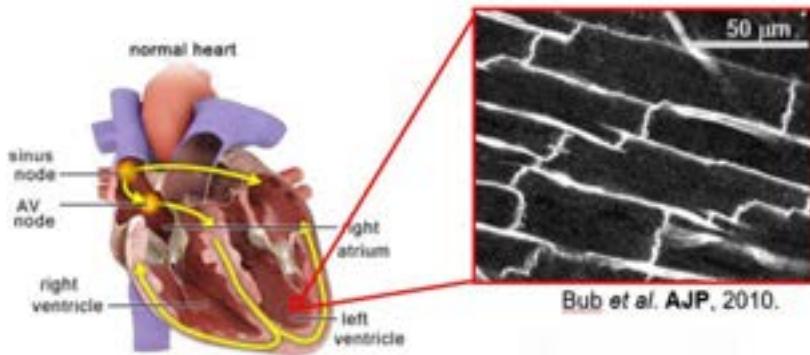


Figure 2.47: Myocytes looking like brick wall.

We can look at the histological slide and see the striated cardiac muscle cells and between the 2 ends of 1 cell, we can see a line which is called the **intercalated disc** separating 2 myocytes (only around $3\mu\text{m}$ in width). If you were too look face-to-face with the disc, you can see cluster of proteins on it and this form the **gap junction**. The protein clusters are tiny pores allowing materials coming in or out.

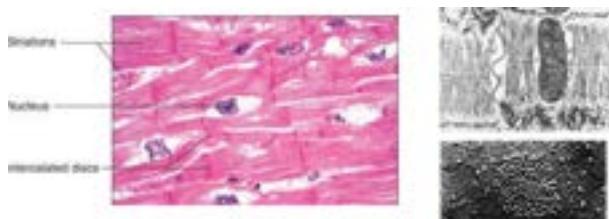


Figure 2.48: Structure of intercalated disc and gap junctions.

Here's a more schematic look at the gap junction along with its pore

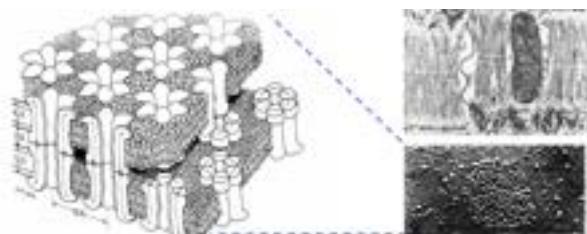


Figure 2.49: Schematic look of gap junction.

What do the gap junction really do? And how can signals propagate?

Cardiac cells and most cells have ion concentration different that makes their inside more negative than the outside. For cardiac cells, at rest, it is at the **hyperpolarized state** with membrane potential of -90mV. When the cardiac cells depolarize to **cardiac threshold**, they generate an action potential to around +20mV.

When a cardiac cell A depolarized, the cell B sitting next to it is still in its . Because of the electrical gradient where cell A is more positive than cell B in the cytoplasm, positive ion: K^+ will flow from cell A to cell B via the pores of the gap junction. At the same time, Na^+ will move from cell B to A in the interstitial space since the outside of B is more positive than that of A. What's most important is the influx of K^+ to cell B because this lead to B depolarizing until **cardiac threshold** which open **voltage gated sodium channels** and allow a higher influx of Na^+ to cell B creating an action potential.

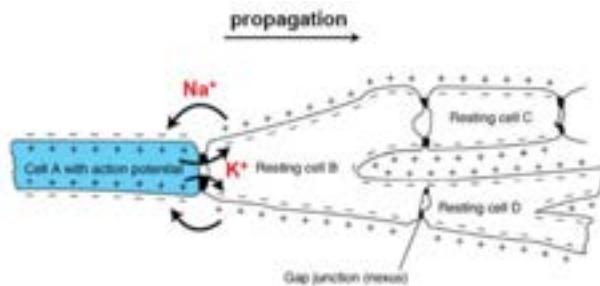


Figure 2.50: Local circuit current.

As you can see the gap junction is important for the flow of K^+ in order to propagate the signal, if there was no gap junction, there's no propagation. In general, what we've said above is called the **local circuit current**. These myocytes also have currents, due to movement of ions, running in the interstitial space called **interstitial current** that can be sensed by electrodes of ECG.

2.4.9 Self-Test

1. (T or F) All deoxygenated blood passes through either the superior or inferior vena cava on its way to right chambers of the heart.

Answer: False! The heart's own circulation empties directly into the right atria: see 'coronary circulation'

2. (T or F) The pulmonary artery transports oxygenated blood from the heart.

Answer: False! In general, arteries carry oxygenated blood, but the exception are pulmonary vessels.

3. (T or F) The Purkinje fibers can fire on their own if an impulse isn't generated by the sinus node.

Answer: True! All the cells of the specialized conduction system have the potential to beat on their own. They usually don't as the SA node is faster.

4. (T or F) The Purkinje fibers form synapses with the myocardium in the ventricles, allowing the ventricles to fire in synchrony.

Answer: False! But here, it's false because Purkinje fibers are muscle

fibers and don't form synapses. Only nerves do that.

5. (T or F) Na^+ ions pass through gap junctions of cells where one is active and the other is resting.

Answer: True! Although Na^+ concentrations aren't nearly as high as K^+ inside cells, they can still pass through gap junctions. Their impact on the local circuit current is mostly in the interstitial space.

2.5 Electrocardiogram and Action Potential

At the end of previous lecture, a question was posed which is **under histological slides, it was observed that gap junctions lies perpendicular to the cardiac cells so why was it in the direction of the cell from previous lecture?** Well...because the intercalated disc is wavy but also depending on the scale of it i.e. At a bigger scale, the waviness of the disc is not noticeable which makes us think that the gap junction is in the direction of the cells. At a smaller scale, the waviness is more distinguished allowing us to differentiate that **gap junctions lie perpendicular to the cell direction.**

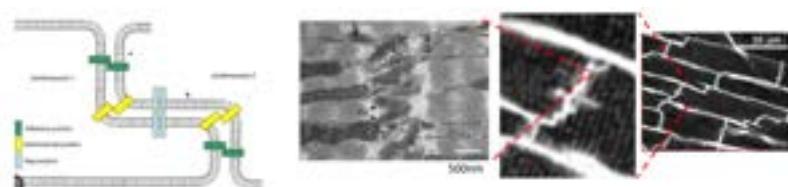


Figure 2.51: Gap junction and perpendicular intercalated disc.

Remark 2.11. *For now, just know that the gap junctions are concentrated at the ends of the cells regardless of orientation.*

The local circuit current was a bit confusing too but all you need to know is that there are cellular and interstitial current generated during propagation (of electrical signals) and recovery. The idea is that we can have electrode on our skin that sense these interstitial currents (the flow of Na^+).

2.5.1 The Electrocardiogram

Definition 2.7. An **electrocardiograph** or **ECG (or EKG)** is a device that detect and record the cardiac propagation which allow us to understand its activity.

Remark 2.12. *Electrocardiograph is the device while electrocardiogram is the recording but they're both abbreviated to ECG (EKG).*

Typically an ECG set up would consist of **electrodes** which are conducting pads that can sense the heart electrical signal. The signal of 1 or more of these electrodes will make up a **lead** (we'll talk about more later on).

Example 2.5.1. In a 5-lead ECG, there are 5 leads (whose signals come from 5 electrodes) connecting to the 2 wrists, 2 feet and the chest. The signals from these leads will be transmitted to the switch which then goes to a voltmeter. The voltmeter is highly sensitive and will read out these signals and you will get an ECG.

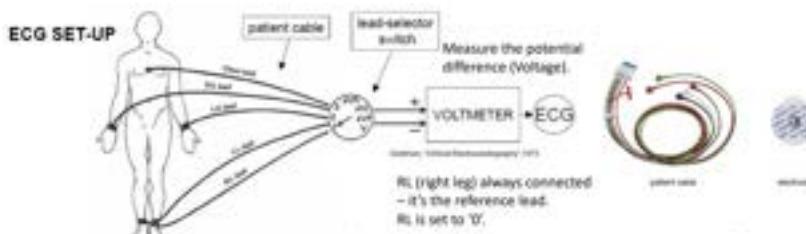


Figure 2.52: 5-lead ECG setup and flow along with its lead cable and electrodes. Also, the electrodes have a gel layer than lower skin resistance.

Essentially ECG is an extracellular recordings that can only be seen if there is a potential difference. Looking at an ECG, you can see a series of blips (fast deviation) at a frequency of around 70 bpm. The graph in the ECG are divided into large boxes (which has even smaller division) whose length indicate 200ms. We can zoom in to see 1 cardiac cycle from ECG which we will look at each of its component.

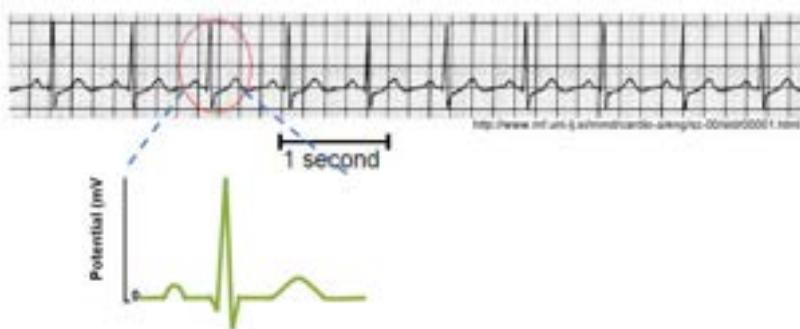


Figure 2.53: A typical ECG with time axis running horizontally and potential axis running vertical

Before beginning, we need to point out that a **deflection** means the vertical deviation from the baseline which is set at 0mV. A **wave** and a **complex**

are deflections that must start and end at baseline.

We begin with the positive deflection that is the **P wave** which represents atrial contraction when the SA node beat thus creates wave propagation through the atria. Note that **the firing of the SA node will not show up on ECG due to its small size**. At the top of the P wave, or half way through atrial contraction, is where the AV node receiving the signal and begins activation (invisible). At the end of the P wave, atria stop contraction and begin recovery (invisible).

Remark 2.13. *We means invisible as "not seen on the ECG".*

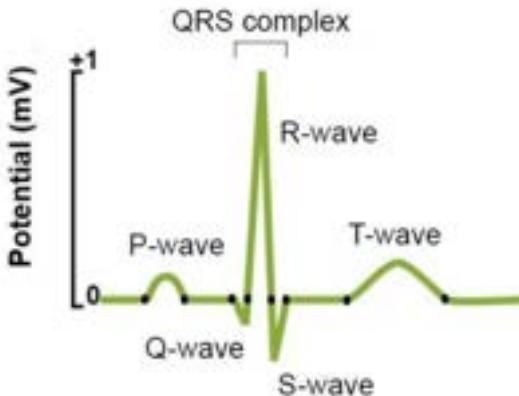


Figure 2.54: ECG of 1 cardiac cycle and the waves that make it up.

AV node will send signals to the His bundle (invisible) then propagate down to the left and right bundle branch (both invisible). The leakage of wave to the septum cause it to contract is shown as a small negative deflection which is the **Q wave**. After, the wave propagates and activates the Purkinje fibres (invisible) which lead to synchronous ventricular contraction; this is shown as a large positive deflection that is the **R wave**. Then there's also a late activation of part of the ventricles shown as a negative deflection that is the **S wave**. Together, The Q, R and S wave make up the **QRS complex**.

When ventricles repolarize, they show up as a positive deflection that is the **T wave** after the QRS complex. **The end of the T wave also marks the**

end of 1 cardiac cycle.

Interval and Segment

We also define some interval and segment that is helpful in diagnosing the heart. The **PR interval** represents the time from the start of P wave to the start of QRS complex; while the **PR segment** is the time between the end of P wave to the start of the QRS complex. An elongation of the PR segment shows a delay in wave propagation to the septum which is indicative of a problem in transmission to the AV node.

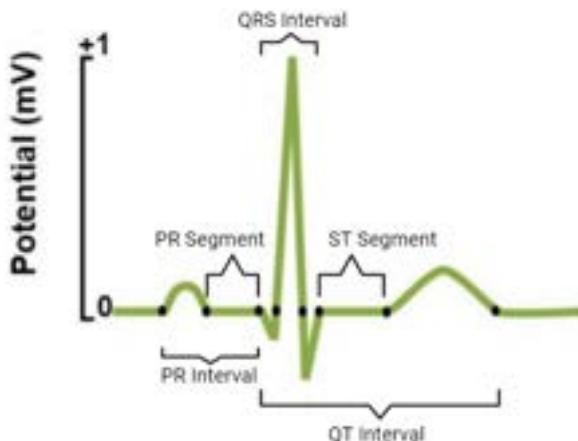


Figure 2.55: Different intervals and segments of ECG.

There is also the **QT interval** which is the beginning of QRS complex to the end of T wave; and the **ST segment** which is the end of QRS complex to the beginning of T wave. The QT interval is proportional to action potential (AP) duration; this means QT interval elongation is indicative of repolarization problems which leads to **arrhythmias** (heart beats in irregular rhythm). An elevation of the ST segment above baseline is representative of cardiac tissues having irregular AP which is indicative of an **infarction**.

Finally is the **QRS interval** which is the beginning till the end of the QRS complex. An elongation of over 100ms of the QRS interval shows a possible problem with the His-Purkinje system (maybe a block in the bundle branch). Additionally, such elongation can be indicative of slow conduction.

tion in cardiac muscles AKA **ischemia**.

Now don't you think that ECG has a very peculiar shape? As in...

Why are ECG waves sometimes negative or positive? And what's behind that?

Well...to answer this, we need to go back to the local circuit current. So to summarize the local circuit current, you have cardiac cell A that is depolarizing which makes its intracellular space more positive than the extracellular's (interstitial). This causes its neighbouring cardiac cell B to slowly begin to depolarize due to an influx of positive ion since its intracellular is more negative to that of A. The depolarization event will reach the cardiac threshold where voltage gated Na^+ channel opens and generates an AP. Additionally, the extracellular of A is more negative than that of B which means positive ions on the outside will flow to A.

Remark 2.14. For negative ions like Cl^- , the flow would be opposite to the positive.

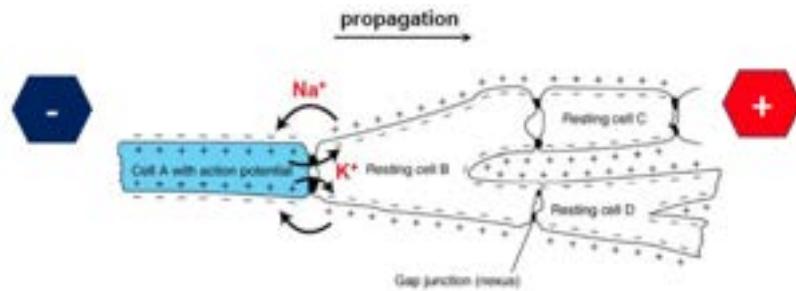


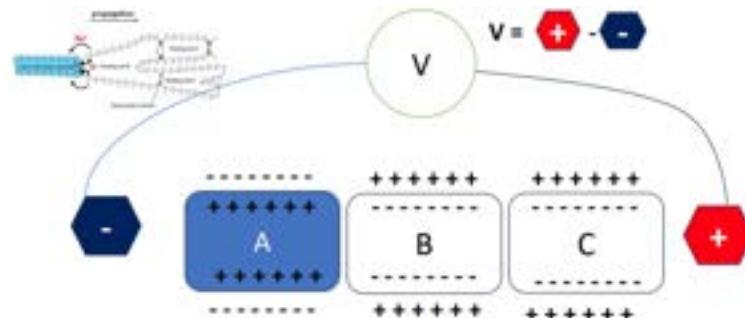
Figure 2.56: Brief overview of local circuit current and electrodes.

There are lots of these ions involved but what we're mainly interested in are Na^+ and K^+ . Now, ECG have electrodes that can sense the change in current in the outside (extracellular space). The positive electrode senses the positive ions while negative electrode senses negative ions (see Figure 2.56). The voltmeter is attached to both electrodes and will compute the difference between them as

$$V = \text{electrode}^+ - \text{electrode}^- \quad (2.12)$$

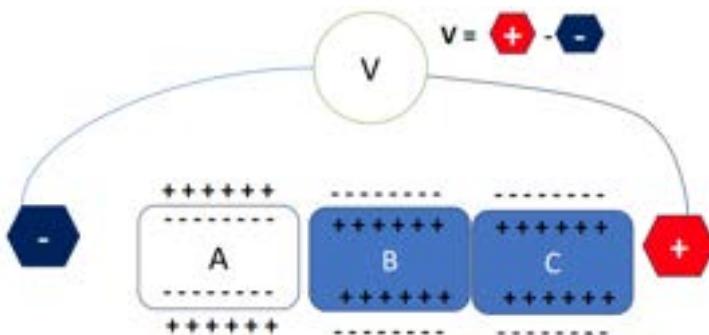
We'll look at some cases when connecting electrodes

- Case 1: cell A is depolarized (active). B is hyperpolarized (resting). Propagation is going from left to right. **Is the voltage positive or negative?**



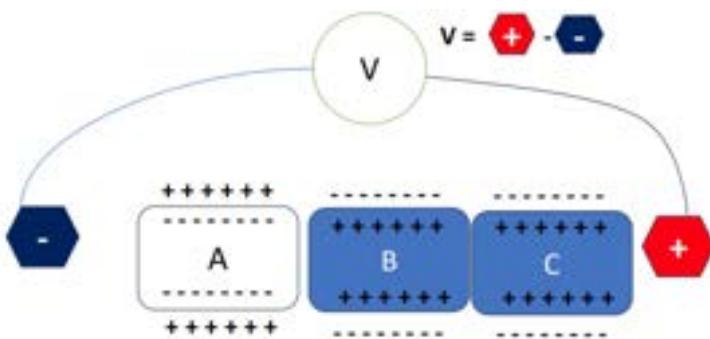
Answer: It will be positive since the positive electrode sense more ions than negative ions from the negative electrode.

- Case 2: cell A is hyperpolarized (resting). B is polarized (active) propagation is going from right to left. **Is the voltage positive or negative?**



Answer: It will be negative since the positive electrode will now sense more negative ions than positive ions sensed by negative electrode. And by equation (2.12), we get negative voltage.

- cell A is hyperpolarized (resting). B is polarized (active). A repolarization (relaxation) wave is going from left to right. **Is the voltage positive or negative?**



Answer: The voltage would still be negative due to the same reason as case 2. The reason is that electrodes do not sense the direction of depolarization but only the ions.

To summarize all of these cases: Depolarization going toward the +ve electrode, V is +ve while depolarization going toward the -ve electrode, V is -ve. The opposite would be true for repolarization. Repolarization going toward the +ve electrode, V is -ve, while repolarization going toward the -ve electrode, V is +ve.

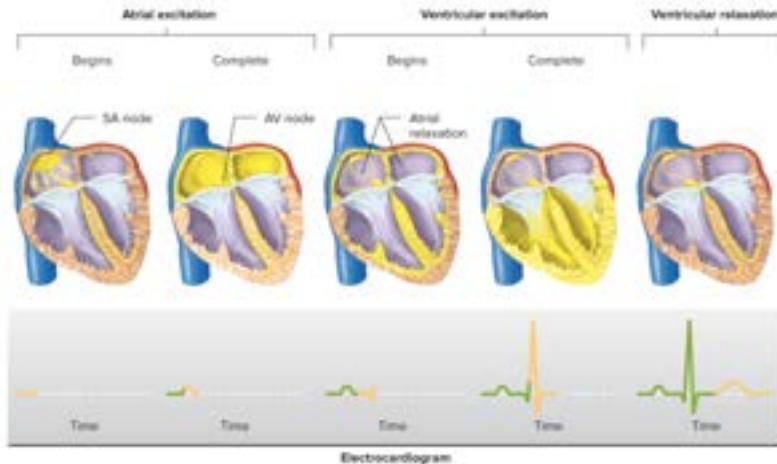


Figure 2.57: ECG and the cardiac cycle.

So now that we grasped a bit on local circuit current and how electrode would sense it, we can come back to the ECG and analyze it more.

When SA node is activated, no signal is detected on the ECG since it's too small. Then when the atria contract from right to left, it generates a P wave. Half way through the P wave is the activation of the AV node. A little delay of around 150ms comes the Q wave which is the activation of the septum from left to right.

As you can see, when depolarization (propagation) happens from right to left it's a negative deflection while left to right is a positive one.

Then after Q wave is immediately the R wave which is the ventricles contracting and the S wave which is the delayed ventricular contraction. Finally is the T wave where the ventricle is on its way to recover. **Why is the T wave positive?** Well...because of a peculiarity that the repolarization wave propagates on the opposite direction as the depolarization wave.

Bipolar ECG

Like we've given the definition before, a lead is made up of signals from 1 or more electrodes together. Now we also consider a lead as the metal wire connecting to the electrode on the body.

Example 2.5.2. In a 3-lead ECG, there are 3 limb lead wires that are connected to the body: the right arm (RA), left arm (LA) and left leg (LL). We also have another lead on the right foot for reference. From these 3 lead wires, we can define a new set of 3 lead using the differences between them. Lead I is defined as the difference between LA and RA, lead II is between LL and RA and lead III is between LL and LA

$$I = V_{LA} - V_{RA}$$

$$II = V_{LL} - V_{RA}$$

$$III = V_{LL} - V_{LA}$$

These leads are also called **bipolar lead** meaning that you get information of 1 lead by subtracting 2 of them.

Unipolar ECG

Sometimes, you can have unipolar lead that are placed at different angle around the chest or around the body.

Example 2.5.3. In a 12-lead ECG, we have 12 unipolar lead. 3 of them are called the **aVL, aVR and aVF** which are unipolar limb lead that are put at the

limb and their voltage sum will be 0V (Kirchoff's law). You can also have a series of electrodes at different position around the chest that is V_1 to V_6 . What this allows us to do is to take cardiac measurement at different angle and different plane of the heart which enable doctor to deduce what happens both on the surface as well as in the interior.

If you were to examine a 12-lead ECG recording, each lead will have a peculiar reading unlike the uniform ECG we described above. This is normal since the leads are different.

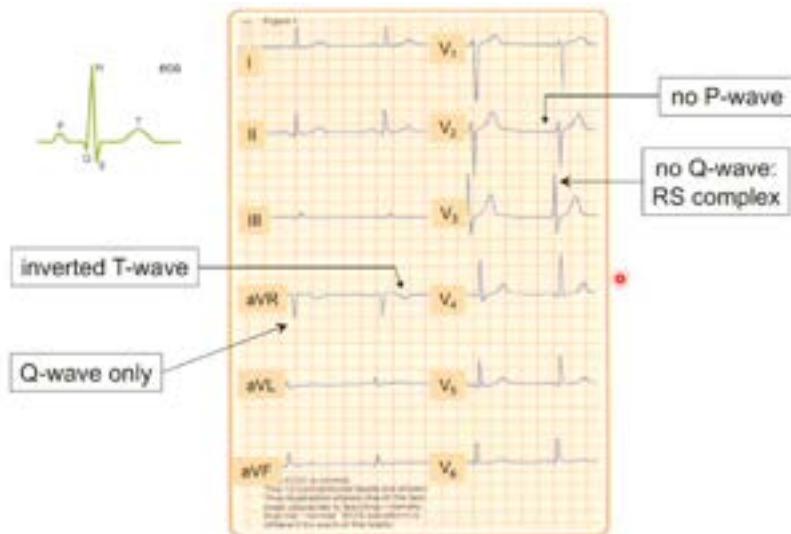


Figure 2.58: 12-lead ECG example. Each lead would have different recording. In V_2 , the ECG has no P wave. In V_3 , there are no Q wave in the QRS complex. In lead aVR, you have only Q wave and inverted T wave.

2.5.2 Action Potential in Relation to ECG

Now, we will look at how AP has anything to do with ECG. We can measure the transmembrane potential during an action potential even of each cardiac cells. Starting with the SA node, they have a typical AP where the membrane depolarize to threshold potential which generate an AP. Interestingly, SA node have the **pacemaker potential** or **pacemaker current** where the supposed constant resting potential is now rising by itself.

We can also look at the AP of a cell in the atria and see that it has the AP, a resting current of roughly -90mV, and a very fast AP upstroke. The AP of the His-Purkinje system is similar to that of the atria but now the AP is much wider and it has pacemaker current i.e. it can beat by itself if SA node is removed.

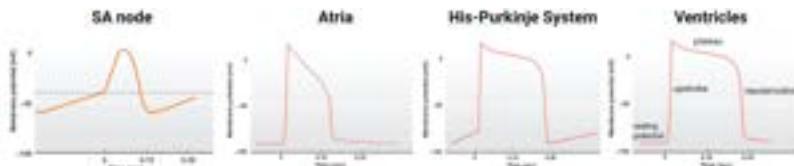


Figure 2.59: AP of different cardiac cells.

Remark 2.15. The pacemaker current is also called the **funny current** and it is a combination of Na^+ and K^+

Looking at the AP of the ventricles, we can see the same shape as before however it is much narrower and the resting potential is stable at around -88mV. Looking further at the ventricular AP, we can see many things. To start, when the cell depolarizes we call that the **upstroke** and once it reaches the top it begins to slowly reduced and is called the **plateau**. Then immediately after plateau it drops down and is called **repolarization**. The main thing we should note that **cardiac AP (around 150-300ms)** last much longer than typical neurons do.

What is driving these AP?

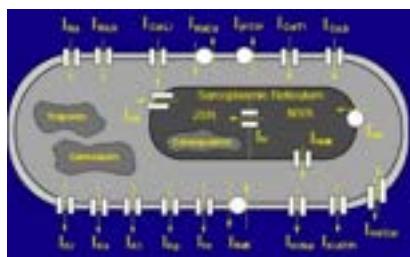


Figure 2.60: Different ion channels of for cardiac AP

Well...these cells have so much different ions channels that responsible for the driving force but for the purpose of this class, we will think of them aggregate together instead of individually.

Mechanism of Action (Ions Channels Drive Cardiac AP): During an AP, we have changes in conductance of these channels. A typical polarized cell has poor Na^+ conductance and won't allow much passage of them however they do allow K^+ to go through hence their resting membrane potential is close to K^+ potential. If the cell depolarizes a bit, the Na^+ channel opens which causes a rapid depolarization of the cell generating an AP. Then K^+ channel, which are normally left open for repolarization, begins to close. At the same time, Ca^{2+} channel opens and allows an influx of Ca^{2+} into the cell making the plateau phase as long as possible. Then K^+ reopens and repolarization takes place.

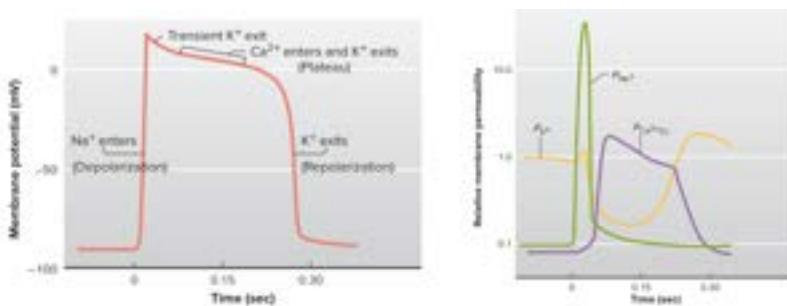


Figure 2.61: Ventricular AP and ion channels permeability.

For SA node, the cells do not have any Na^+ channel and rely only on the flux of Ca^{2+} to generate the upstroke hence they have slower AP generation. On the other hand, the His-Purkinje system has Na^+ channel which allows them to create a sharper upstroke during AP. Hence SA node has a slower upstroke velocity hence depolarizes and propagates slower than His-Purkinje system.

Furthermore, because the AV node delays electrical signal, the ventricle will beat around 150ms before the ventricle beats.

What does this has anything to do with ECG?

Well...what's happening is that you have different AP shape for the ECG. Looking at the P wave in comparison with the AP of the atria. The atrial AP is relatively shorter than ventricular one's this also means that atria are activated in the short PR segment. Repolarization of the atria cannot be detected as it is lost in the QRS complex (of the ventricle which has larger signal).

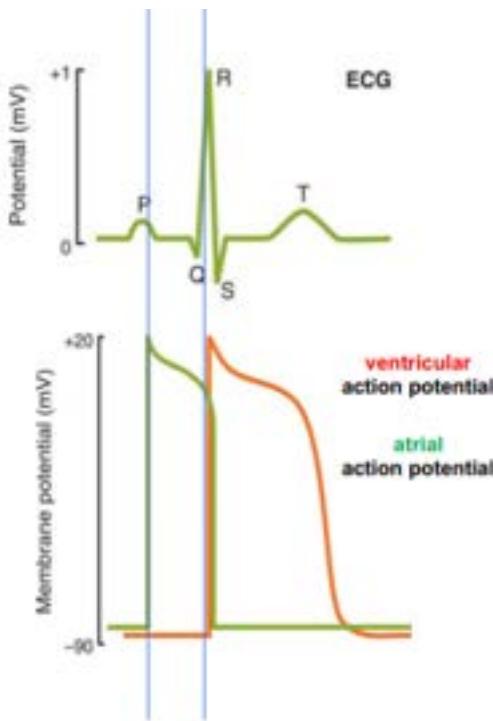


Figure 2.62: Ventricular and atrial AP in comparison on an ECG.

When the atrial repolarizes, the ventricles and the septum depolarize and contract creating that large signal masking atrial repolarization. After ventricular and septum depolarization, it begins to repolarize and since nothing is hindering it, it shows up as T wave on ECG.

We can create a general summary for all of what transpired i.e. we look at all the AP generated by only the atria and the ventricular and "super-

impose" each of those AP onto the ECG with colour as a representative of each AP. We can see the small activation of the SA node then atria contraction then etc.

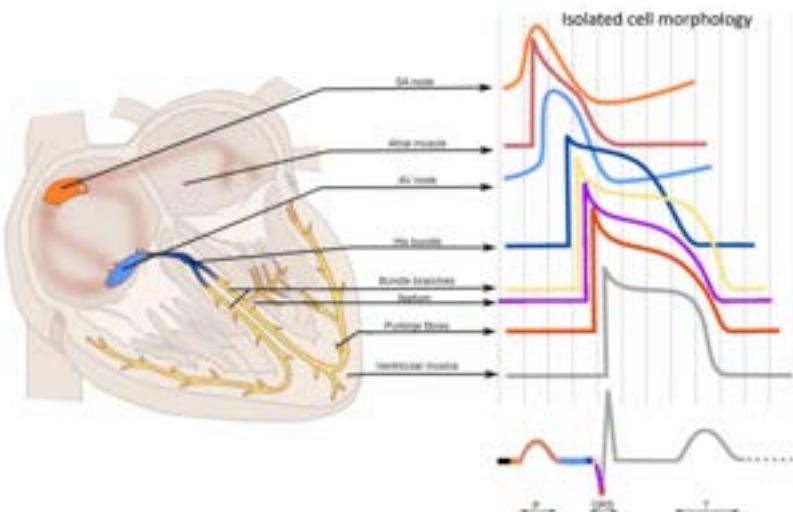


Figure 2.63: Summary ECG and AP of different cardiac cells.

2.5.3 Self-Test

1. (T or F) The left bundle branch is blocked. This will lead to a long QRS, and no Q wave.
Answer: True! The septum is activated early by the left bundle branch, which gives the Q. And the left ventricle will contract more slowly as the His system can't trigger synchronous contract.
2. (T or F) The left bundle branch block can result in a change of direction of the R wave.
Answer: Tricky! Both True and False. True – in that the left ventricle isn't going to contract synchronously (endo-epi), and this could result in a change of the waves direction relative to the electrodes. But also false, as we defined the R wave as a positive deflection. Terrible question.
3. (T or F) A repolarization wave deflecting in the same direction as an

activation wave on the same lead means that the direction of the repolarization wave changed.

Answer: True! If that didn't happen, the direction would reverse as the charge at the two electrodes has switched.

4. (T or F) The sinus node beats twice in a row, 50 milliseconds apart. We therefore see two P waves.

Answer: False! The sinus node doesn't have enough cells in it to cause a deflection in the ECG. To do so, it would have to trigger the atria. But the atrial action potential duration is 150 ms, and it wouldn't be possible to do that so quickly.

2.6 Cardiac Arrhythmias

We will begin by establishing some confusion that the students had. First off, the diagram of local circuit current might be misinterpreted by some, the Na^+ didn't flow into the cell A from cell B, it simply moves a few micron toward cell A. Yes, there are Na^+ entering cell B during depolarization, but in this context, it's a migration of Na^+ and not influx.

The next confusion is that **why is the voltage 0 on the ECG when the ventricles were excited?** Well..because we need to remember that the ECG has electrodes that measure the difference in potential of the cardiac cells. So if all of the ventricles are activated, electrode⁻ would sense, let's say 30mV and the electrode⁺ also senses the same thus the difference between is 0 hence it's 0 on ECG.

Finally, **why does repolarization wave cause a deflection in the opposite direction? Then why would T wave be positive?** Well...the T wave is a positive deflection even though it is the repolarization wave is due to the ventricular cardiac cells have different relaxation time i.e. if the outside has a faster relaxation time, then the ventricles relax from the outside in thus the T wave, theoretically is a negative deflection, will be flipped into a positive one which is what was observed.

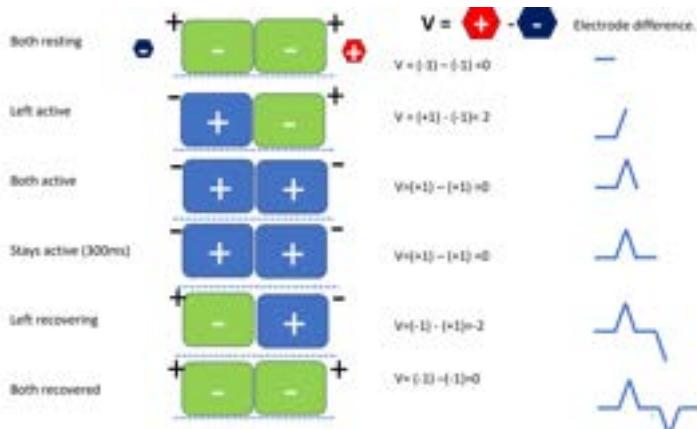


Figure 2.64: Summary illustration of how electrodes would measure the voltage difference and its corresponding ECG recording.

Now, the reason that the repolarization wave is moving toward the electrode⁺ i.e. the cell closest to the electrode⁻ repolarizes first and then move toward the negative.

2.6.1 Excitation – Contraction Coupling

Now it's important that cardiac cells can sense and propagates AP however it's main function still is mechanical as it needs to contract in order to pump blood. It's contraction is mediated by a process called **excitation – contraction coupling**.

Mechanism of Action (Excitation–contraction coupling): When cardiac cells membrane depolarizes and reaches the plateau phase, it will open the **L-type Ca^{2+} channel**, located in the invaginations of the membrane called **T-tubules**, allow Ca^{2+} to flow into the cytosol (inside of the cardiac cell). This Ca^{2+} will find and bind to the **ryanodine receptors** which cause an even large efflux of Ca^{2+} into the cytosol. These Ca^{2+} can create Ca^{2+} -troponin complex in the myofilaments which will lead to contraction (already discussed in PHGY 209).

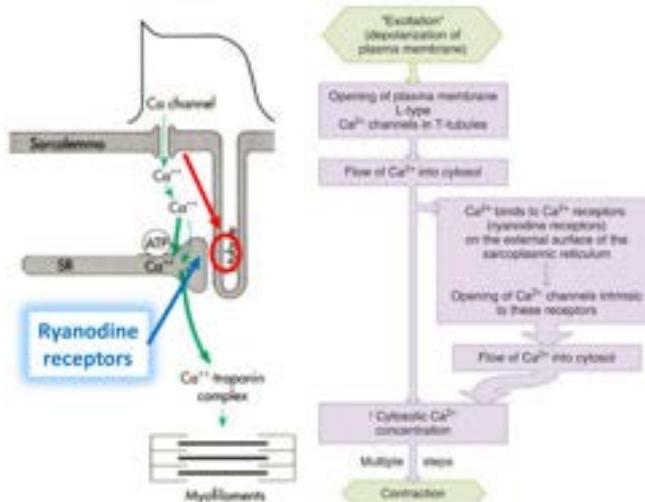


Figure 2.65: Excitation–contraction coupling illustration.

One thing to notice is that there's a slight delay between the AP (voltage transient) and the influx of Ca^{2+} (Ca^{2+} transient) of around 8ms. This is the same for the mechanical activity of the heart whereby it lags behind a generated AP. In certain cases, there could be damaged and uncoupling between the electrical and the mechanical activity of your heart e.g. In **pulseless electrical activity**, the heart has irregular rhythm and additionally, the electrical activity is too low to make your heart pump which can lead to **cardiac arrest**.

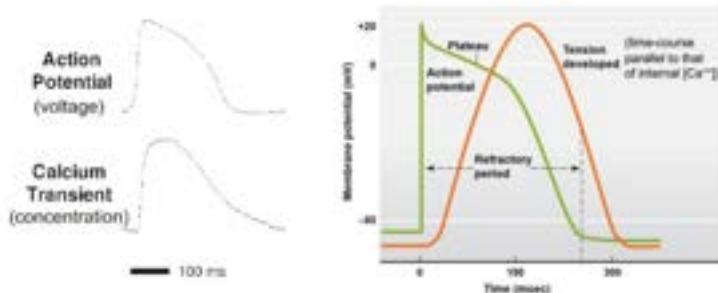


Figure 2.66: Electrical and mechanical activity of the heart and its Ca^{2+} transient.

2.6.2 General Consideration of Arrhythmias

The heart normally beats at around 70bpm (beat per minutes) which is roughly the same rhythm as the sinus node. When you have an abnormally slow heart rhythm of < 60bpm, we call it a **bradycardia**; otherwise, if it's an abnormally fast heart rhythm of > 100bpm, we call it a **tachycardia**. These 2 are both classified under **arrhythmia** which is a heart condition characterized by an abnormal heart rate/rhythm.



Figure 2.67: ECG of a normal and healthy individual.

With healthy and normal individual, you can have physiological arrhythmias which is when your heart beat at a different pace than normal due

to changing condition or metabolic state.

Example 2.6.1. A typically athletes tends to have a more efficient heart than others which means the heart do not have beat as much for blood to flow around. This also means their heart rate can be as low as 40bpm which is considered bradycardia. On the other hand, when a person exercises, they increase their metabolic rate which drive up heart rate hence tachycardia.

Another interesting thing is that breathing can change how your sinus node beat and this is called **respiratory sinus arrhythmia** (completely normal).

2.6.3 Pathological Arrhythmias

In case where you have irregular heart rhythm or rate not due to changing condition or metabolic state, you're experiencing a pathological condition that result in arrythmia.

Example 2.6.2. When you're resting and your heart rate is >100bpm, given that your heart is driven by the sinus node, then you're experiencing **pathological sinus tachycardia**.

Atrioventricular Block

Atrioventricular (AV) Block or is an arrhythmia characterized by the repeated loss of QRS complex on the ECG. The possible reason for an AV block is obviously an obstructed AV node or any obstruction downstream from the AV node: blockage of the His bundle, bundle branches etc. If it was a blockage of the bundle branches then both of them have to be blocked or else if only 1, the other ventricle can still contract due to the activity of the His-Purkinje system.

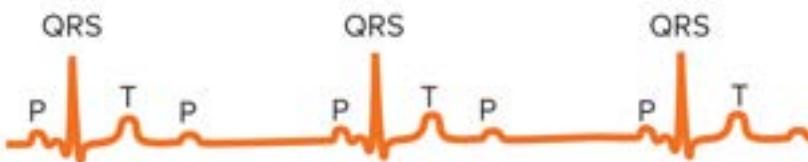


Figure 2.68: ECG of a 2:1 AV block where there's a missing QRS every second heart beat hence a 2:1 ratio

Though AV block isn't a deadly condition, the patient might experience discomfort due to missing heart beat. Additionally, this condition if left

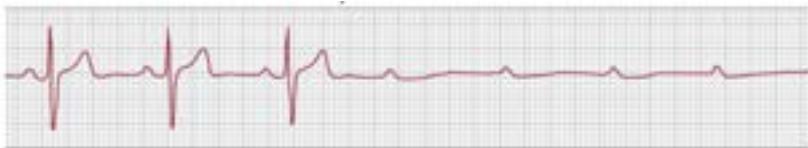


Figure 2.69: ECG of a complete AV block where the QRS complex is missing for every coming heart beat.

untreated can be worsened overtime that is: a patient with 2:1 AV blocks and become 3:1 and then finally **complete AV block** which poses a higher threat. A way to treat AV block is to use artificial pacemaker.

Premature Ventricular Complexes/Contraction

Premature ventricular complexes (PVC) is an arrhythmia characterized by an abnormal deflection of during ventricular contraction. Looking at an ECG of a patient, we can see normal ECG wave but then all of the sudden, there is this massive deflection that is out of the ordinary. This deflection happens *premature* (before) to ventricular contraction. The reason this happens is some of the cardiac cells, called **ectopic pacemakers**, can be excited during ventricular contraction but they're out of sync with each others hence causing the abnormal deflection.

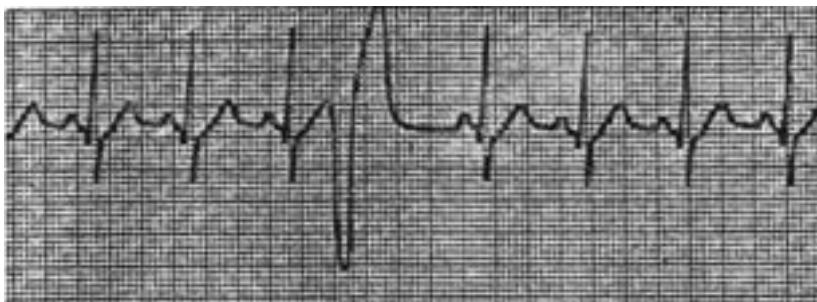


Figure 2.70: ECG of premature ventricular contraction where there's a large deflection at a QRS complex.

This condition is, in fact, quite common to all individual. If one has PVCs and has no secondary effect then it is called **parasystole** and is completely benign (unharmful). However, PVC can trigger a worst arrhythmic condition



Figure 2.71: ECG of ventricular parasystole.

Example 2.6.3. After a PVC is found on a patient, they immediately underwent **ventricular tachycardia** which is an arrhythmia characterized by rapid heart rate and abnormal deflection and can potentially lead to **fibrillation**, which is a very rapid and irregular beating of the heart.

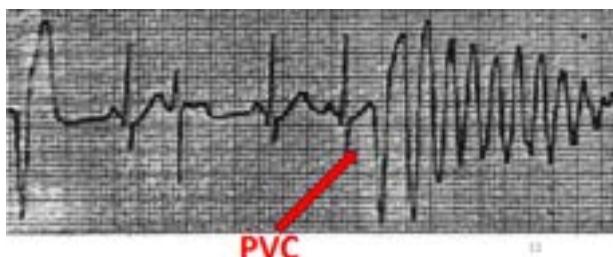


Figure 2.72: ECG of ventricular tachycardia becoming fibrillation cause by PVC.

In fibrillation, you get a non-organized wave propagation through the ventricles which lead to the non-synchronous contraction of the heart. On the ECG this is shown as a tightly packed "squiggly line" where each ECG wave and complexes are unrecognizable.

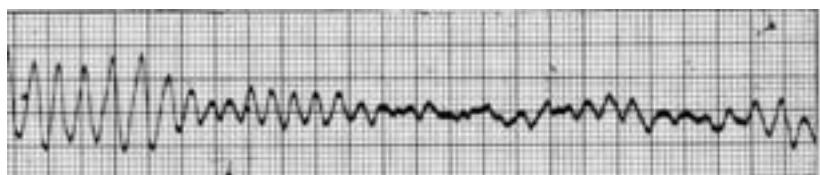


Figure 2.73: ECG of ventricular tachycardia and fibrillation where complexes and waves are reduced to squiggly reading.

When the ventricles don't beat as efficient nor synchronously, the arterial pressure and pulse will drop and can possibly lead to a stroke or heart

failure which is fatal if not treated properly. The best known treatment when a person is experiencing fibrillation is via an **automated external defibrillator (AED)**.

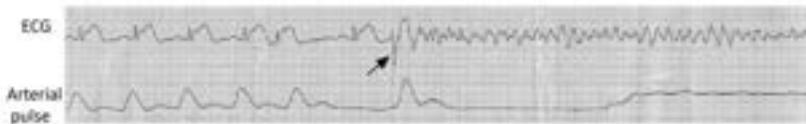


Figure 2.74: ECG and arterial pulse during fibrillation.

Atrial Fibrillation

Atrial fibrillation is an arrhythmia characterized by fibrillation in the atria and is caused by **paroxysmal (premature) atrial contraction**. The atria is not as important as the ventricles although it does help with the heart efficiency. Atrial fibrillation is prevalent with old age and is not deadly, although it may cause some discomfort for patient manifesting it.



Figure 2.75: ECG of atrial fibrillation.

This arrhythmia cannot be treated through surgery but by **pulmonary vein isolation**.

Procedure: First, physician needs to localize the origin of the pulse that causes atrial fibrillation. This is done by inserting a mapping catheter through a vein and allow physician to spot for the origin. We found that these pulses come from the pulmonary veins. The catheter is then used to burn a scar all around pulmonary and electrically isolate it thus preventing it from sending pulses.

Now because the atria has irregular beating and rhythm, it can also cause the ventricles to have such irregular activation which is why it causes discomfort.

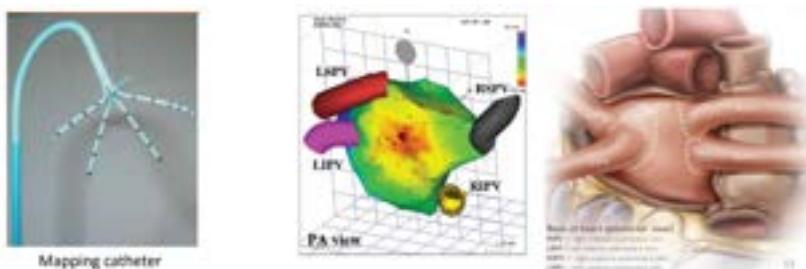


Figure 2.76: Pulmonary vein isolation illustration.

2.6.4 Tachycardia Mapping

So what's going on in all of these conditions? Well...in the early days, we have no clue but with advancing techs, we were able to understand what happened, which we will look at later on. In the early days, during surgery, they would attach lots of surface electrode called **sock array** which enable surgeon to see which waves are activating.

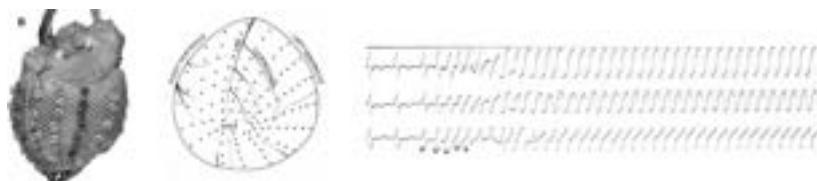


Figure 2.77: Sock array electrodes during surgery

Researchers then do the same on people with having arrhythmia or even inducing arrhythmia by giving the heart rapid low voltage shock. They then take all of the data and generate an **isochronal map** (see Figure 2.78). As you can see, each line on the isochronal map represents the activation wave at a point in time. In fact, we can see that the activation impulses propagate in a circular motion around a scar (in grey) and we call this **reentrant arrhythmia**. This circular motion forms a **reentry circuit**.

In normal patient, we wouldn't observe this circulation since impulses will move down to the heart apex and dies out instead of forming a reentry circuit. In a patient with ventricular tachycardia, we would observe the reentry wave forming a loop. Eventually, this loop will break up into smaller

ones since the tissues become exhausted. This breakage into smaller reentry circuit is what lead to fibrillation.

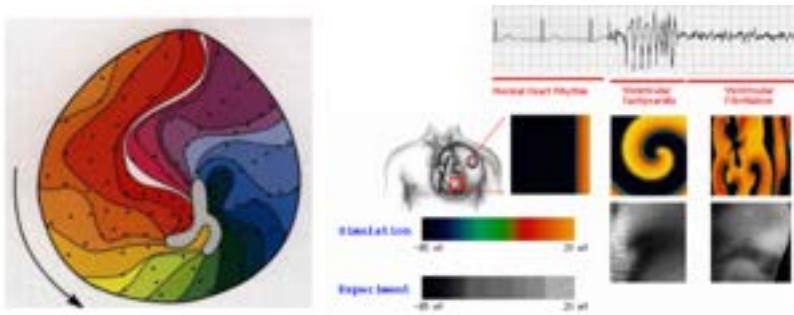


Figure 2.78: Isochronal and tachycardia mapping.

Here's more more rotation mapping but for voltage and Ca^{2+} signals

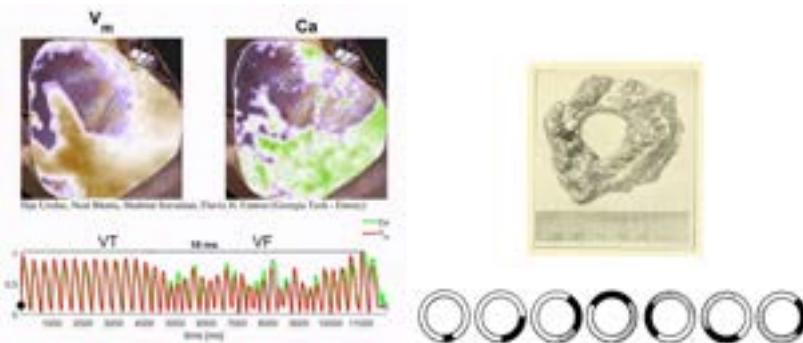


Figure 2.79: Rotating map of Ca^{2+} and voltage signals in the heart and George Ralph Mines experiment

George Ralph Mines was a professor of McGill University in the early 1900s and discovered the reentry circuit. In his experiment, he took cardiac tissue where a hole was cut through it. The tissue is slightly inexcitable and is allowed to have propagation on 1 direction only. And essentially, he sent pulses through the cardiac tissues and it begins to circulate around and this could possibly be the mechanism behind tachyarrhythmia.

2.7 Blood Pressure and The Cardiac Cycle

To begin with today's lecture, we need to address that Figure 2.64 (slide 6 from last lecture) was incorrect so here's the updated version.

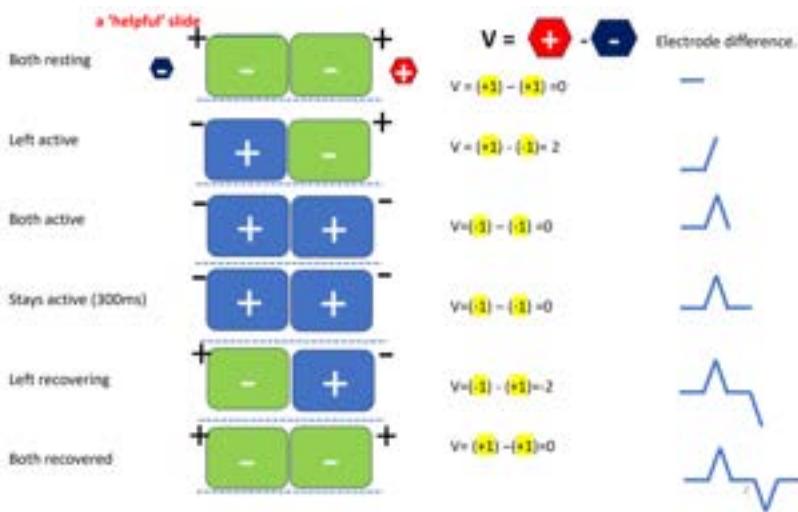


Figure 2.80: Correction of Figure 2.64 from last lecture.

Now last class we ended with George Ralph Mines' experiment about reentry wave as well as perform a little demonstration about it (which we won't talk about in the notes). So just to remind ourselves of his experiment, he got a cardiac tissue with a hole cut out. He then sent electrical wave such that it will propagate (circularly) in 1 direction only. From the image, we can see the black section are the excited cardiac cells while the dotted black are cardiac cells in its **refractory period** which is the time when cardiac cells cannot be excited. Nevertheless, the **circulation of the excitation wave is just long enough that by the time it reaches the refracted cardiac cells, they can be excited again hence creating the reentrant circuit.**



Figure 2.81: George Mines' reentry circuit experiment.

All excitable cells, specifically cardiac cells have refractory period (100-300ms). The reason that it has a time of being unable to be excitable is because all of its channels are open so it needs to return to its normal value of -90mV to be excited again. You can think of this wave of excitation and refractory period as a forest fire spreading. When the fire burns a forest, it begins to spread and whatever it leaves behind cannot be burned again but we have to wait for it to grow back to burn again (Please, do not actually burn the forest and grow it back to burn it again)...



Figure 2.82: Forest fire analogy

All in all, George Mines's experiment worked because he took a piece of cardiac tissue out which can be heterogeneous i.e. the refractory period, excitation, etc. of each cardiac cell are different from each other. This means when he sends an excitation wave out, it would go for all directions however some cells may not be excited from it and thus the wave dies out from that direction leaving only 1 direction left.

2.7.1 Blood Pressure

The main job that your heart does is to maintain the **blood pressure (BP)** gradient across the arteries and the veins that can lead to organ perfusion. Typically, during a heart beat of 1 second, the ventricles contract only 1/3 of that time.

At the beginning, the pressure of the ventricles is lower than that in the

aorta. When the ventricles contract, ventricular pressure increases until it reaches above the aortic pressure. At which point, the aortic valve is forced opened. The aortic pressure roughly track along with the ventricular pressure. Then as the ventricles begin to relax, ventricular pressure drops until it's lower than the aortic pressure. Then the aortic valve closes.

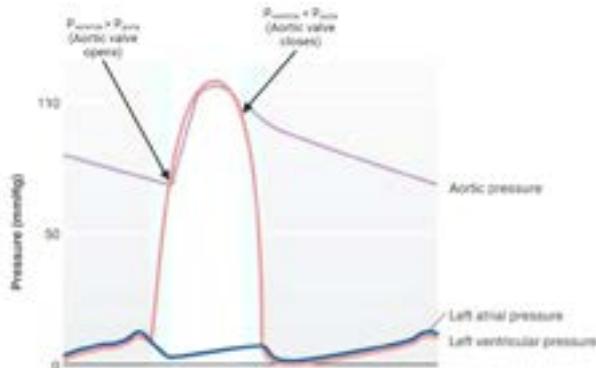


Figure 2.83: Ventricular and aortic pressure during ventricular contraction.

We can define the **pulse pressure** as the pressure difference between systolic and diastolic pressure in the aorta shown as the following diagram

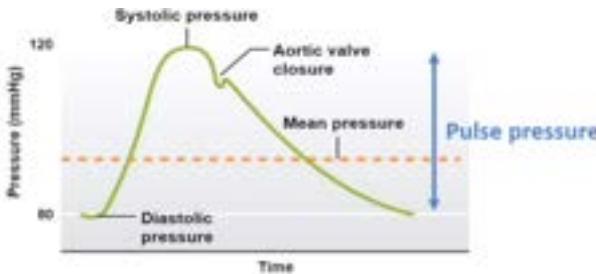


Figure 2.84: Pulse pressure in the aorta.

With the pulse pressure we can calculate the **mean arterial pressure (MAP)** as the following

$$MAP = P_{\text{diastolic}} + \frac{1}{3}P_{\text{pulse}} \quad (2.13)$$

If we plug in numbers, we would get roughly 100mmHg. **Why is it not 1/2?** Well...because the pressure wave shape is unusual where the base is larger

than the top. Typically, mathematician would take the area under the curve of the above graph to get the accurate MAP.

Now we know that the ventricles contract which generate pressure for only 1/3 of the time during a heart beat so **why doesn't your BP drops to 0 every second? Why is that our pressure is 120/80mmHg and not 120/0mmHg?** Well...the reason pressure isn't 0 is due to **Windkessel effect**.

Remark 2.16. Remember, when we look at BP, we give 2 value which correspond to $P_{\text{systolic}}/P_{\text{diastolic}}$.

Windkessel Effect

This effect arose from old firefighter pressure pump. Usually, the water hose is connected to a pump which is connected to an air chamber (German translated to *Windkessel*) then finally to the hose outlet. What happened is that when the pump is in the down stroke (producing pressure), the air will move up and store energy. In the up stroke, no pressure is generated by the pump, now **the air (holding energy) will move down transferring its energy to pressure and push the water out**. This allows a somewhat continuous stream of water flowing out.

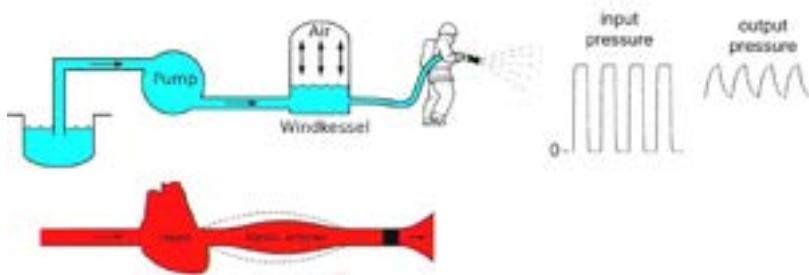


Figure 2.85: Windkessel effect illustration with water hose.

Now this is similar to the aorta. During systole (1/3 of cardiac cycle), the pressure will push onto the aorta and it will distend and hold some of those energy in the form of elasticity. Then, during diastole (2/3 of cardiac cycle), when no pressure is made by the ventricles, the elastic energy of the aorta will compressed down and thus BP isn't 0 during diastole. The amount of pressure the aorta can make is all come down to the compliance of the aorta.

$$C = \frac{\Delta V}{\Delta P} \quad (2.14)$$

This concept doesn't stop to only physiology but can extend to, let's say, electronics' capacitor that can store energy and release it.

Direct Blood Pressure Measurement

Now that we know about BP, **how do we actually measure it?** Well...there are 2 ways to measure it, the direct way (invase) or the indirect way (non-invasive).

In the direct BP measurement, we will have to puncture artery and insert a small tube into it. As the heart beats, the blood will increase to the tube to a certain level and that level is the BP for that individual.

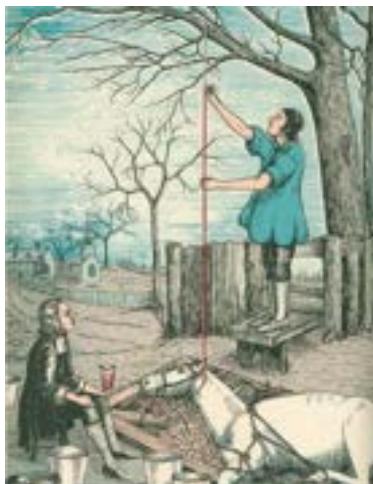


Figure 2.86: Blood pressure measured for a horse by creating a puncture in the artery and inserting a long tube in. This allows blood to be pushed up the tube when the heart beats, we can then record the height of blood as h . Knowing the density of blood ρ and gravitational acceleration of the earth g , we can get the blood pressure as $P = \rho gh$.

Luckily, we do not measure BP that way, instead, we perform indirect BP measurement and there are 3 ways: **Palpation, auscultation and oscillometry**.

In all 3 methods, they utilize an **aneroid sphygmomanometer** which is a cuff with a bladder and an inflating bulb which is connected to an aneroid gauge. When you squeeze the bulb, air is pumped into the bladder of the cuff thus inflating it. At the same time, air comes in to the aneroid gauge, pushing down onto its vacuum chamber which is connected to a pressure needle that allows us to know the cuff pressure.

There are also the used to **mercury sphygmomanometer** which is the

same setup as above but instead we use a mercury column. We don't use much of the mercury sphygmonanometer because of how toxic mercury is.



Figure 2.87: 2 different types of sphygmomanometers.

Indirect Blood Pressure Measurement: Palpation

In the palpation method, you use your hand to directly sense the pulse in the **radial artery** at the wrist to help with BP measurement.

Procedure: The sphygmomanometer's cuff is wrapped around the subject's arm (roughly at the bicep). The cuff is inflated until the pressure overcome the pressure in the artery thus blocking blood flow and you won't be able to sense a pulse. Then you slowly lower the pressure until a spurt of blood can flow through.

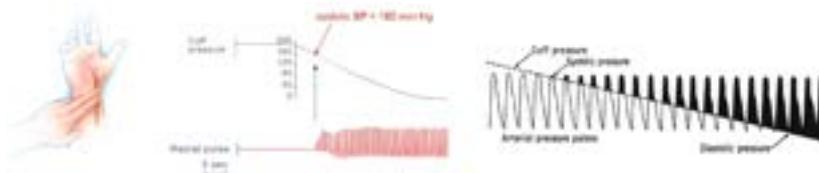


Figure 2.88: Palpation method to measure BP.

What happened is that as you lower the cuff pressure, there will be a brief moment that the pulse pressure will be higher than the cuff pressure. We can read that pressure in on the gauge and it will be close to its maximum that is the arterial systolic pressure.

Remark 2.17. *You need to release pressure slowly or else pressure error could be introduced.*

Indirect Blood Pressure Measurement: Auscultation

In the auscultation method, you use a stethoscope to hear the turbulent flow in the arm artery to help with BP measurement.

Procedure: We perform the same setup as the palpation with the cuff. Then instead of sensing pulse, we will be listening to the so-called **Korotkoff sound** which is the sound of turbulence flow of blood (laminar blood flow has no sounds). When the cuff is at maximal pressure, there would be no sound due to obstruction and then as cuff pressure lowers there will be a window of Korotkoff sound. Then as cuff pressure lowers further, the blood flow becomes a laminar flow and produces no sound again.

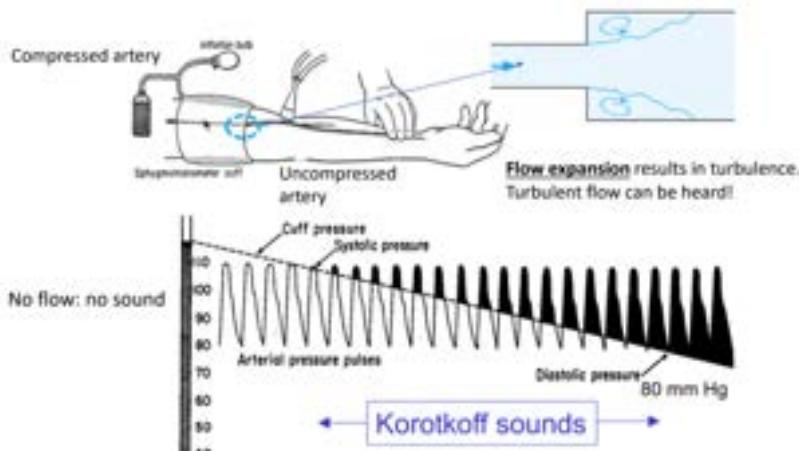


Figure 2.89: Auscultation method to measure BP.

The beginning and ending of the Korotkoff sound window correspond to the arterial systolic and diastolic pressure (at laminar flow). So the main advantage with auscultation is the ability to measure both systolic and diastolic pressure.

Indirect Blood Pressure Measurement: Oscillometry

Nowadays, we measure BP using oscillometry. Instead of the sphygmomanometer, we have this cuff that directly connects to a machine that can sense as well as pump pressure to the cuff. As the heart beats, we can sense these pressure waves moving through the cuff. The machine then does similar

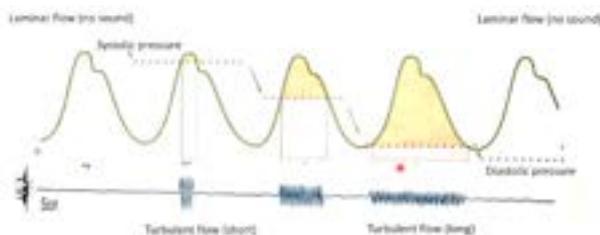


Figure 2.90: A better demonstration for auscultation.

thing as before where it will slowly decrease the cuff pressure but in oscillation (beyond the scope of this course).

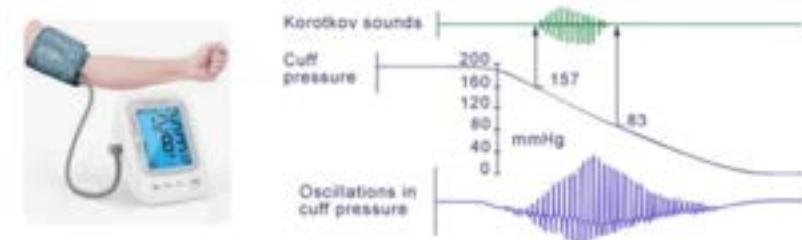


Figure 2.91: Oscillometry method to measure BP.

Why is this important? Why is BP important? Well...BP is important because it relates directly to organ perfusion. Essentially, we need BP gradient across the organ in order for blood to flow through its capillaries system and provide nutrients and take away waste. From previous lectures, we know that flow is defined with perfusion as

$$\text{Flow} = \frac{P_{\text{Perfusion}}}{R}$$

where R is the vessel resistance. We also know that perfusion pressure is defined as

$$P_{\text{perfusion}} = P_a - P_V$$

where P_a and P_V is the arterial and venous pressure. But because $P_a \gg P_V$, we can say that $P_a - P_V \approx P_a$. From all of what we've said above, we would have $P_a = MAP$ so now we can define flow as

$$\text{Flow} = \frac{MAP}{R} \quad (2.15)$$

Having BP is good but we need to regulate it correctly so that it does not go to high nor too low (in a narrow range). The system of BP regulation will be discussed in later lectures but for now, we just need to know a few things. BP is regulated and changed according to the metabolic need e.g. exercises. Flow in organs is kept at a constant rate despite changing BP and lastly the body will minimize fluctuation of arterial BP (neuro-hormonal control).

Total Peripheral Resistance

A key component to this control is the **total peripheral resistance (TPR)** which is the total resistance experienced by blood flow as it goes through the systemic circulation (includes all organs and capillaries). Another term that is used synonymously is **systemic vascular resistance**.

Now we can do some manipulation from equation (2.15) to get the TPR. We know that the flow for the entire systemic circulation is the cardiac output (CO) which means that we can rewrite equation (2.15) as

$$TRP = \frac{MAP}{CO} \quad (2.16)$$

We can rearrange them to $MAP = TRP \times CO$. We know from previous lectures that CO is defined as heart rate (HR) multiply by stroke volume (SV) which means that

$$MAP = HR \times SV \times HR \quad (2.17)$$

Pulmonary Vascular Resistance

We have a similar thing to TPR but at a lower pressure that is the **pulmonary vascular resistance (PVR)**. The reason that the pulmonary circulation has a lower pressure than the systemic is due to the right heart is much thinner and will generate a lower pressure than the left heart.

What are the changes in the pulmonary circulation? Well...the mean pulmonary artery pressure is around 15mmHg (instead of 100mmHg) while that in the vein is only 5mmHg.

Remark 2.18. *When calculate the perfusion pressure of pulmonary circulation, we cannot discount the venous pressure since it'd have an error of 30%.*

From here we get $P_{\text{perfusion}} = 10\text{mmHg}$. Now, because the flow in the pulmonary is equal to that in the systemic circulation which means that

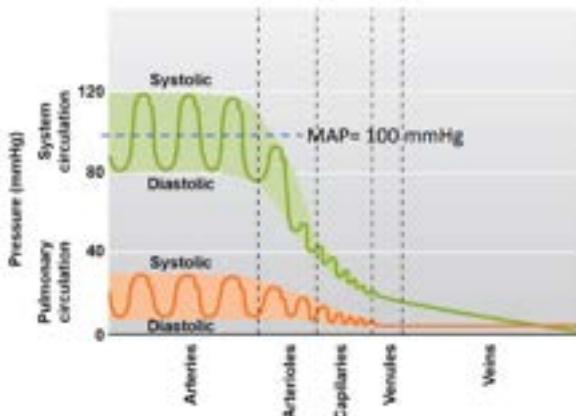


Figure 2.92: Pressure differences in the pulmonary and systemic circulation.

the PVR is much smaller than the TPR. This is why flow are the same: in the systemic, BP is high but TPR is also high while in the pulmonary, BP is low and PVR is also low.

2.7.2 The Cardiac Cycle

We will now look at the **cardiac cycle** and how it relates to BP.

The cardiac cycle is divided into 2 main events: **systole and diastole**. In systole, the heart contracts and forces blood out of the heart; while in diastole, the heart relaxes.

We shall begin with the **isovolumetric ventricular contraction phase** of systole. In this phase, around 10ms after systole started, the heart begins to contract and the ventricular pressure increases which close the AV valve. The reason it's called *isovolumetric* is because the volume of blood stays the same (only pressure changes). This phase begins 10ms after, is because the phase before is ventricular filling, where the atrial pressure is higher than the ventricles' thus blood flow in them.

After is the **ventricular ejection phase**. In this phase, ventricles contract more and ventricular pressure increases until it's higher than that of the aorta and pulmonary trunk. This causes the pulmonary and aortic

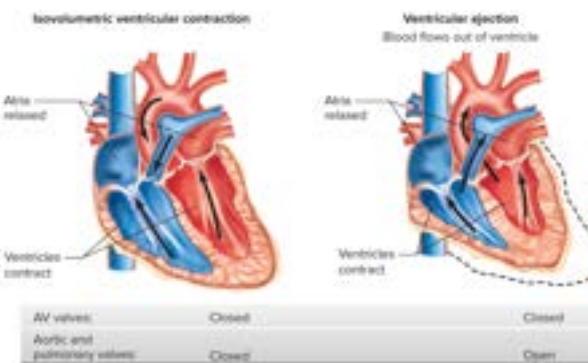


Figure 2.93: 2 phases in systole event.

valves to open and blood flow out of the ventricles. As the ventricular pressure reaches its peak in this phase, diastole begins and the pressure falls.

Now is the diastole event and we begin with **isovolumetric ventricular relaxation**. In this phase, ventricular contraction stops and its pressure falls. Then, the aortic and pulmonary valve close while their pressure is still high due to the Windkessel effect. When the valves close, ventricular pressure will drop to almost 0 but there's no change in its volume. At the same time, the vena cava will fill deoxy blood into the atria.

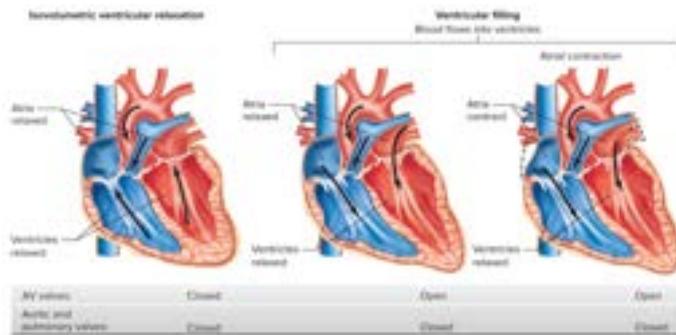


Figure 2.94: 2 phases in diastole event.

Then it is the **ventricular filling phase**. First, the atria relax thus lowering its pressure but is still higher than the ventricular pressure which means

AV valve slightly open and allow blood to flow in. Then, the SA node fires and causes the atria to contract thus increases its pressure and force more blood into the ventricles. After this, we return back to isovolumetric ventricular contraction and then the cardiac cycle restarts.

Wiggers Diagram

Another useful way of thinking about cardiac cycle is through the **Wiggers diagram**. Note that this diagram is specific for only left ventricles.

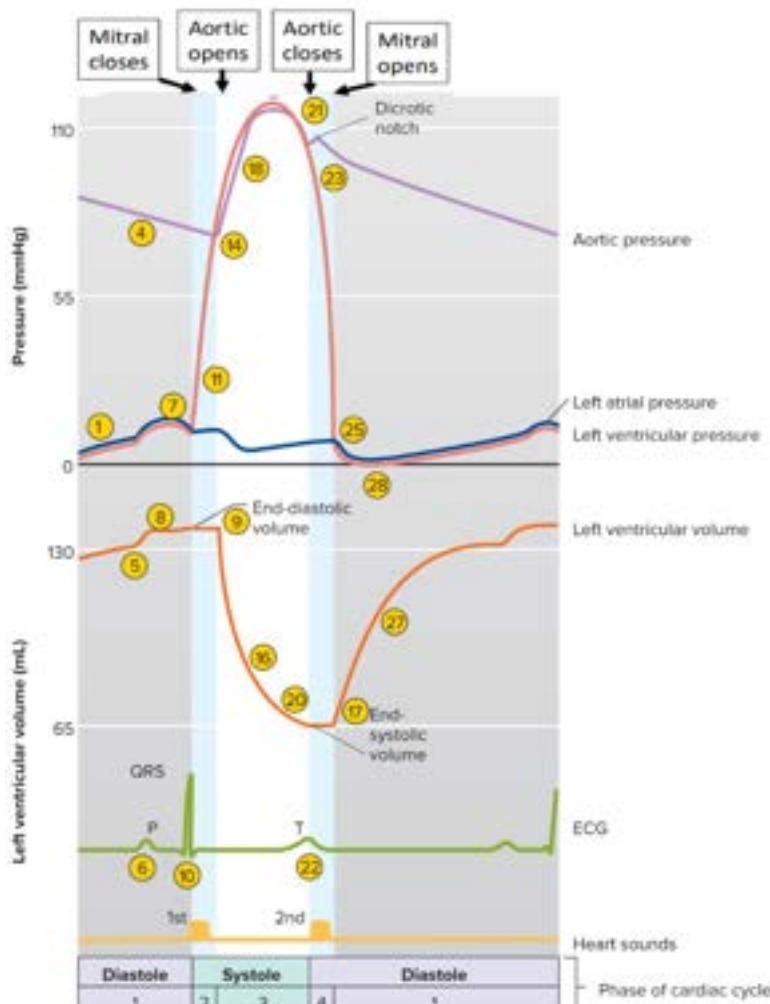
We will start from the beginning of diastole event of **(1) ventricular filling phase**. Here the left ventricular pressure drops lower than the atrial pressure. The mitral (left AV) valve and most atrial blood will begin to flow into the left ventricle.

Then the SA node fires leading to atrial contraction creating the P wave on ECG. Here, it's the "atrial kick" where it will force the rest of its blood into the ventricles. The amount of blood added into the left ventricle would probably be 10 – 15% of its volume. The signal from the SA node now reaches AV node and then to the His-Purkinje system leads to ventricular contraction creating QRS complex on the ECG. Here, as the ventricle contracts, its pressure slowly increases. The pressure will then increases higher than the atria's around 10ms after ventricular contraction started. This causes mitral valve to close while the aortic valve is "pre-closed" and this is the **(2) ventricular isovolumetric contraction phase**.

Now pressure will increase more in the left ventricle until it is higher than the aorta. Then, the aortic valve opens and begin the **(3) ventricular ejection phase**. The ventricular pressure increases more and the aortic pressure increases with it but is still slightly less than the ventricular. At the peak ventricular pressure, diastole begins and the left ventricle relaxes. The pressure, still high, begins to drop. As it falls, it will drop below aortic pressure which closes the aortic valve. The ventricular pressure will drop to almost 0 and all valves close and this is **(4) ventricular isovolumetric relaxation phase** and this is 1 cardiac cycle

Ventricular pressure drops below atrial pressure, the mitral valve opens and the ventricular filling phase begins; the cardiac cycle restarts.

If you ever see doctor using their stethoscope to listen to the heart (sounds



- 1 = Ventricular filling
 2 = Isovolumetric ventricular contraction
 3 = Ventricular ejection
 4 = Isovolumetric ventricular relaxation

Figure 2.95: Wiggers Diagram. Please ignore the number on the diagram, it was copied from textbook which have different explanation.

like "Lub-Dub"), they're not listening to the heart beat but rather the closing of the mitral and aortic valve. In the first heart sound (lub), it is the mitral valve closing, and in the second heart sound (dub), it is the aortic valve closing.

Remark 2.19. *The same event happens in parallel in the right heart where it's the closing of the tricuspid and pulmonary valve.*

Here are some important value and equations to characterize the dynamics of the heart mentioned above.

Stroke volume is the amount of blood pumped out of the ventricles after each beat.

Stroke Volume (SV) = end-diastolic volume (EDV) – end-systolic volume (ESV)

$$\begin{aligned} SV &= EDV - ESV \\ &= 120 - 50 = \boxed{70\text{mL}} \end{aligned}$$

Ejection fraction is the fraction of blood in the ventricle that will be ejected out.

$$\begin{aligned} \text{Ejection Fraction (EF)} &= \frac{\text{Stroke Volume (SV)}}{\text{end-diastolic volume (EDV)}} \quad (2.18) \\ EF &= \frac{SV}{EDV} \\ &= \frac{70}{120} = \boxed{60\%} \end{aligned}$$

If you have infarction or cardiac diseases, it can decreases the efficiency of the heart and EF could decrease.

Cardiac output is the quantity of blood pumped out of the heart for a given amount of time.

$$\begin{aligned} \text{Cardiac Output (CO)} &= \text{Heart rate (HR)} \times \text{Stroke volume (SV)} \quad (2.19) \\ SV &= HR \times SV \\ &= 70 \times 70 = \boxed{4900\text{mL/min}} \approx \boxed{5\text{L/min}} \end{aligned}$$

In the Right Heart

What we've just talked about happens in the left heart, but we also must realize that the a parallel event happens at the same time in the right heart.

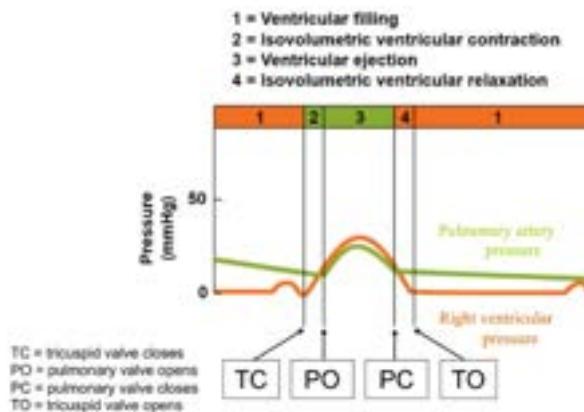


Figure 2.96: Cardiac cycle in the right heart.

The only difference is that the right heart involved with different set of valve but also at lower pressure.

2.8 Blood Pressure Control I

Before begin this lecture, here's the review question from the previous lecture.

1. (T or F) The ventricle generates pressure over the duration of the cardiac cycle.

Answer: False! - it only generates pressure over about 1/3 of the cycle. The rest is due to the Windkessel effect.

2. (T or F) The Windkessel effect generates pressure over the cardiac cycle except during the contraction of the ventricle.

Answer: False! Systole starts the instant that the ventricle contracts. There is a period of isovolumetric ventricular contraction when the aortic valve is closed, and no pressure is generated by the ventricle in the aorta.

3. (T or F) The BP measures of palpation, auscultation and oscillometry measure the same thing in different ways.

Answer: False! While they all can estimate systolic pressure, only auscultation and oscillometry measure diastolic pressure.

4. (T or F) A patient has a muscle twitch in their bicep. This might give abnormal readings using an automated BP machine, but not using the stethoscope method.

Answer: True! The cuff pressure in the oscillometry measure is used to estimate BP. Twitches in the muscle would change the cuff pressure, but wouldn't affect the Korotkov sounds, which are downstream. But this is just a guess! – the manufacturers probably have algorithms in place to counter this.

5. The two valves of the left ventricle are either open or closed. There are 4 possible ways the valves can present: (closed, closed), (open, closed), (closed, open) or (open, open), and each defines a phase. Is this true?

Answer: False! The two valves are never open at the same time. Blood would flow in the wrong direction!

There are some questions from students concerning materials of previous lecture so we will go through that as well:

what is pulse pressure and is it different from the aortic pressure? Well...pulse pressure is the maximal pressure in the aorta vs the minimum pressure in the aorta. so essentially, it's the difference between the aortic systolic pressure and aortic diastolic pressure.

What does pulse pressure do? Well...physiologically, it doesn't do anything since it's a calculation of 2 different times (diastole vs systole). Nevertheless, pulse pressure can give an insight to a possible manifestation of a disease i.e. it's a diagnostic tool.

which arteries are responsible for the Windkessel effect? Well its the wall of the large elastic arteries e.g. aorta, common carotid, subclavian etc. the smaller arteries don't

We will look at how the body control the BP. The main thing to keep in mind is that we care more about the flow of blood and not the pressure itself, but because pressure is related to flow, maintaining it directly influence BP.

2.8.1 Frank-Starling Mechanism

In **Frank-Starling Mechanism** or **Starlings law of the heart**, it states that if you stretch a cardiac muscle, it will contract with a greater force. Basically the Frank-Starling mechanism allows a greater stroke volume (SV) when the end-diastolic volume (EDV) increases .

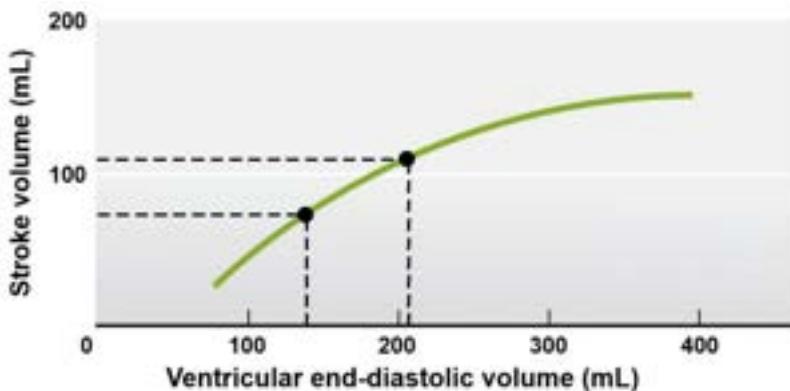


Figure 2.97: Frank-Starling mechanism graph.

We can plot this relationship where SV is a function of EDV on a graph (see Figure 2.97) and see a gradual increase of SV as we increase EDV. e.g. The normal EDV is roughly 140mL which corresponds to roughly SV of around 70-85. As we overfill the ventricles up to 210mL, the cardiac muscles stretch which lead to a greater contractile force thus bringing SV to 110. This mechanism is important for exercise.

Remark 2.20. We defined the ventricle wall stretch as **preload**. We can measure EDV which can lead us to know the preload.

2.8.2 Autoregulation

Autoregulation is a concept where some critical organs can control their own blood flow. To conceptualize this, We're going to attach 2 tubes to the coronary artery (thought experiment). The aorta is now not going to be what dictate the **coronary perfusion pressure** anymore and we have full control of it.

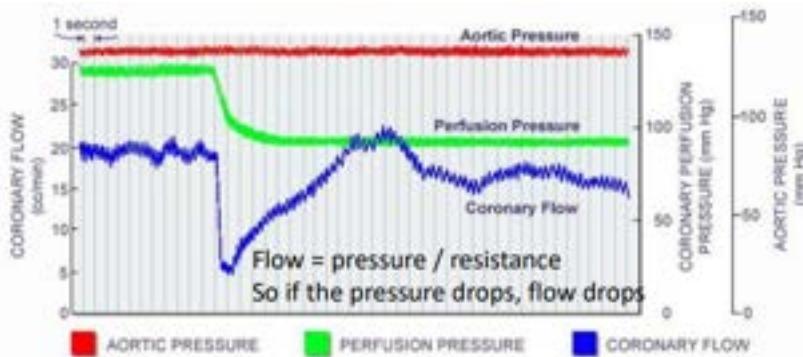


Figure 2.98: Autoregulation experiment graph.

We now lower the coronary perfusion pressure and the flow of the coronary also drops but much more rapidly. Nevertheless, what you would find is that over around 10s, the pressure begins to climb back up. **What happened?** Well...it's a compensatory mechanism, when the blood pressure drop, the resistance drops with it to bring flow back to near normal.

Remark 2.21. This type of regulation does not require neural control and happens locally at the organ.

We define the period where there was an instant drop in flow when we lower perfusion pressure as the **immediate effect**. While, the period where flow is slowly build back to its normal range even with lower perfusion pressure as **steady state effect**.

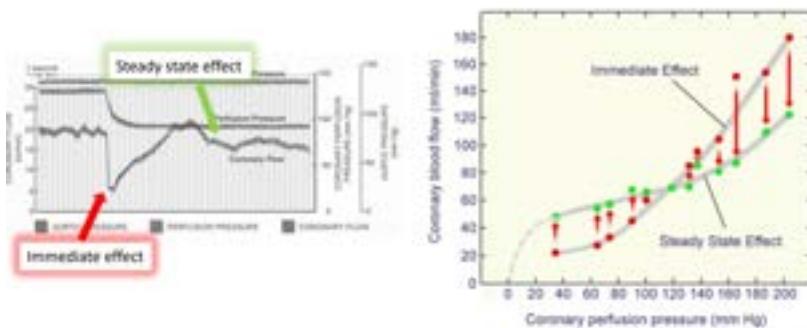


Figure 2.99: Immediate vs steady state effect plot.

We can plot this immediate effect and the steady effect of the experiment. At first is the curve of the immediate effect where a change in perfusion pressure lead to a sudden drop in flow (the reverse would happen if pressure is too high). Now, after 10s, the immediate effect curve would reorient itself to become the steady state curve.

Remark 2.22. *This is a powerful effect given the perfusion pressure range of around 40-160mmHg. Beyond this range, the effect flatten while lower than this range, it breaks off.*

Metabolic and Myogenic Autoregulation

There are 2 kinds of autoregulation: **metabolic** and **myogenic autoregulation**.

Example 2.8.1. If P_a drops in organ, blood flow in it also drops. This means there's a decrease in O_2 concentration and increased in **metabolite** (waste products). Then, due to autoregulation, it causes **vasodilation** in organ. This is the same with muscle when you exercise. This is called the **arteriolar dilation** in organ. By having arteriolar dilation, you decrease massively resistance (due to Poisseuille's law) thus restoring the flow through the organ.

At the same time, you have pressure drops downstream which means the

vessel wall stretch less in organ and they're independent of waste product and oxygen.

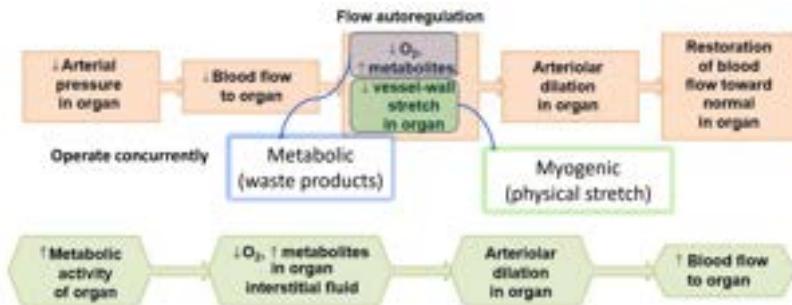


Figure 2.100: Metabolic and myogenic regulation.

These vessels have mechano-sensitive channels that are sensitive to stretch. These channels are opened when there's a stretch and can let in Ca^{2+} which allow muscular contraction of the vessel lining which lead to a decrease in vessel diameter. The opposite is true where a lower stretch of these vessels lead to lower contraction.

Essentially, you have 2 mechanism for autoregulation that is metabolic and myogenic regulation. Metabolic deals with the build up of waste product and decrease oxygen, while myogenic deals with physical stretch of the vessel. They tend to work in parallel which each other.

If you work out, metabolic rate goes up, O_2 decrease and metabolites increase again. The exact same mechanism will occur however there's no lowering BP which means your flow increase. Basically, you're using the same process for different outcome i.e. this process when used on lower P_a result in restoration of flow but if applied on to exercising individual boost flow.

When there's an increase in blood flow in your organs (maybe due to increased in exercise), we call it **hyperemia**. When there's a local hyperemia, it is synonymous to **local metabolic control**.

2.8.3 Neural Control of The Heart

Both the parasympathetic (PSNS) and sympathetic (SNS) nervous system, which are part of the autonomic nervous system, has effects on heart rate (HR), vessel tone, and contraction strength as well as vessels in the periphery. This also means that it can control the CO, which depends on HR, SV; and MAP, which depends on HR, SV and TPR. In general, the PSNS modulate HR while the SNS affect HR, SV and TPR. They work together to have the desired effect.

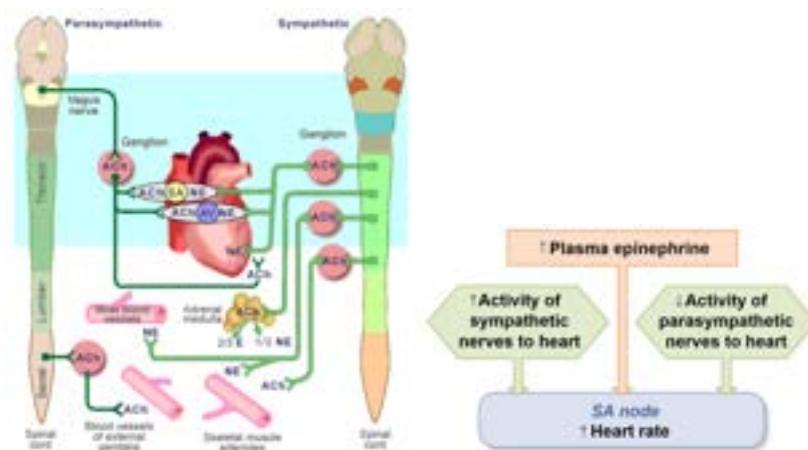


Figure 2.101: Outline of controls to the heart by the PSNS and SNS.

The SA node firing rate is increased by an increased in plasma EPI. This has the similar effect as the activity of SNS increase but it opposite for PSNS i.e. as PSNS activity increases, SA node firing rate (which makes HR) decreases.

Heart Rate

The SNS and PSNS can change the HR but it's the not only the thing that control it i.e. the heart can beats on itself without their input because SA node fires automatically. **The rate of the SA node firing would be changed because of the SNS and PSNS.**

Mechanism of Action (PSNS HR Control): From the medulla, pre-ganglionic axon go to ganglion (neuron clusters) located in the fat pads on the surface of the heart. The fat pads then send projections to the SA node and also to AV node. The preganglionic nerves release a molecule called **acetylcholine (ACh)** to the ganglion which bind to its the **nicotinic acetylcholine receptors (nAChR)** making the ganglion release ACh. Then ACh is released by the ganglion to the SA node, which binds to **muscarinic receptors**. This ultimately leads to increase neural activity of PSNS but decrease in HR.

Remark 2.23. A drug called **atropine** can bind and block muscarinic receptor thus allow HR increase if it was low before.

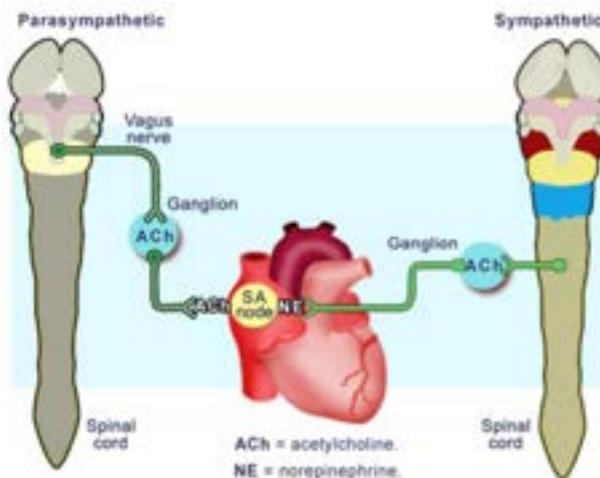


Figure 2.102: SNS and PSNS control of HR.

Mechanism of Action (SNS HR Control): Preganglionic axons move out from the spinal cord to the ganglion that is relatively close to the heart (not on fat pads). Similarly, preganglionic axons release ACh to the ganglion thus activating it; however, the ganglion will release **norepinephrine (NE)** (AKA noradrenaline) to the SA node which binds to **β -adrenergic receptor**. This leads to an increase in

neural activity of SNS as well as increase in HR.

Remark 2.24. A drug class called **β -antagonist (blocker)** can bind to the β -adrenergic receptor and inhibit NE from binding to it thus lowering HR. The opposite would be β -agonist which increase NE binding thus increase HR.

Stroke Volume

SNS can also effect contraction. Going back to the SNS ganglion, we can see that it will also project to the cardiac wall and not only the SA node. Then, it can release NE to the myocytes which lead to an increased in contractility of the muscle which lead to an increased in SV. Likewise, introduction of a β -blocker also decrease SV i.e. **β -blocker not only decrease HR but also decrease contraction strength of the heart.**

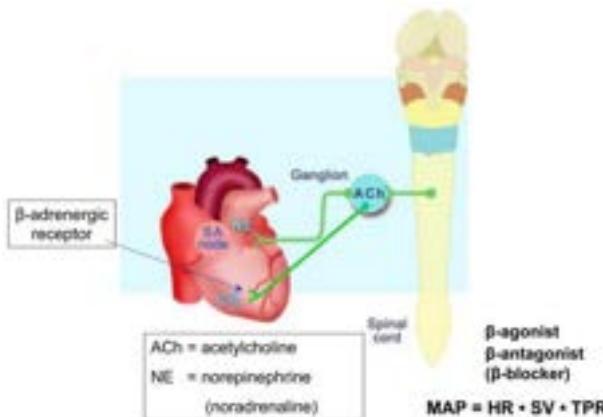


Figure 2.103: SNS control on SV.

Increasing contractility does not only increase the maximal force but also decrease duration of contraction and increase the rate of applied force. This allows myocytes to have more AP into a same period.

Increase in contractility does something interesting. If you increase EDV, you would get an increased in SV (Frank-Starling mechanism); however, if you increase contractility, you would shift the entire EDV-SV curve up which means EDV variation is the same but at higher SV only.

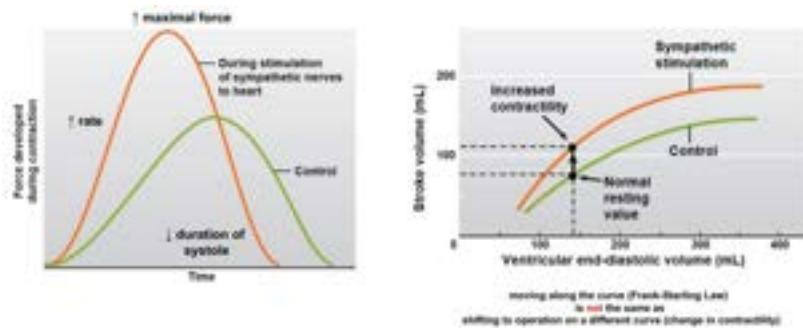


Figure 2.104: Increase contractility with decrease duration (left graph) and up-shifting EDV-SV curve with increase contractility (right graph).

Vessel Diameter

The SNS can also control the vessel diameter which is an important parameter to change locally in organs or even globally for MAP.

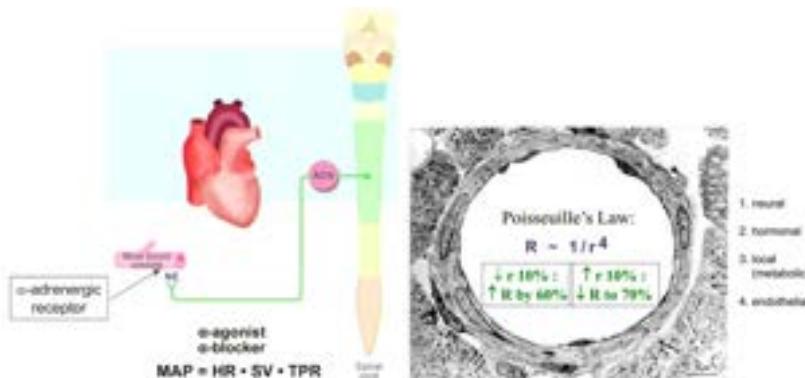


Figure 2.105: SNS control of diameter and Poisseuille's law.

Mechanism of Action (SNS Vessel Diameter Control): Similar pathway to SV and HR, preganglion axons from the spinal cord sends ACh to the ganglion thus activating it. From the ganglion, there are projection toward the arteries where the ganglion release NE that can bind to the arteries' **α -adrenergic receptors**. The NE

binding will lead to the muscle lining of the arteries contract and thus reduce vessel diameter.

Remark 2.25. A similar drug to β is **α -antagonist (blocker)** that can block the binding of NE and thus reduce TRP and MAP. α -agonist would be the opposite

Definition 2.8. **Tone** is state of contraction of smooth muscle in the walls of the vessel.

Importantly, most vessels have α -adrenergic receptors but capillaries do not since they have no smooth muscle.

Control of Adrenal Glands

Mechanism of Action (SNS Adrenal Glands Control): From the spinal cord, a projection goes directly toward the adrenal glands (small glands lies superior to the kidney). Such projection causes the adrenal glands to release **catecholamines** which are NE and **epinephrine (E)** into the blood stream. The NE and E molecules are α and β agonist which will have global effect on HR, SV and TPR because these molecules are in the blood stream.

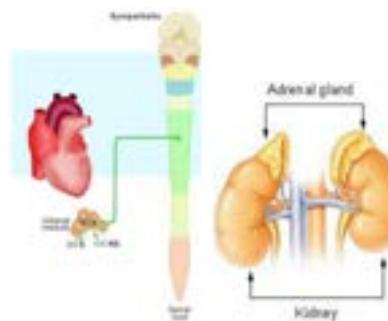


Figure 2.106: Adrenal gland control.

We've just talked about the mechanism of changing these parameter but we never talked about things that are responsible to track/make these decision.

2.8.4 Blood Pressure Control Systems

There are lots of component to the control systems but we will look at only some of it.

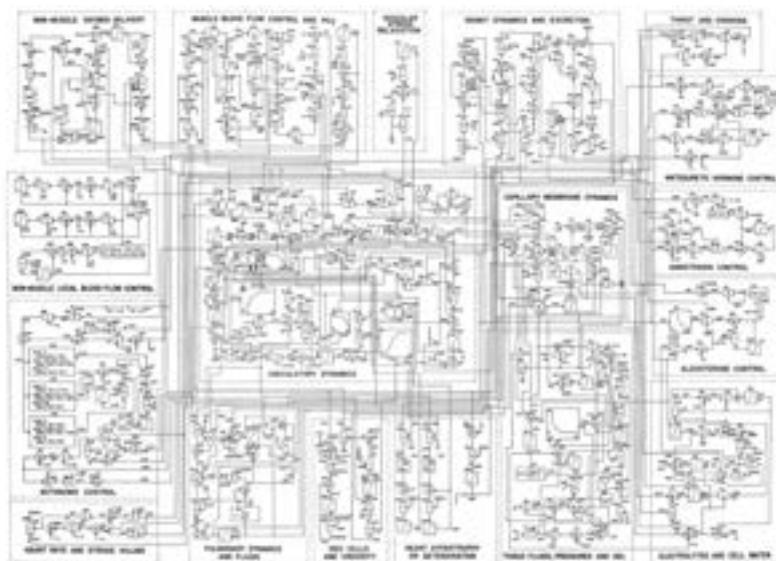


Figure 2.107: Drawn out control system of BP in 1972, this could've been changed and added more in recent years.

We can take some important control system and plot it on a graph of regulation vs time, and 1 things about all of these systems we've found is that **they all have different activity period** e.g. The **baroreceptors reflex** allows you to stand up without a quick decrease in pressure leading to faint; because of this, they tend to have a very quick activity time. **Renal-body fluid pressure control** allows you to control of total fluid volume; because of this, they tend to act more slowly. We will mainly to about the baroreceptor reflexes, renal-body fluid pressure control and the renin-angiotensin control.

Another observation can be made that there are different ranges of BP that these receptors can control e.g. baroreceptors can control a wide range from 50 to 225mmHg, while the CNS ischemic response control only when BP is dangerously low. The most powerful of them is the renal-blood volume

pressure control as it's functional at all range of pressure.

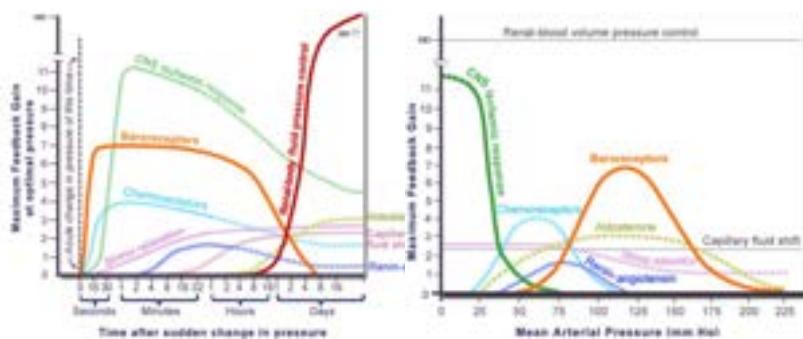


Figure 2.108: Control system feedback gain (left graph) and its operational range (right graph).

Baroreflex

The **baroreceptor reflex (baroreflex)** is a fast respond to BP changes and they're located on **carotid arteries** that sense pressure. They have a sensory arm that sense the change in pressure but also a motor arm that can create the reflex (response to the change in pressure).



Figure 2.109: Baroreceptors.

With every HB, aorta and carotid sinus stretch opens mechano-sensitive channels of baroreceptor which signal to the brain. When there's a normal range of P_a , the baroreceptors fires at a frequency with a slight increase at every peak of the pressure. If BP increases, then the firing frequency at the pressure peak would increase and similarly but opposite when BP decreases.

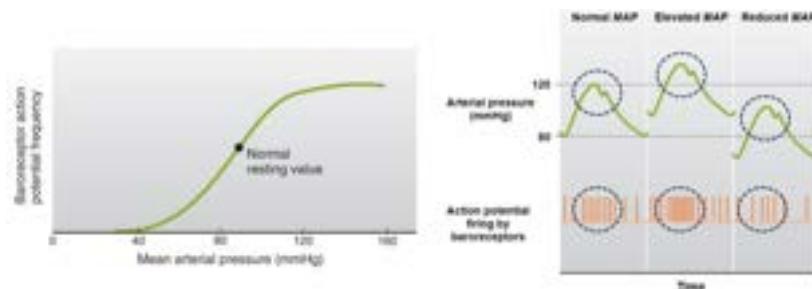


Figure 2.110: Firing rate of baroreceptors depending on pressure.

If you stand up suddenly, there's a large blood flow from the trunk to the leg and this result in drops of baroreceptor firing rate which is reported back to the brain. This immediately activate the SNS and PSNS to do their respective work. Activation and inhibition of SNS and PSNS respectively will drive up HR. The SV (increased contractility) and TPR (arterioles constriction) will also increase due to SNS activation. With all of that, it will build up to an increased in MAP which allow you to not faint or fall over when you stand up.

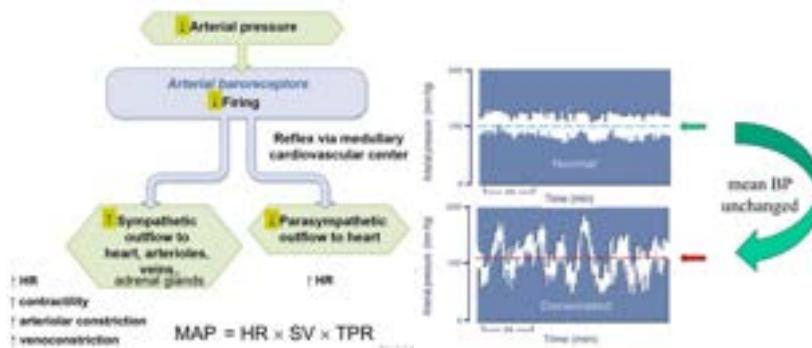


Figure 2.111: Baroreceptor activating SNS and PSNS which changes the arterial pressure (left) and cutting baroreceptor experiment with its P_a variation effect (right).

We can do an experiment by removing the baroreceptor. Doing so, we can see that the P_a , that typically stayed relatively constant, varies rapidly and widely. This is because there are no negative feedback response by the

baroreceptor to have P_a at a constant level. This condition with P_a variation due to possible failure of baroreflex is called **labile hypertension**.

Interestingly (no need to know), you can manually stimulate the carotid sinus thus activating the baroreflex. A carotid sinus massage can lead to its decreased in activity. Additionally, some people have hypersensitive baroreceptors or carotid sinus and they can faint simply tilting their head to tying a tie.

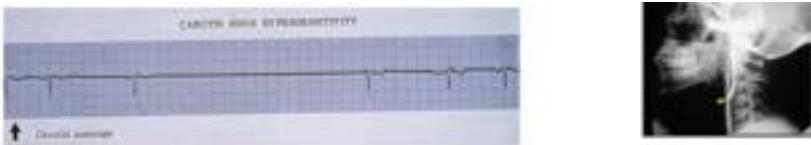


Figure 2.112: Carotid sinus hypersensitivity ECG and its location on X ray.

2.9 Blood Pressure Control II

In today's lecture, we will look at more control systems of blood pressure (BP) that is essential for long-term (baroreflex was short-term). Nevertheless, there was 1 more rapid-acting system for BP that we need to get into that is the peripheral chemoreceptors.

Peripheral Chemoreceptors

The **peripheral chemoreceptors** are located into the **carotid body** (located on arteries ascending to the brain) and **aortic body**. Because they're chemoreceptors, they can sense the change in P_{O_2} , P_{CO_2} and pH in the arterial blood. They primarily act on respiration; even then they have some effect on the heart rate.

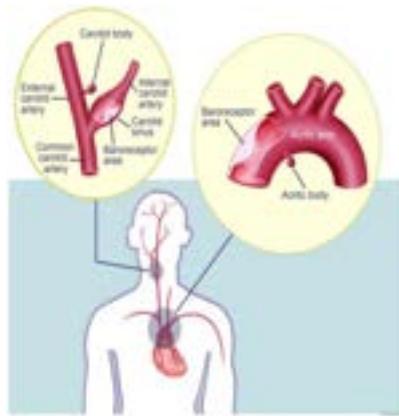


Figure 2.113: Location of peripheral chemoreceptors

Example 2.9.1. As P_{O_2} and P_{CO_2} in the arterial blood decreases and increases respectively, the peripheral chemoreceptors can detect the change and cause respiration but also heart rate (HR) to increase. This allows the body to get rid of CO_2 more and increase the amount of O_2 .

Now we can talk about a longer control of BP. Long term BP control can be done through the renal system since it controls how much liquid is going in or out of the entire body. This process takes a long time. So we'll be focusing on 2 main systems and it is pressure diuresis and the RAA system.

2.9.1 Pressure Diuresis

In general, pressure diuresis is a negative feedback mechanism where an increase in arterial blood pressure while drive up filtration of Na^+ and water in the nephrons of the kidneys which makes the body excrete more of them through urine. The reverse mechanism also happens in pressure diuresis.

Mechanism of Action (Pressure Diuresis): An increased in mean arterial pressure (MAP) causes an increase in Na^+ and water filtration in the nephrons (increase in urine). This lead to a decrease in plasma volume and thus decrease blood volume. This leads to other mechanism that also drives down venous pressure, then venous return and EDV. This leads to cardiac SV decreases as well which causes CO to decrease. Because MAP is defined by SV, decrease in SV also decrease in MAP. The opposite is true where a decrease in MAP would subsequently go through pressure diuresis to bring it back up.

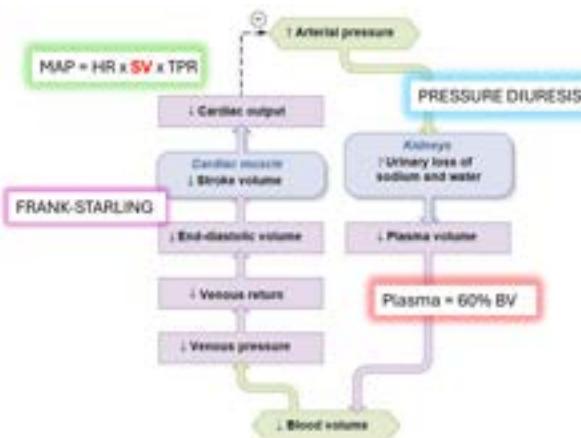


Figure 2.114: Pressure diuresis mechanism.

A class of drug that can deal with fluid in the body which can change BP is called **diuretics**.

2.9.2 Renin Angiotensin Aldosterone System

The **renin angiotensin aldosterone (RAA) system** is a major pathway for the body to control BP over a long period of time. It is controlled by either the kidney or the brain. In the kidneys, they can sense the change in pressure via the filtration rate and how much Na^+ and water is being excreted. This can trigger specialized cells that release renin (will discuss later). In the brain, the pressure is sensed by baroreceptors directly and osmoreceptors indirectly which connect toward hypothalamic neurons. This then cause a release of a molecule called ADH (will discuss later).

RAA System: Renin

Mechanism of Action (Renin Pathway): When there's a decreased in MAP in your body, specialized renal cells can sense the change in BP due to low Na^+ filtration. In turn, they release an enzyme called **renin** into circulation. Renin can come and catalyze **angiotensinogen** (a protein synthesized in the liver) into **angiotensin I**. Angiotensin I can move to the lung where an enzyme, called **angiotensin converting enzyme (ACE)**, can catalyze it into **angiotensin II** and released into circulation. Angiotensin II is a vasoconstrictor thus driving up TPR and subsequently MAP ($MAP = CO \times TPR$).

Like before, you have a negative feedback system where low MAP lead to an increased in renin which increase MAP and vice versa.

RAA System: Vasopressin/ADH

Mechanism of Action (Vasopressin/ADH Pathway): When there's a decreased in MAP, baroreceptors output decreased triggers hypothalamic neurons to synthesize **vasopressin** or **antidiuretic hormone (ADH)** that will be released by the pituitary gland. ADH can directly act on blood vessel and lead to its contraction hence TPR increase, which then increase MAP. It can also travel to the kidney and decrease its Na^+ and water filtration, which trigger the pressure diuresis (everything increase because low Na^+ and water excretion) and drive up SV and CO. An increased in CO subsequently increase MAP like before.

Similar like renin, you also have a negative feedback system where a low MAP lead to increase of ADH, which increase MAP and v.v.

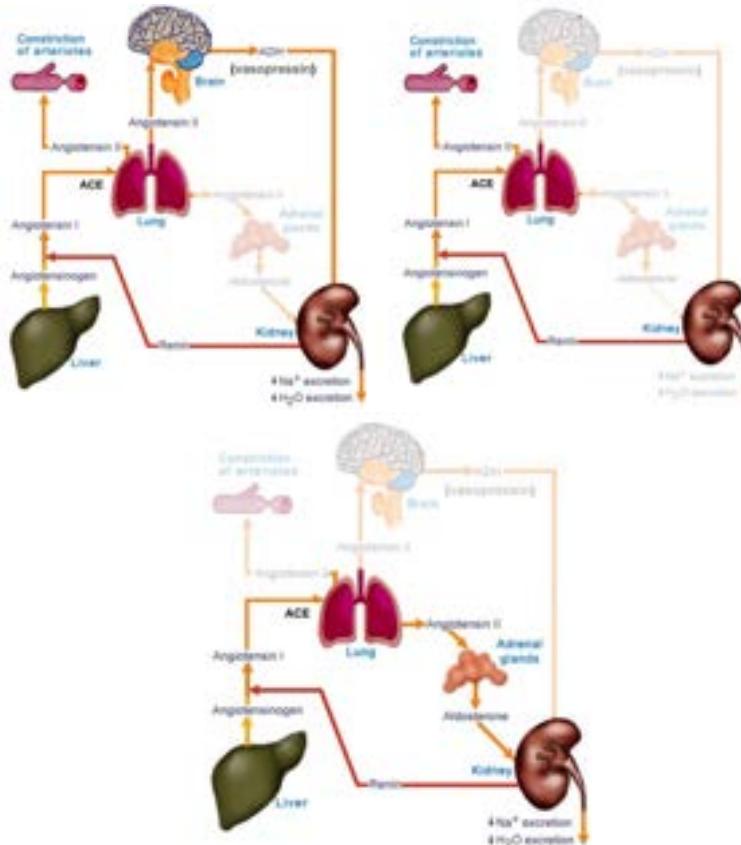


Figure 2.115: Vasopressin/ADH (right), renin (left) and aldosterone (bottom) pathway of RAA system

RAA system: Aldosterone Pathway

Mechanism of Action (Aldosterone Pathway): When MAP decreased, renin is released due to renin pathway which also release angiotensin II by the lung. Angiotensin II can also travel to the adrenal glands and bind to its receptors, which cause it to release a hormone called **aldosterone**. Aldosterone can bind to the kidneys' receptor, which cause it to reduce Na^+ and water excretion, which via the pressure diuresis cause an increased in CO and subsequently MAP.

Like before, it is also a negative feedback system where a low MAP leads to an increase in aldosterone resulting in an increased of MAP and v.v.

Pharmacology of RAA System

Diuretics

- Increase urinary excretion of sodium and water to reduce blood volume and pressure ([Chapter 14](#))

Renin-angiotensin-angiotensin II receptor antagonists (ARBs)

- Decrease cardiac output

Calcium channel blockers

- Decrease entry of Ca^{2+} into vascular smooth muscle cells leading to vasodilation and decreased total peripheral (systemic vascular) resistance

Renin-angiotensin-aldosterone system inhibitor/antagonist ([Chapter 14](#))

- Angiotensin-converting enzyme (ACE) inhibitors: Decrease angiotensin II production, leading to vasodilation/decreased total peripheral resistance; also decrease aldosterone allowing more sodium and water excretion.
- Angiotensin receptor blockers (ARBs): Decrease binding of angiotensin II to its receptors, leading to a decrease in total peripheral resistance; also leads to a decrease in aldosterone allowing more sodium and water excretion.
- Mannose-6-sulfatase receptor (M6R) antagonists: Decrease binding of aldosterone to its receptors in the kidney, allowing more sodium and water excretion.
- Direct renin inhibitors: Inhibit production of angiotensin I, leading to a decrease in angiotensin II (see ARB inhibitors above).

Sympathetic nervous system modulators

- Central alpha receptor agonists: Act on targets within the brain to decrease sympathetic outflow

- Peripheral alpha receptor antagonists: Relax the vascular smooth muscle, which leads to a decrease in total peripheral resistance.

All of the molecules and enzymes we talked about are the main targets in pharmacology for drug design i.e. we make drugs that binds to these target to induce a BP change effect. These targets make up the following drug class that can decrease BP:

I **Aldosterone receptor antagonists:** Binds to aldosterone receptors, prevents binding by aldosterone.

II **Angiotensin II receptor blockers (ARBs):** Prevents binding of angiotensin II in the brain, arterioles, and adrenal glands.

III ACE inhibitors: Prevents conversion of angiotensin I to II

IV Renin inhibitors: Prevents conversion of angiotensinogen to angiotensin I.

2.9.3 Orthostasis Hypotension

Hypotension is the condition where BP is very below normal range, unlike hypertension where BP is higher than normal. **Orthostasis hypotension** is a condition where there's a drop in BP due to standing up.

To see this condition, we have a subject laying down then immediately stand back up; at the same time, we do measurement on lots of different parameter of their body. We can see with the arterial BP that when the subject stands up, their systolic BP drops a little while the diastolic increases a little. This is to maintain your MAP.

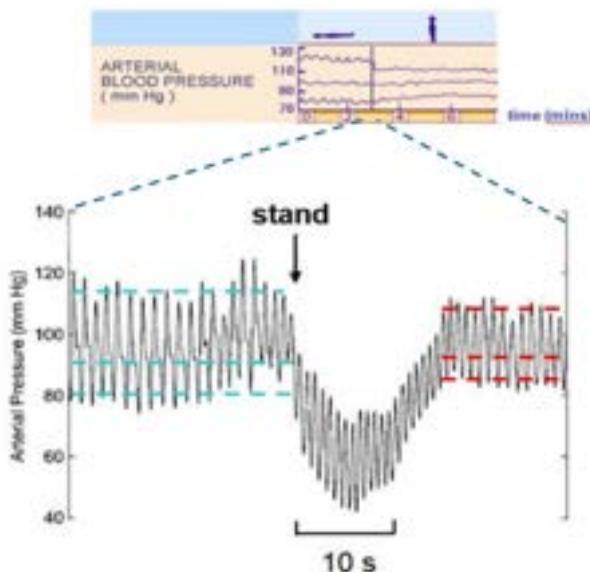


Figure 2.116: Arterial BP of systolic, diastolic and MAP when standing up as well as the zoom in version of BP measured with arterial probe, where top, bottom and middle line are systolic, diastolic and MAP respectively.

Observation: When subject stands up, there's an immediate drop in their

BP that goes from 120/80 to 75/40 (measured using an arterial probe). Roughly 10s after, the BP starts to restore through increased of HR. Now, the systolic pressure is much lower (top line), the diastolic is much higher (bottom line) but the MAP (middle line) stays relatively at the same position. All of this is thanks to the immediate action of your baroreceptors; without it, BP will continue to drop.

Remark 2.26. *The line of MAP is slightly lower toward diastolic because MAP is defined as $P_{diastolic} + \frac{1}{3}P_{pulse}$.*

Why would there be an immediate drop in BP when standing up?

Well...This is due to 2 things: **venous properties and hydrostatic pressure.** When the subject stands up, the hydrostatic pressure (pressure exerted on fluid against gravity) will be greater in the thorax than in the foot (because $P = \rho gh$). Additionally, if we remember from previous lectures, due to venous high compliance, a small change in its pressure lead to a large change in its volume.

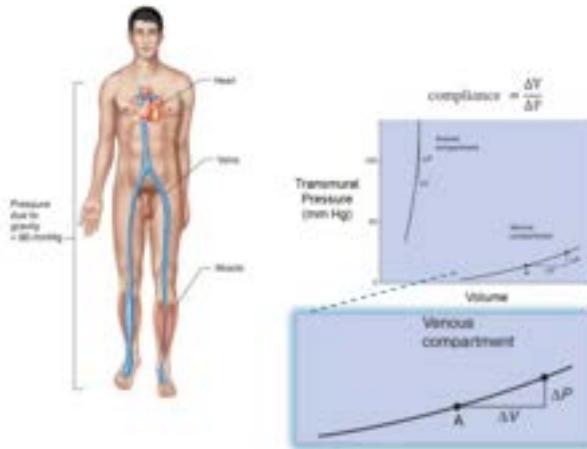


Figure 2.117: An immediate drop in arterial BP is due to compliance of the veins and high hydrostatic pressure reaching thorax.

So all of this put together, you have an increasing in hydrostatic pressure toward the thorax, which cause the veins increasing in size, eventually leading to having a pool of blood in the leg but not so much in the thorax.

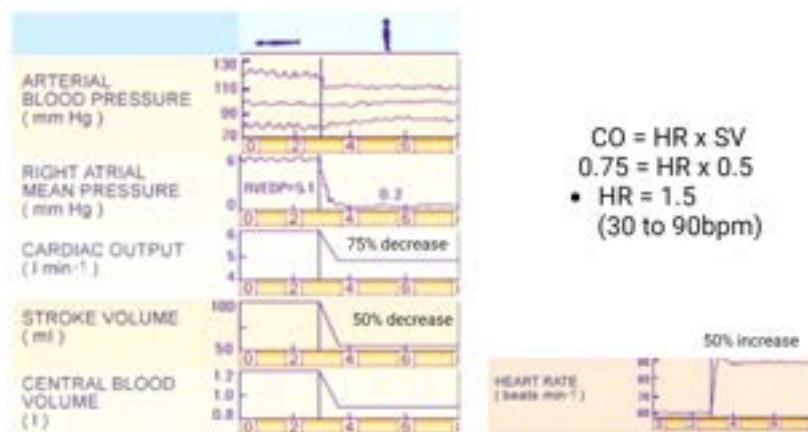


Figure 2.118: The drop of different parameter of BP when subject is standing (left) and increase in HR by 50% due to baroreflex.

Observation: We begin with the **central blood volume** (blood in the thorax, lung, heart and major vessels) where standing up leading to its massive drop from 1.2 to 0.9L (300mL removed from the system). Because there's more blood removed, the pressure from venous return also drops (right atrial mean pressure falls). Due to low venous return, SV also drops with it by 50%. If SV drops, CO also drops but not by 50% but by 75%. **Why is that?** Well...because HR increases by 1.5 or 50% ($CO = HR \times SV$), which means it goes from 60 to 90bpm.

Fundamentally, when the subject stands up, their **baroreflex increased HR to recompensate for the drop in SV**. Furthermore, it also increase cardiac contractility but not to the point that it recompensate the 300mL loss in blood volume.

Wait...but if your CO is still less than before, how is your MAP preserved?

Well...We can think of how MAP is defined, which is $MAP = CO \times TPR$ i.e. if your CO drops but you want MAP to be constant, your TPR (total peripheral resistance) must increase to recompensate the loss in CO.

This is true when you measure blood flow in the arm and other organ where it decreases dramatically due to baroreflex increasing TPR.

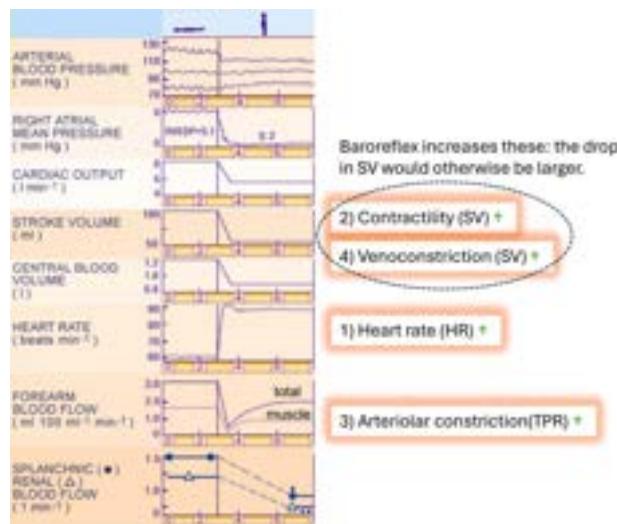


Figure 2.119: Summary of all measured parameter and the effect made by baroreflex.

To sum up what baroreflex do, it increase HR, contractility of both the veins and heart (which drives up SV), and increase arteriolar constriction (which increase TPR).

Remark 2.27. *Although the contractility effect is not well presented an observed in the measurement, without it, SV would decrease more.*

2.9.4 Prolonged Standing

Have you ever noticed, once in a while, there would be 1 soldier in a long standing line suddenly faint? **why is that the case?** Well...it's caused by 2 things venous blood pooling and plasma volume loss.

To understand how blood can pool in the venous system, we must remember back how veins return blood. There are many mechanism but the most important is through muscle pump i.e. when you flex your skeletal muscle, it will squeeze onto your veins and force blood to return. In prolonged standing, you do not use much of your leg muscle; therefore, there is no venous return from your leg which causes pooling and thus cause hypotension and then fainting.



Figure 2.120: British Royal guard faints due to prolonged standing (left). Muscle pump illustration (middle) and the rise of plasma volume loss due to prolonged standing (right).

Additionally, when you're standing, your feet and legs are experiencing a high amount of pressure (also due to the pool of venous blood) which forces plasma in the capillaries in your feet to flow out into the interstitial space. When this happens, blood volume is reduced which creates a greater effect and worsens the hypotension and fainting.

So how can other guards do it for so long?

Well...because they simply have to flex their calf muscle. When they flex their calf muscle, they restore and increase venous return which results in higher SV and thus not required for higher HR to recompensate if no muscle was flexed.

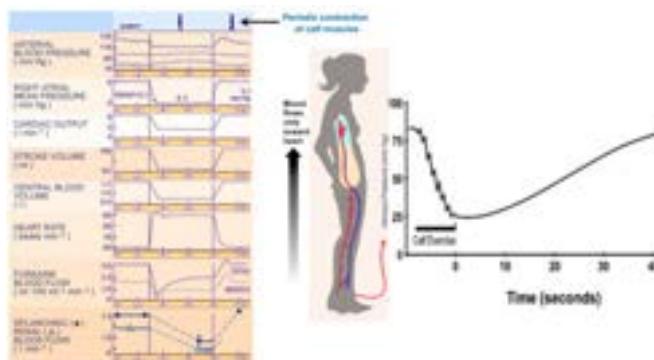


Figure 2.121: Prolonged standing with calf contraction/flex increases SV thus decreases HR (left) and venous pressure drop through various muscle contraction (right graph).

For the loss of plasma volume, when you flex your calf muscle, you're pumping blood out of the leg. This lead to lowering pressure in veins because you're emptying blood from it. With 1 contraction, you would get a small spike drop but with multiple, it drops even more dramatically (see Figure 2.121, right). This lead to lowering venous pressure and thus lower plasma volume loss.

Fluid Recovery by Lymphatic System

It is known that we lost around 4L of fluid per day via blood. Wait...but we have 5L of blood, where 3L is the actual fluid (plasma), **how does that work?** Well...we do not lose it actively by leaking out or through urine like usual. We lose it passively out of the blood vessels but can be recovered. So...**how do we recover it?** Well...we have the **lymphatic system** that run parallel with the CVS to collect loss fluid that will drain back to the venous return.

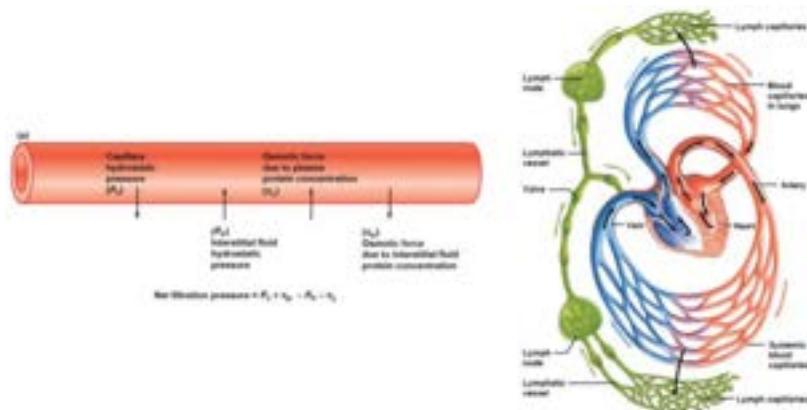


Figure 2.122: Lymphatic system and water return.

Lymphatic system is essential, if there is a problem, it can lead to many dangerous water retention problems.

2.10 Physical Exercise

We will begin this class with some question from students.

- **Don't veins lack muscle?** Veins do have smooth muscle since P_{venous} is low. You can have sympathetic response that lead to venoconstriction thus lowering its capacitance but increase in return, which means increase CO.
Veins are also different from artery is that it has 1 way valve. Arteries do have them but only in major ones.
- **What is diuresis?** It's basically production of urine (usually an increase). 'Pressure diuresis' means greater urine production due to increased pressure, in our case high MAP. Sometimes you may come across the term **natriuresis**, which is sodium excretion in the urine by the kidneys.
- **If the lymphatic system does not work well to collect and return the extra fluid to circulatory system, will I get hypotension due to reduced venous return?** Yes...but what was described is similar to a disease called **chronic venous insufficiency**.

This disease starts with venous hypertension: the valves in the legs no longer work well, resulting in a build-up of pressure in the legs, and 'leaky' veins, and eventually oedema and leg ulcers. Venous hypertension can be caused by systemic hypertension over time!

And in this disease, you can get orthostatic hypotension. Blood vessels fail to constrict, which causes a sudden drop in blood pressure when standing up from lying down due to low venous return. **So you're right! But at short timescales.**

- **Are the mechanisms of autoregulation for blood flow only vasodilation and vasoconstriction? Only vessels with smooth muscles can dilate or constrict (excluding capillaries) ?** Yes!
- **Does autonomic nervous system to control the flow (CO) or the blood pressure? Which one need to be constant?** I recalled from the previous lecture that flow is always constant in closed system
Firstly, the baroreceptors sense pressure directly, whereas the kidneys indirectly estimate pressure through flow. Secondly, flow is constant in the sense that the right and left circulation systems have the same average flow as they are a closed system, but flow varies during each heartbeat and can differ between organs. The system keeps

MAP constant, in order to allow the organs to have sufficient blood flow. Finally, remember the pressures in the systemic and pulmonary systems are very different, but the average flow in both is the same.

We also have some question on the demo that is **why do PVCs sometimes trigger tachycardia?** Well...there's no answer to this question because it is an on-going research question, all you need to know is that PVC can trigger it.

Take-Home Points from the Demo

1D Demo: Reentry wave can be generated around an obstacle (e.g. scar) leading to tachycardia. Initiation caused by refractory cells on 1 side of the stimulus that become excitable again when the reentry wave return.

2D Demo: Spiral wave generated by PVC merged with the normal excitation wave of the heart leading to tachycardia. This is hard to get which is why PVC is benign.

2.10.1 Cardiovascular Effect on Physical Exercises

In this study, we will look at **aerobic exercises** and its effect on the CVS. The ACMS defines aerobic exercises as activities that utilize a large muscle group that can be maintained in a rhythmic continuous fashion e.g. swimming, biking, running etc. Additionally, aerobic exercises have high emphasis on the utilization and excretion of O_2 , which can induce aerobic metabolism.

The subject in this study will perform aerobic exercises at a **steady state** power with increasing in power i.e. Subject will perform the exercises at a specific constant power level and then the subject will perform it at a higher power level, so on and so forth.

Remark 2.28. *Power is simply work per unit of time.*

Effect on Heart Rate

We can see that there's a linear progression when it comes to the heart rate (HR) vs the power put into the exercise. This means that HR is a very good index (indicator) for work done during an exercise. The maximum HR can vary from 1 to another, however we can approximate it as the following.

$$\text{Max HR} = 220 - \text{age} \quad (2.20)$$

During aerobic exercises, HR increase by 3× than the typical HR. HR increases due to increase in sympathetic tone and decrease in parasympathetic tone.

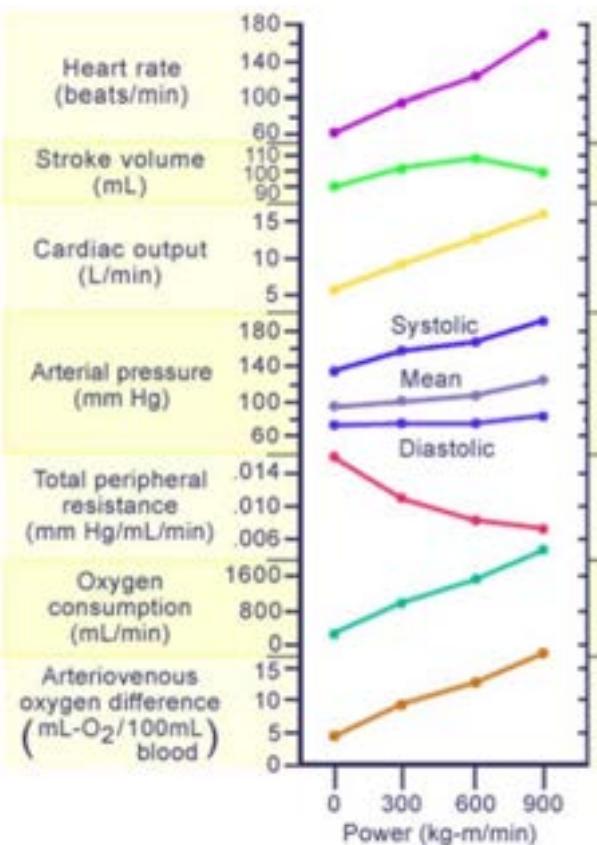


Figure 2.123: CVS effect on aerobic exercises

Effect on Stroke Volume

In this case, SV increases a little and then dips, and it's most likely that this individual is untrained **Why?** Well... Initially, there's an increase in sympathetic activity, which lead to higher contractility, and subsequently SV increases. At high HR, your cardiac cycle decreases where your systole

shortens but your diastole takes even less time than before. Now because diastole and systole drops, cardiac filling time also drops and subsequently EDV falls. And by the Frank-Starling mechanism, SV also drops.

Effect on Cardiac Output

The CO goes up linearly and is dependent on HR and increases with it almost 3x. This is because SV does not vary as much as compared to HR. The reason that CO increases during exercise is thanks to the adrenal gland. During exercise, they release more epinephrine into circulation which can bind to β -receptors of the heart and muscle leading to increase in contractility. All of this effect increases CO but decreases SV when HR is very high.

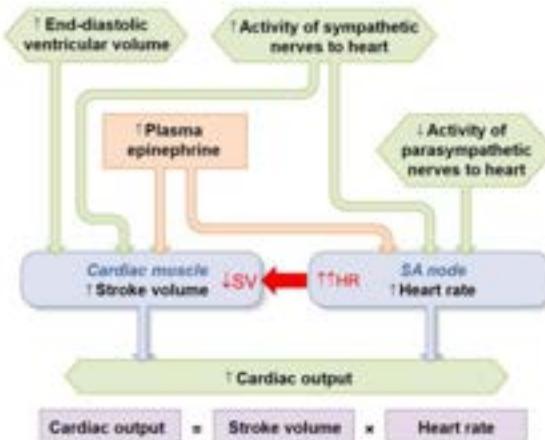


Figure 2.124: Adrenal gland and epinephrine.

Effects on Blood Pressure

Most interesting of all, mean arterial pressure (MAP) increases by a small amount of ~ 20% i.e. CO increases by 3 times while MAP increases by 1.2 times. If we look at $P_{diastolic}$, we see no changes; but if it was $P_{systolic}$, there is a large increase from 120 to 190mmHg.

Remark 2.29. If one experiences cardiac problems, they might have to perform the **cardiac stress test**, which is a test to determine if ventricles can generate force. **A low value is indicative of damage.**

Now, going back to MAP, **Why is it changing?** Well...it's because there's another component that changes that lead to MAP changes, which is the total peripheral resistance (TPR).

Effects on Total Peripheral Resistance

If MAP is 1.2, and CO is 3, we can use equation (2.16) way back to see that $\text{TPR} = \frac{1.2}{3} = 0.4$, so TPR decreases by 40%. **Why?** Well...this has to do with metabolic autoregulation. When you're exercising, you're increasing metabolic activity and the release of metabolites and requirement of O_2 also increases. Thus, **your body wants to have the greatest possible flow in these major organs** so they went through these dramatic changes.

Effects on Oxygen Consumption

Your O_2 consumption would be $9\times$ the normal rate but **why?** Well...first off, if CO increases by $3\times$, this also means $3\times$ the O_2 -carrying blood are available. Furthermore, you also have an increase in O_2 gradient between cells that need it and hemoglobin, which means blood can transfer more O_2 to cells that need it.

Essentially, at rest, you have 20mL of O_2 blood for every 100mL of arterial blood while that would be 15mL in the case of venous blood. So the 5mL per 100mL are extracted and used up. However, this changes during exercises because now the extraction increased to 15mL. So now you have an increased by $3\times$ for O_2 extraction.

Knowing that availability of O_2 -carrying blood increases by 3 and also the extraction of O_2 from the blood also increases by 3. The total multiple would be an increase by 9. This can be summed up by the **Fick's principle** which is given as the following equation

$$V_{O_2} = CO \times (a_{O_2} - v_{O_2}) \quad (2.21)$$

where V_{O_2} is the volume of O_2 consumed, CO is the cardiac output, a_{O_2} and v_{O_2} are the arterial and venous content of O_2 respectively.

2.10.2 Exercise Regional Blood Flow

During exercises, the body will prioritize blood flow in certain organs which lead to TPR decrease because there's an increase in flow over there. At the highest flow increased by $7\times$, it is the muscle. They count for 73% of the

total CO.

Next is the skin with an increase in flow by $5\times$. Majority of these flows and muscles usage by the skin is flow heat dissipation. This heat dissipation is important, otherwise you would get a **heat shock**.

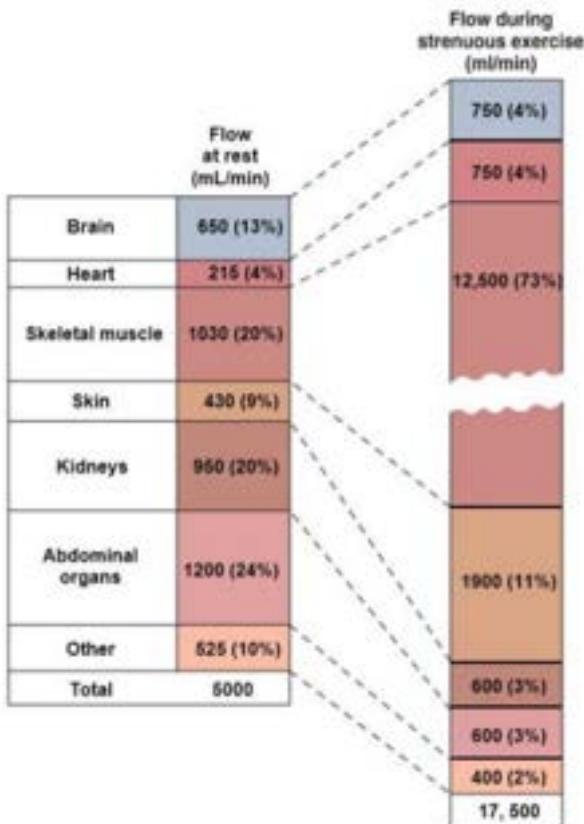


Figure 2.125: Regional blood flow changes

Next is the increased of blood flow by $3.5\times$ to the heart.

Finally, in other organs that are not so important for the exercising will have a drop in flow. Basically, there would be vasoconstriction to those organ that isn't needed.

In general, an untrained person tends to have $3.5\times$ increase in flow

while a trained athlete would be 7×.

Cardiovascular Changes During Moderate Exercise		
Variable	Change	Explanation
Cardiac output	Increases	Heart rate and stroke volume both increase, the former to a much greater extent. $CO = HR \times SV$
Heart rate	Increases	Sympathetic stimulation of the SA node increases, and parasympathetic stimulation decreases.
Stroke volume	Increases	Contractility increases due to increased sympathetic stimulation of the ventricular myocardium; increased ventricular end-diastolic volume also contributes to increased stroke volume by the Frank-Starling mechanism.
Total peripheral resistance	Decreases	Resistance in heart and skeletal muscles increases more than resistance in other vascular beds.
Mean arterial pressure	Increases	Cardiac output increases more than total peripheral resistance decreases. $MAP = CO \times TPR$
Pulse pressure	Increases	Stroke volume and velocity of ejection of the stroke volume increase.
End-diastolic volume	Increases	Filling time is decreased by the high heart rate, but the factors favoring venous return—recirculation, skeletal muscle pump, and increased respiratory movements—more than compensate for it.
Blood flow to heart and skeletal muscles	Increases	Active hyperemia occurs in both vascular beds, mediated by local metabolic factors.
Blood flow to skin	Increases	Sympathetic activation of skin blood vessels is inhibited reflexively by the increase in body temperature.
Blood flow to viscera	Decreases	Sympathetic activation of blood vessels in the abdominal organs and kidneys is increased.
Blood flow to brain	Increases slightly	Autoregulation of brain arterioles maintains constant flow despite the increased mean arterial pressure.

Figure 2.126: Summary CVS effect on physical exercises.

2.10.3 Vascular Tone Neural Control

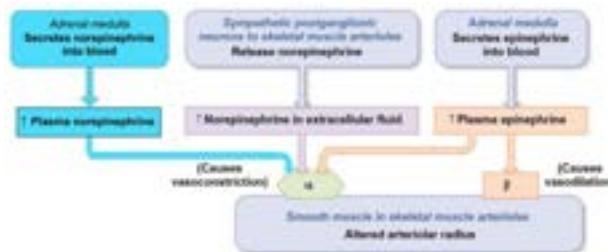


Figure 2.127: neural control of vascular tone.

There are 3 main systems when it comes to the neural control of vascular tone: secretion of epinephrine, norepinephrine from the adrenal gland and norepinephrine by sympathetics systems. We know already previously that epinephrine and norepinephrine can act on the α -receptors which

leads to vasoconstriction. Epinephrine, on the other hand, can act on β -receptors which leads to vasodilation.

At rest, the activation of α and β receptors are equal i.e. both of them determine vascular tone. However, in exercising muscle, metabolic control will override these input of neural control. Additionally, during exercise, organs and muscle that is not used will have greater α receptors activation, which lead to more constriction and thus increases resistance.

2.10.4 Endurance Training

Endurance training does not increase HR but increase CO **why is that?** Well...because you're increasing SV, but then **how can SV increases?** Well... because contractility increases due to an increase in myocyte hypertrophy. Basically, the cardiac cells gets bigger although having the same amount of neural connection. What you would notice is that the HR at rest would fall; this is because the heart is contracting which much more force now so it doesn't need to contract as frequent to yield a similar effect.

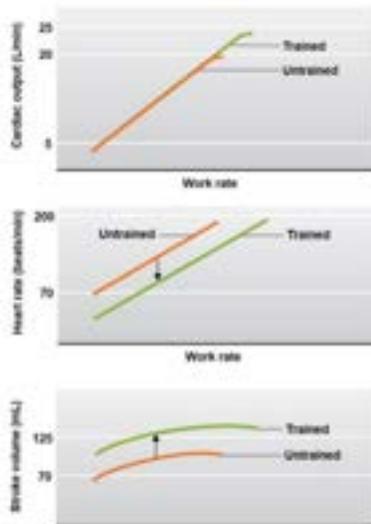


Figure 2.128: Endurance training changing CO.

Chapter 3 Endocrinology will cover the all of lectures on endocrine system spanning from February 16th to February 26th, 2024.

Definition 3.1. The **endocrine system** is a system of chemical messaging between different tissues in the body.

The endocrine system provides a mean for all other systems in the body to coordinate and perform physiological process simultaneously. It, along with the central nervous system, create a communication system throughout the body via chemicals (endocrine) or electrical (CNS). It also helps with forming long comuncation in the body.

3.1 Endocrine Signalling

Definition 3.2. **Hormones** are signalling molecules that coordiante different function of your body and travel through the blood stream.

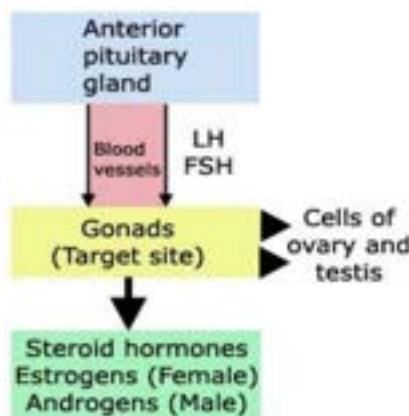


Figure 3.1: Endocrine signalling pathway starting from the anterior pituitary gland.

Hormones are secreted into the blood stream by **endocrine gland**, one of the major endocrine gland you will learn is **pituitary gland**.

Neuro-endocrine signalling

Neuro-endocrine signalling is a special and different type of endocrine signalling as the release of hormones is made by neurons instead of endocrine glands.

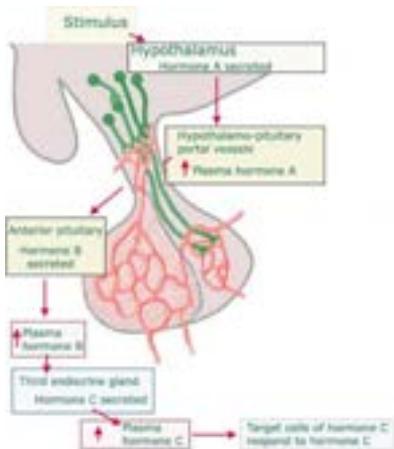
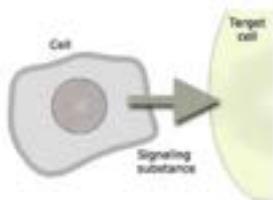


Figure 3.2: In the hypothalamus-pituitary axis, hormones are released from neurons in the hypothalamus toward the pituitary gland, that can either suppress it or activate it in releasing a certain hormones. Because of this axis, we can sometimes have situation like a cascade where series of hormones are released to pituitary gland and etc.

Division of Endocrine Signalling

There are 2 main categories to endocrine signalling: **paracrine** and **autocrine** signalling.

Paracrine Signaling



Autocrine Signaling

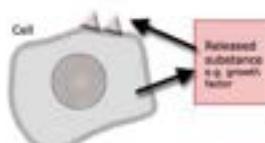


Figure 3.3: Types of endocrine signalling pathway.

In paracrine signalling, it involves 2 different cells where hormones travel from the signalling cell to the target cell, thus activating its function. In autocrine signalling, it involves a single cell creating the hormonal signal which activates itself.

In both cases, the endocrine signalling communication are the same which involves the following steps:

1. **Synthesis:** The cell synthesize hormones.
2. **Release:** The synthesized hormones are released to the blood stream.
3. **Transport:** The hormones now travel through the blood stream toward the target site.
4. **Detection:** The hormones bind to specific receptors of target cells.
5. **Cellular metabolism change:** The binding of such receptors induce a change in the cell's metabolism.
6. **Elimination:** Once the signalling is done, the hormones are removed and cellular response cease.

Remark 3.1. *These 6 steps are important as they can be regulatory control point for the signalling pathway.*

Hypothalamic-Pituitary Signalling

The hypothalamus-pituitary signalling pathway, also called the **Hypothalamic - Hypophyseal Portal System**, which is a major endocrine signalling pathway connecting the hypothalamus and the hypophyseal (anterior pituitary gland).

We begin at the hypothalamus, where its neurons communicate to the **anterior pituitary gland** by releasing hormones to the blood vessel of the **pituitary stalk**. These release neuro-hormones can either be **releasing hormones**, which cause the anterior pituitary gland to release hormones; or it **inhibiting hormones**, which inhibit the anterior pituitary gland from releasing hormones.

The hypothalamus also directly projects down toward the **posterior pituitary gland**, which you can think of as an extension of the hypothalamus instead of the pituitary gland. The posterior pituitary gland releases a set of hormones different from the anterior.

Remark 3.2. Essentially, posterior pituitary gland is different histologically and hormonally (releasing).

3.1.1 Hormones Classes

Hormones can be divided into 4 typical major classes of: glycopeptide, polypeptide, steroid and amines.

Remark 3.3. Glycopeptide and polypeptide can be all classified under proteins hormones since peptide and proteins (cut off at 50 amino acid.) are synonymous

PEPTIDES AND PROTEINS			
GLYCOPROTEINS	POLYPEPTIDES	STEROIDS	AMINES
- Follicle Stimulating Hormone (FSH)	- Adrenocorticotropin Hormone (ACTH)	- Aldosterone	- Epinephrine
- Luteinizing Hormone (LH)	- Growth Hormone (GH)	- Cortisol	- Thyroxine (T ₄)
- Thyroid Stimulating Hormone (TSH)	- Prolactin	- Estradiol	- Triiodothyronine (T ₃)
- Human Chorionic Gonadotropin (HCG)	- B-Lipotropin (B-LPH)	- Progesterone	- Melatonin
	- B-Endorphin	- Testosterone	
	- Insulin	- Vitamin D	
	- Glucagon		
	- Insulin-like growth factors (IGF's) or (Somatomedins)		
	- Parathyroid Hormone (PTH)		
	- Calcitonin		
	- Oxytocin		
	- Vasopressin		
	- Angiotensin (ADH)		
	- Relaxin		
	- Somatostatin		
	- Corticotropin Releasing Hormone (CRH)		
			IONIC CALCIUM

Figure 3.4: Classes of hormones.

Interestingly, we also have a larger classification for these 4 hormones: genetically or enzymatically synthesized. For genetically synthesized hormones, they are the glycoproteins and polypeptide because we have genetic sequences that encode for them. For enzymatically synthesized hormones, we have genes encode for enzymes that can make the hormones from a precursor; and these hormones are steroid and amines.

You can see that we also include Ca^{2+} . This is because it was discovered that there are receptors exclusively for them that can trigger biochemical change in cells.

Proteins Hormones

Proteins hormones (glycoprotein and polypeptide) can be synthesized in by the cell via genes. When these hormones are first synthesized, it has a modified N-terminus with a **pre-pro-sequence**. This sequence is almost like a "barcode" that mark it to enter the cell secretory system. As it travels through the secretory system, the sequence is removed.

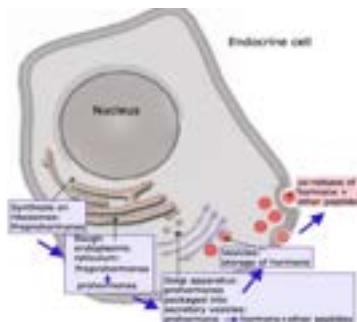


Figure 3.5: Secretory pathway post-synthesis of proteins hormones.

Steroid Hormones

Steroid hormones have typical 4 ring structure (ABCD).

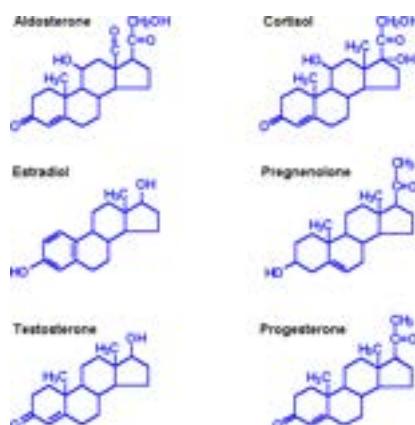


Figure 3.6: Steroid hormones.

Now, 1 interesting thing about them is that testosterone always want to become estradiol, which is aromatics and thus more stable. Testosterone cannot aromatize itself because its carbon would have 10 electrons which is chemically incorrect. Instead, there is an enzyme called **aromatase** that can remove the methyl group converting it into an alcohol as well as aromatize the ring

Thyroid Hormones

Thyroid hormones are evidently produced by the thyroid. They exist in 2 forms: T3 ad T4 where the number corresponds to how many iodine on the structure. We also have a so called reverse T3 that is in circulation but is not a thyroid hormones (cannot bind to thyroid hormone receptors).

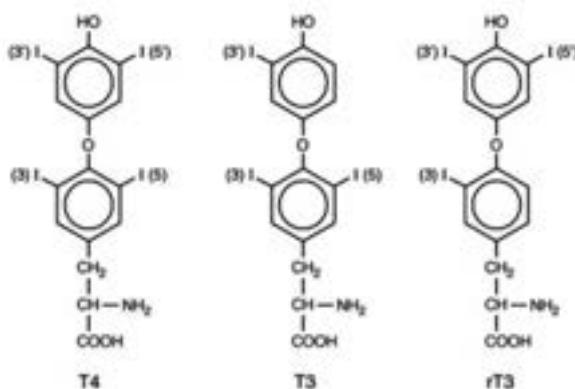


Figure 3.7: Thyroid hormones and rT3.

3.1.2 Hormones Receptors

Hormones receptors is said to have a **lock-key mechanism** which simply demonstrate the high affinity and specificity of the receptors and the hormones i.e. the hormones must have the right shape and bonding to the receptors in order to bind to it and activate it.

This concept leads to properties of hormones receptors. First they have high **specificity**, which means receptors allow binding of only certain hormones or family of hormones. They also have **affinity** where the binding

likelihood is dependent on the concentration of the hormones i.e. high hormones concentration corresponds to high affinity v.v.

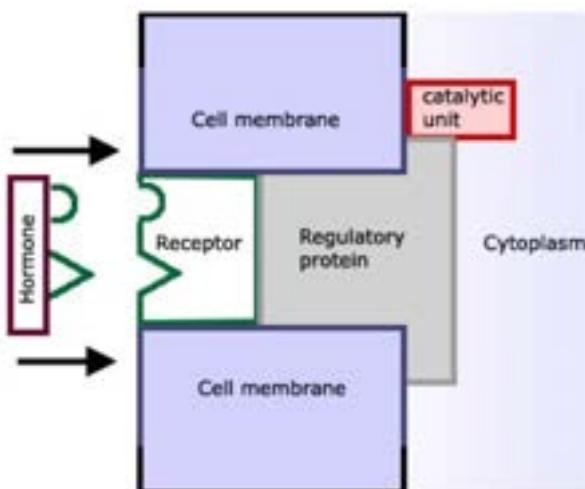


Figure 3.8: Lock-key mechanism of hormones.

They have to show **saturability**, which means a number of such receptors can be saturated passing certain hormones concentration. Finally, they must lead to a **measurable biological effect**.

Receptors must be regulated too. The receptors can be **upregulated** by increasing in its response to the hormone or the synthesis of such hormones. On the other hand, it can be **downregulated** by decreases its response or the synthesis of its hormones.

Mechanism of Hormones Affect Cells

The first 1 is the **direct effect** which is the more uncommon one. In this effect, when the hormone bind to the receptor, it directly activate a change e.g. in the membrane.

You can see this with insulin receptors where upon its activation by insulin, a transporter activate right away allowing glucose to flow into the cell cytoplasm. The insulin receptors also interact indirectly to the nucleus which lead to changes in gene transcription. This indirect changes

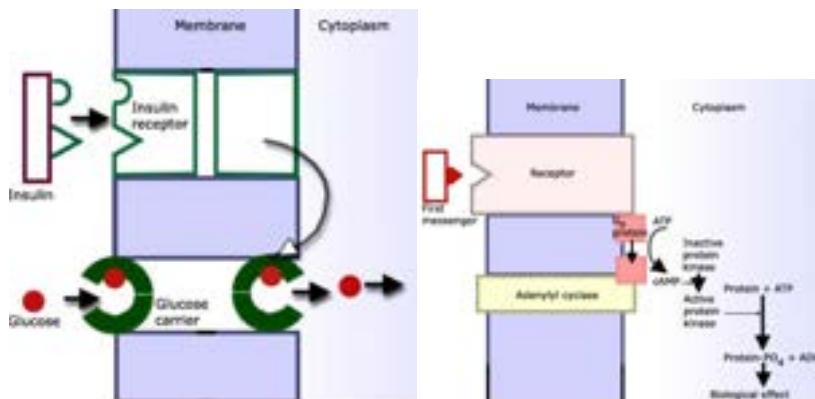


Figure 3.9: Direct effect with insulin and secondary messenger signalling with G-proteins.

is mediated by the **intracellular secondary messenger signalling**. In this mechanism, a primary messenger will bind to the receptors which trigger a biomchemical cascade of the secondary messenger which lead to the a cellular change

Example 3.1.1. Hormones receptors binding lead to activation of the G-proteins coupled receptors that turns ATP into cAMP. The cAMP activate protein kinase that can phosphorylate proteins and lead to a cellular change.

Finally, we have **intracellular genomic signalling**.

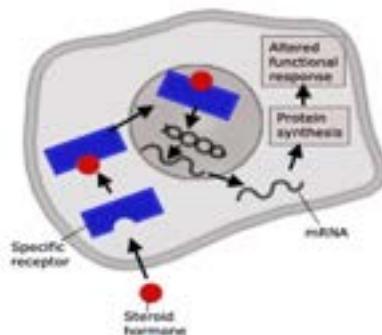


Figure 3.10: Intracellular genomic signalling.

In this mechanism, a steroid hormone can cross through the cell membrane and enter the cytoplasm. Here it will bind to a receptor. This receptor becomes activated and moves into the nucleus called **nuclear receptors**. In the nucleus, it can trigger a transcription of a specific gene, which translates into proteins that lead to an altered functional response.

3.1.3 Feedback Mechanism

Hormones secretion is regulated by a feedback mechanism, which is a secretion dictated by the amount of product.

Example 3.1.2. Ca^{2+} concentration in circulation is maintained at a precise concentration range. If the $[\text{Ca}^{2+}]$ drops in plasma, you'd get stimulation toward the parathyroid gland to release parathyroid hormones that increase $[\text{Ca}^{2+}]$. The increase in $[\text{Ca}^{2+}]$ activates a negative feedback loop to the parathyroid gland that decreases the release of parathyroid hormones.

These are not like an ON-OFF switch but more like a dim-brighten switch because instead of shutting off the release right away, the mechanism decreases it only. The above example we described is that of Ca^{2+} homeostasis.

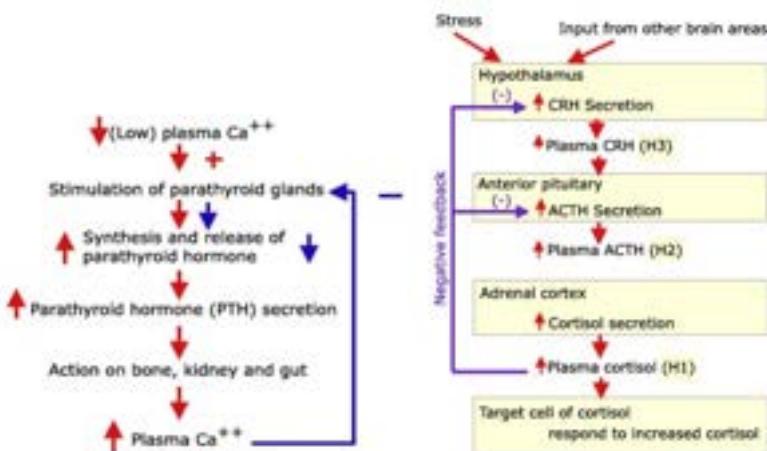


Figure 3.11: Negative feedback mechanism of Ca^{2+} (left) and hypothalamic-pituitary-end organ axis (right).

Example 3.1.3. One important feedback is the **hypothalamic-pituitary-end organ axis** hormone production. First is the hypothalamus, it releases

corticotropin releasing hormones (CRH) into the pituitary gland, which in turn releases adrenocorticotropic hormones (ACTH). ACTH travels down to the adrenal gland and stimulate it to release cortisol (glucocorticoid) which is important for circadian rhythm. The level of cortisol can create a negative feedback to the CRH and ACTH secretion.

3.2 Endocrine Glands and Their Secretions

In this lecture, we will look at some endocrine glands (anatomical feature) and the hormones that they secrete. We will also touch upon the chemical nature of the hormones, its effects, mechanism of action, ways to control it, disorder and treatments.

3.2.1 The Pituitary gland

The **pituitary gland** is made from 2 anatomically different glands whose tissues are also different histologically. These are the **anterior** and the **posterior pituitary gland**.

The tissues made up the anterior pituitary gland are endocrine tissues. This gland is located below the hypothalamus and is in the "front" or above relative to the posterior pituitary gland. They're also called **adenohypophysis**. *Adeno* means glands e.g. adenoma = benign gland growth, adenocarcinoma = malignant gland growth. *Hypo* means below and *physis* means growth.

The tissues made up the posterior pituitary gland are neural tissues. This gland is also located below the hypothalamus and is to the back or below relative to the anterior pituitary gland. It's also called **neurohypophysis**.

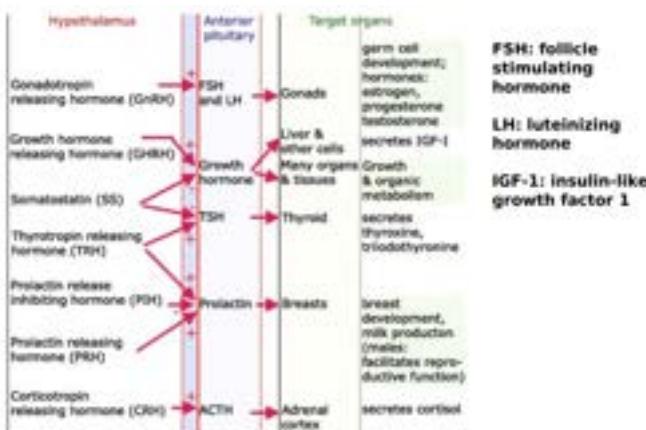


Figure 3.12: Signalling between pituitary gland and hypothalamus.

We won't get into much of signalling between the hypothalamus and the pituitary gland today (we will look into it in later lectures).

Hypothalamic/Posterior Pituitary Gland Hormones

The following tables are the hormones produced by either the posterior pituitary gland or the hypothalamus.

Hypothalamic/Posterior Pituitary Hormones	Structure
Posterior pituitary hormones	
Arginine vasopressin	[\square]-Gln-[\square]-Asn-[\square]-Gly-[\square]-Phe-Tyr-Tyr-Gly-Gly-Pro-Asp-Gly-NH ₂
Oxytocin	[\square]-Gln-[\square]-Asn-[\square]-Gly-[\square]-Cys-Phe-Ile-Gly-Asn-Cys-Pro-Lys-Gly-NH ₂
Hypophyseotropic hormones (target anterior pituitary)	
Thyrotropin-releasing hormone (TRH)	[pyro]-Glu-His-Pro-NH ₂
Gonadotropin-releasing hormone (GnRH)	[D-pyro]-Glu-His-Trp-Ser-Tyr-Gly-Lys-Arg-Pro-DTr-NH ₂
Somatostatin ¹	[\square -Ala-Ala-Gly-Lys-Asp-Pro-Phe-Tyr-Lys-Tyr-Phe-Tyr-Ser-Gly] _n
Growth hormone-releasing hormone (GRH)	Tyr-Ala-Asp-Ala-Ser-Phe-Thr-Ala-Ser-Tyr-Arg-Lys-Tyr-Lys-Gly-Gln-Leu-Lys-Ala-Ala-Lys-Lys-Gln-Ala-Ser-Tyr-Tyr-Arg-Gln-Gly-Ala-Asp-Ala-Asp-Lys-NH ₂
Prolactin-inhibiting hormone (PIH, dopamine)	
Corticotropin-releasing hormone (CRH)	Ter-Gly-Gly-Pro-Phe-D-Val-Lys-Lys-Lys-Tyr-Phe-Ile-Lys-Lys-Lys-Tyr-Lys-Ala-Ala-Gly-D-Val-Lys-His-Gly-Ala-Ala-Ala-Ala-Ala-NH ₂

Figure 3.13: Hormones released by the hypothalamus or pituitary gland.

Looking at **arginine vasopressin** and **oxytocin**, we can see that they're both peptide hormones i.e. they're encoded as a DNA sequence in the posterior pituitary gland. They both share the same sequence except the amino acid before the last (at N-terminal) is different (arg vs leu). There could be a duplication event of a gene during evolution which lead to slightly different structure. Nevertheless, all we need to know is that **arginine vasopressin is important for BP maintenance while oxytoxin is for reproduction.**

Remark 3.4. They may sounds different with the function described above however what both of them do is control the tone of smooth muscle.

Next, we have the **hypophysiotropic hormones** which are hormones that target the anterior pituitary gland. The name is from the fact that when one has *-tropism* for another thing, then it is attracted to such thing e.g.

gonadotropins are hormones that target or are "attracted" (has tropism) to the gonads.

Out of all the hypophysiotropic hormones, **dopamine** is the hormone that stands out because it's an amine hormone instead of peptides. It is a derivative of an amino acid called **tyrosine**.

More on the Posterior Pituitary Gland

The posterior pituitary gland is simply an extension of the hypothalamus that is connected via the **pituitary stalk**. We said above that it secretes arginine vasopressin and oxytocin which are **antidiuretic hormones** i.e. hormones that decrease peeing (urination).

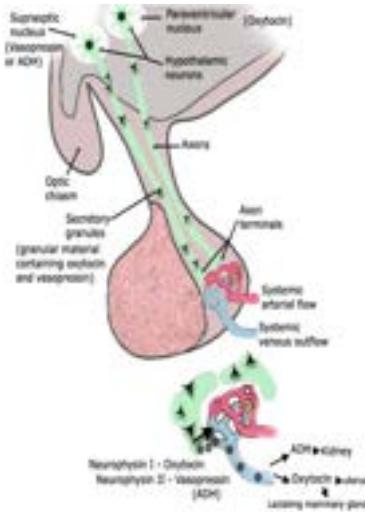


Figure 3.14: Supraoptic and paraventricular nucleus in the hypothalamus synthesize ADH like oxytocin and arginine vasopressin. These 2 ADH can be transported in pituitary stalk, which are axons, down to the posterior pituitary gland. Here the pre-pro sequences are removed, after which they're released into circulation with half-life of 1-3min.

Remark 3.5. Many "on-drug" athletes use ADH to clear drugs from their body before testing, which is why it's now illegal in testing.

Both of these ADH hormones are synthesized by the **hypothalamic nuclei** (cluster of similar functioning neurons), to be more specific: **supraoptic** and **paraventricular nucleus**. Hormones synthesized by these 2 will move down the stalk into the posterior pituitary gland where capillaries are located. Because they're peptide hormones, they have pre-pro sequences that will be processed as they enter circulation.

Remark 3.6. They have circulating half-life of 1-3 minutes i.e. after 1-3 minutes, half of the oxytocin and vasopressin is gone.

Oxytocin

Oxytocin are hormones produced by both female and male with important function (even though 10y ago, it was thought that oxytocin has no function in the male).

In female, oxytocin is important for child-birth or **parturition** as promotes uterine contraction when the uterine cervix is dilated by the fetal head. Oxytocin allows the production of milk (milk ejection) via inducing peristalsis effect on lactating mammary glands. It is also called the **love hormones** as it is released during bonding time between mother, even father and the child, which can reduce anxiety.

In male, oxytocin surges during ejaculation which promotes the passage of sperm via peristalsis (rhythmic contraction and relaxation of smooth muscle).

3.2.2 Thyroid Gland

The thyroid gland is filled with a fluid called **colloid**. The colloid has a major component, that is large proteins called **thyroglobulin**. The thyroid gland weighs roughly 15-20g depending on age, sex, etc. Nevertheless, we only utilize 3g of the gland to have a maintain a normal thyroid homeostasis.

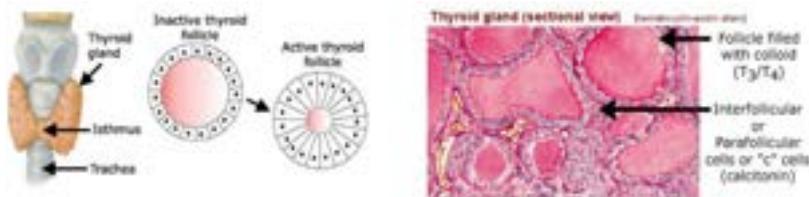


Figure 3.15: Thyroid gland.

The thyroid hormones T3 and T4 are synthesized (from tyrosine) and stored on thyroglobulins, which will be iodinated later on (we don't know why). T3 and T4 will break off from the thyroglobulin and enter circulation.

Thyroglobulin are produced by the **follicular cells (follicles)** of the thyroid and its production is controlled by **thyroid-stimulating hormones (TSH)** of the pituitary gland. Another cells to look at is the **parafollicular cells (C cells)** (cells between the follicles) which is important for **calcitonin** production, that is useful in calcium homeostasis.

The most common form of thyroid hormone is T4 and some of it would be T3. We also have a small amount of rT3 that cannot bind to the thyroid receptors, this shows that the process of synthesizing T3 is not perfect. The newly synthesized T3 and T4 must be iodinated (attaching an iodine onto its benzene ring).

Iodine, Thyroid Hormone Synthesis and Control

Iodine is not very abundant to vertebrate animals like us. Nevertheless, our thyroid glands have developed mechanism to capture these iodine via active transport. Essentially, Iodine enter our circulation in its ionic form I^- . It's then actively transported (uses ATP) into the thyroid since the concentration of iodine is higher than in circulation. I^- can then be used to synthesize thyroid hormone.

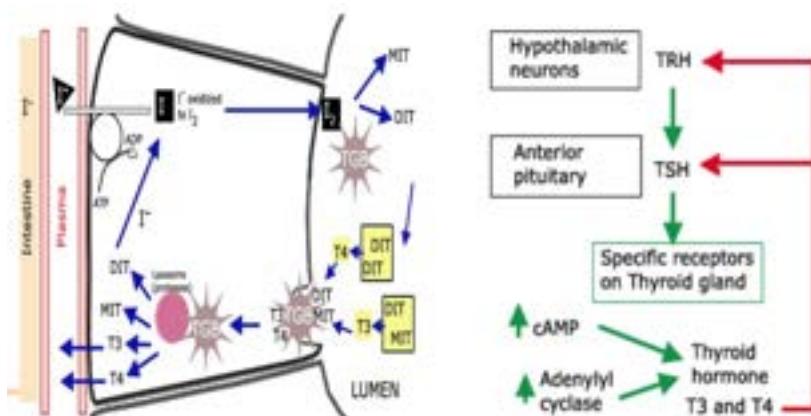


Figure 3.16: Thyroid Hormones synthesis and control

Mechanism of Action (Synthesis of Thyroid Hormones): Once entered, iodine is oxidized to I_2 . used for iodination of tyrosine residues of thyroglobulin (TGB) to form **monoiodotyrosine (MIT)** and **diiodotyrosine (DIT)**. Oxidative coupling of 2 DIT forms thyroxine (T4), while that of 1 MIT with one DIT forms triiodothyronine (T3).

The control of the thyroid activity (synthesis of these thyroid hormones) is mediated by the hypothalamus-pituitary-end organ axis.

Mechanism of Action (Control of Thyroid Activity): The formation of T3 and T4 is increased by TSH via interaction with receptors on follicular cells. The synthesis and release of TSH controlled by hypothalamic **thyrotropin releasing hormone (TRH)**. When T4 and T3 level increase, a negative feedback is sent to the hypothalamus and pituitary glands to decrease release of TRH and TSH.

Iodine Deficiency

When there's a decrease supply of iodine, the amount of circulating T3 and T4 decreases. Due to a decrease in T3 and 4, TSH is release more which causes the follicular cells to be constantly stimulated. This subsequently lead to **hyperplasia of the thyroid gland i.e. follicular cells amount increases and thyroid gland increases in size**. This can then form a **goiter**.

If the goiter is formed because of thyroid's inability to do T3 and 4 synthesis due to iodine deficiency, we call it a **non-toxic goiter**.

Effects and Mechanism of Action of Thyroid Hormones

Both T3 and 4 can increase **basal metabolic rate (BMR)**, which is the amount of calories an organism burns to perform basic life-sustaining function. Thus, they have a big effects on carbohydrates, lipids and proteins metabolism (calorigenesis). Due to this increase in metabolic activity, we also increases O_2 consumption.

If your thyroid is hyperactive, BMR increases over the normal rate which means you burn more calories thus lead to weight-loss.

Not only they can increase BMR, they also play an important role in linear growth and neuronal development (promotes synthesis of **nerve growth factor (NGF)** that lead to dendritogenesis). In the absence of T3 and 4 in early stage of development can lead to lack of linear growth and neuronal development which is called **cretinism**.

Thyroid hormones can do these because they can change the state of the cells and its mechanism of action is similar to that of steroid hormones.

Mechanism of Action (Thyroid Hormones Actions): T3 and T4 enter target cell nucleus, bind to their **thyroid hormone receptor**. Alters the transcription of specific genes, and thus levels of encoded proteins.

There is another T3/4 receptor type that isn't the same with plasma membrane or the inner mitochondrial thyroid receptors. **These receptors' effects cannot be blocked by inhibitors of protein synthesis.** i.e. If you were inserting T3/4 hormones into a cell along with an inhibitor, the nuclear receptors' effect stop but that of mitochondria still works. For the T3/4 receptors on the plasma membrane, it leads the cell to an increase in amino acid uptake and is independent of protein synthesis.

Is it true that nuclear power plant workers take iodine supplement? Well... Yes, excess stable iodine (127I) is used to protect the gland from radioactive iodine isotopes (131, 126, 123, etc). They saturate the iodine transport system diluting (isotopically) the amount of radioactive iodine entering the gland.

Can you use radioactive iodine to treat thyroid cancer? Well... Yes, radioactive iodine is used to treat thyroid cancer. Fortunately, this is quite differentiated most of the time and under appropriate stimulation may take significant amounts of radioactive iodine.

3.2.3 Abnormalities of Thyroid Function and Treatment

The thyroid gland can have some abnormalities related to its function that can manifest at birth or later in life. If it functions too little, it's known as **hypothyroidism** and is characterized by a low level of thyroid hormones. On the other hand, if it functions too much, it's known as **hyperthyroidism** and is characterized by a high level of thyroid hormones.

Here are some symptoms and physiological consequences of hypothyroidism and hyperthyroidism

Hyperthyroidism	Hypothyroidism
Elevated $T_4 - T_3$ levels	Decreased (or absent) $T_4 - T_3$ levels
Elevated BMR (hypermetabolism)	Low BMR (hypometabolism)
Increased perspiration	Decreased perspiration
Rapid pulse (increased cardiac output, hypertension)	Slow pulse (decreased cardiac output, hypotension)
Increased body temperature	Lowered body temperature
Heat intolerance	Cold intolerance
Warm, moist palms	Coarse, dry skin, subdermal thickening
Nervousness, anxiety, excitability, restlessness, insomnia	Lethargy, decreased mentation, depression, paranoia, sleepiness, tiredness
Weight loss	Weight gain
Muscle wasting	Loss of hair, dry and brittle texture
Increased appetite	Edema of face and eyelids
Menstrual irregularities	Menstrual irregularities
Exophthalmos (in some individuals)	Carotenemia (increased plasma carotenes)
Goiter (primary or secondary origin)	Goiter (may or may not be present)

Hypothyroidism

Pathophysiology of hypothyroidism can be classified into **primary, secondary and tertiary** according to its cause along the hypothalamus-pituitary-thyroid axis.

Primary hypothyroidism happens at the level of the thyroid which is an inability to synthesize active thyroid hormones. It is caused by **atrophy** of the thyroid due to unknown reason or **idiopathic**; **autoimmune thyroiditis**, such as Hashimoto's disease that can be supplemented with **synthroid**; and **goitrous hypothyroidism** (non-toxic goiter) which is blockage of T3/4 synthesis pathway.

For Secondary hypothyroidism, it happens at the level of the pituitary gland due to synthesis of little or no TSH. For tertiary hypothyroidism, it happens at the level of the hypothalamus due to synthesis of little or no TRH.

We also have another type called **infantile hypothyroidism** which is hypothyroidism that happens at birth. This type is characterized by **dwarfism** and cretinism.

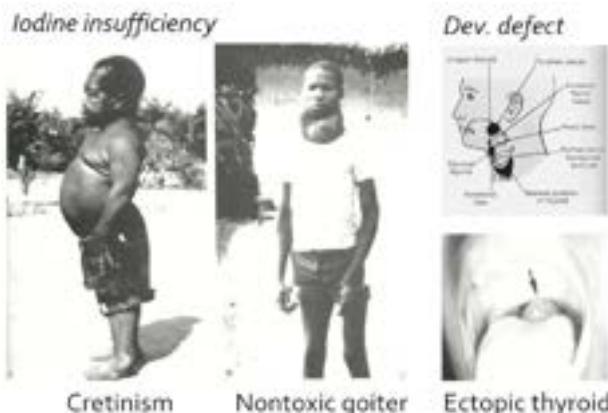


Figure 3.17: Hypothyroidism can lead to dwarfism, cretinism and non-toxic goiter. Sometimes patients may have **ectopic thyroid** which is thyroid gland located at a wrong place.

The general treatment for this is simply administration of thyroid hormones.

Hyperthyroidism

Like hypothyroidism, hyperthyroidism can be divided according to its pathophysiology with respect to the hypothalamus-pituitary-thyroid axis.

Primary hyperthyroidism happens at the level of the thyroid gland which is overproduction of active thyroid hormones. It is caused by many disease but 1 of the main is **Grave's disease (toxic diffuse goiter)**. This is an autoimmune disease characterized by presence of substance produced by lymphocytes called **long acting thyroid stimulator (LATS)**, an antibody that mimics the action of TSH and stimulates the release of T₃/T₄. In this case, it does not matter if TSH is shut down due to the negative feedback or not, because LATS will continue to attach to the TSH receptors in the thyroid gland causes an increase in T₃/T₄ production. This constant stimulation by LATS lead to the thyroid increases in size and subsequently lead to a goiter but this one is toxic.

Another cause is due to **thyroid adenoma** or **thyroid cancer**, where there's a synthesis of T3/4 independent of TSH.

For Secondary hypothyroidism, it happens at the level of the pituitary gland due to constant synthesis of TSH (no negative feedback from high T3/4); and is caused by a pituitary tumor. For tertiary hypothyroidism, it happens at the level of the hypothalamus due to constant synthesis of TRH (no negative feedback from high T3/4); and is caused by a hypothalamic tumor (rare).

The general treatment depended on the severity of hyperthyroidism. The most common way is through surgery and thyroid hormones administration.

There could also be administration of radioactive Iodide (^{131}I) about 5 mCi. The radioactive iodide concentrates in the cells of the thyroid follicles and destroys them. Replacement therapy may be administered as needed.

Finally, the last treatment is an administration of antithyroid drugs such as **propylthiouracil** (which blocks addition of iodine to thyroglobulin). Care must be taken not to inhibit the synthesis of thyroid hormones to a great extent and cause hypothyroidism.

3.2.4 Brief Introduction to Calcium Homeostasis

Ca^{2+} is important for many biological processes such as:

- Structural component of skeleton.
- Blood clotting factor.
- Help with maintain membrane potential in cells.
- Important in excitability of nervous tissue.
- Important in contraction of muscles.
- Important in release of hormones and neurotransmitters.

In circulation, around 50% Ca^{2+} are free while the other half is bound to albumin. Majority (99%) of Ca^{2+} is reserved and stored in bone.

The maintenance of plasma calcium is achieved mainly by exchange between bone and plasma under influence of hormones. Hormones also affect intestinal absorption of calcium and excretion of by kidneys. These

hormones are Parathyroid hormone (PTH), calcitonin and vitamin D. PTH are produced by parathyroid gland that can increase circulating Ca^{2+} , while calcitonin are produced by the parafollicular cells (or C cells) that lower circulating Ca^{2+} . Vitamin D can be ingested and can increase circulating Ca^{2+} .

Ca^{2+} can be obtained through your diet (milk, eggs, etc.) and is absorbed in your digestive tract and this absorption is increased when there are vitamin D and PTH presence. Once Ca^{2+} gets into your circulation, it can be stored in your bones, in cells or some will be eliminated from your body in urine made by the kidney.

Remark 3.7. If Ca^{2+} in plasma drops below 10mg/100ml, PTH will stimulate reabsorption of Ca^{2+} from the kidney as well as from bones.

Stability of $[Ca^{2+}]$ in circulation is dependent on hormonal influences that lead to Ca^{2+} exchange between plasma and bones.

3.3 The Calcium Cycle and Its Hormones

We will start from the end of last lecture on the Ca^{2+} cycle. This cycle allow the body to absorb or eliminate ingested calcium.

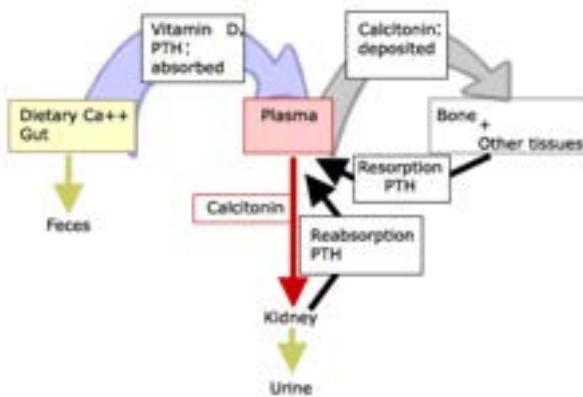


Figure 3.18: The Calcium cycle.

From the left of this diagram, we can see dietary Ca^{2+} enters from the gut and is absorbed into the plasma with the help of PTH and vitamin D. If plasma $[Ca^{2+}]$ is elevated, it tends to be deposited in bones and tissues or will be excreted out by the kidney. If $[Ca^{2+}]$ is low then PTH is release which help with kidney Ca^{2+} **reabsorption** and bone Ca^{2+} **resorption** back to circulation. Note: $[Ca^{2+}]$ is Ca^{2+} concentration

3.3.1 Parathyroid Hormone

Parathyroid hormone (PTH) is a hormone made and released from parathyroid chief cells embedded in surface of the thyroid. These parathyroid chief cells make up the **parathyroid glands** that is located at 4 different position at the back of the thyroid. Removal of this gland can lead to severe drop in Ca^{2+} and ultimately lead to **tetanic convulsion** and death.

Structure of PTH

PTH was a preproparathyroid hormones as it was synthesized. Its mature (released) form is an 84-amino acid polypeptide hormone after proteolytic cleavage, however only 34 of those amino acid at the N-terminal is useful.

Why? Well...because the 34-amino acid at the N-terminal is where it will bind to the parathyroid receptors.

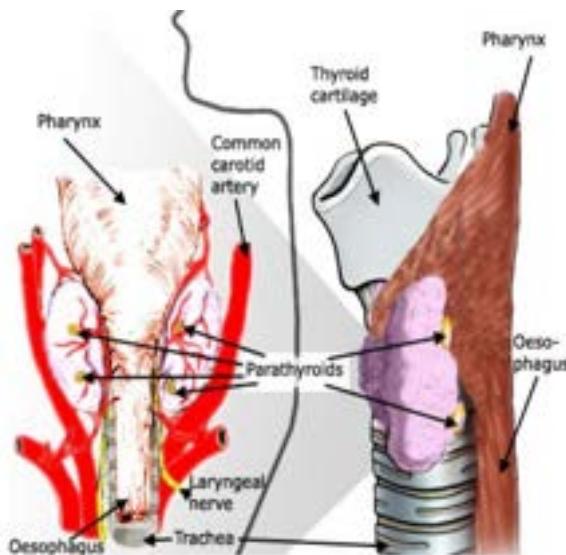


Figure 3.19: The parathyroid gland.

It has a half-life of only 3-18min. This means that the system of PTH is finely controlled.

Functions of PTH

The main function of PTH is to increase plasma $[Ca^{2+}]$ which is done through the following process:

- 1. Resorption of Bone:** Bones are demineralized more which increases $[Ca^{2+}]$.
- 2. Reabsorption of Kidney:** Reabsorption of Ca^{2+} in the **proximal convoluted tubules** of the kidney will increase.
- 3. Vitamin D Synthesis:** It stimulates the conversion of 25-hydroxyvitamin D3 to 1,25-dihydroxyvitamin D3 (1,25D3; biologically active form of vitamin D) primarily in kidney.

4. **Gut Absorption:** They (PTH and 1,25D3) helps with Ca^{2+} absorption in the gut.

The release of PTH is controlled by circulating $[\text{Ca}^{2+}]$. Essentially, parathyroid glands have surface receptors where Ca^{2+} can bind to a reduce the production of PTH. Remember that this is a reduction and not a shut down completely of PTH production.

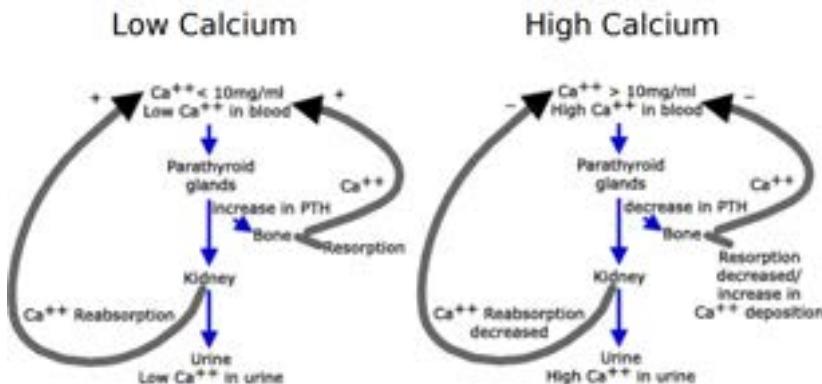


Figure 3.20: A low $[\text{Ca}^{2+}]$ lead to an increase production and secretion of PTH which lead to higher Ca^{2+} absorption from gut, resorption of bone and reabsorption from the kidney. All of this increases back $[\text{Ca}^{2+}]$. If the $[\text{Ca}^{2+}]$ is high, the opposite effect will happen.

3.3.2 Abnormalities with Parathyroid Glands

Like the thyroid, patients can have abnormalities with their parathyroid gland. These abnormalities can be characterized by its hyper or hypofunction.

Hypoparathyroidism is a condition characterized by the low levels of PTH in circulation. Some symptoms arise from this condition can be low plasma $[\text{Ca}^{2+}]$ or **hypocalcemia**, active vitamin D production decreases, tetany (involuntary muscle contraction) and convulsions. When $[\text{Ca}^{2+}]$ is $<7 \text{mg}/100\text{mL}$, it would lead to muscle spasm due to neural overexcitability. **Spasm of the laryngeal muscle can lead to death by asphyxiation.**

This can be treated with administration of 1,25-dihydroxyvitamin D and calcium supplements. **Why not drink some PTH?** Well...because PTH is a

peptide hormones and if it's ingested, your gut will break it down. You can however inject it but this is mostly for bone condition.

Hyperthyroidism is a condition characterized by a high level of PTH in circulation. This is often caused by **parathyroid adenoma** of parathyroid producing too much PTH. High production of 1,25D3 and PTH leads to an increase of $[Ca^{2+}]$ in circulation via reabsorption and resorption. This leads to a high $[Ca^{2+}]$ in plasma or **hypercalcemia**. Chronic hypercalcemia if unattended can lead to a form of **kidney stone**, deposition of Ca^{2+} on blood vessels, cartilages, decrease neuromuscular excitability and even cardiac arrhythmias.

A treatment for this is through removal of the affected parathyroid with a replacement therapy of 1,25D3 and Ca^{2+} .

3.3.3 Vitamin D

Vitamin D is a limited dietary source that can be found mainly in cod liver oil and fatty fish. There are 2 sources of vitamin D: **Vitamin D3** and D2. For D3, it's an animal source while D2 is from a plant/fungal source.

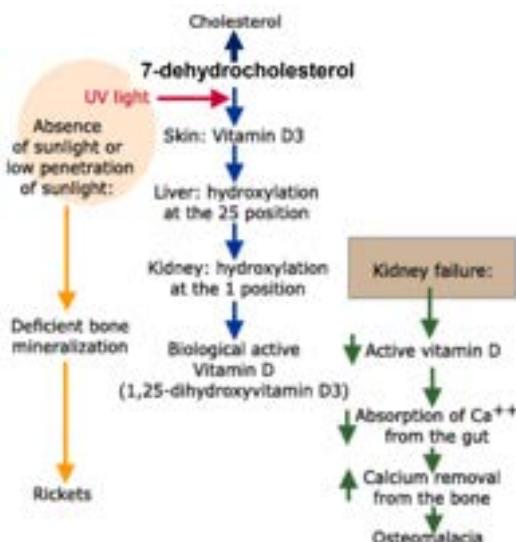


Figure 3.21: Synthesizing Vitamin D.

Strictly speaking, Vitamin D is not a vitamin you can make with the sun. What happened is that UVB light from the sun can radiate the last intermediate in cholesterol biosynthesis in the skin called **7-dehydrocholesterol** which vitamin D3. If sunlight help with vitamin D synthesis, **why would there be vitamin D deficiency be prevalent?** Well...because UVB are mostly blocked by ozone unless the sun is shining at approximately 45°. Now, vitamin D3 will pass through the liver and be hydroxylated at the 25th position and this is the inactive form. It then needs to be 1-hydroxylated in the kidney and other tissues to become its active 1,25D3 form.

Physiologically, it is used to increase calcium absorption from the intestine. Not only that, it can also regulates the immune system which protects against infection, anti-inflammatory. Interestingly, it also have some anti-cancer properties when introduce 1,25D3 on a cancer model



Figure 3.22: **Rickets** is a hereditary disease that is characterized by vitamin D resistant. This is due to a inactivating mutation of the vitamin D receptor. These individuals tends to have shortened clavicles, deformed bone, and baldness. It also main a disease in children.

Like PTH, the regulation of vitamin D synthesis is $[Ca^{2+}]$ i.e. it is increased in conditions of low calcium, when PTH is also increased. It is depressed by high calcium. Knowing that the vitamin D is sort of dependent on sunlight, we expected that population from the tropic region is less vitamin D deficient, as compared to those who are in the pole where there could be days without sunlight. **Turns out it's not but the opposite! But why?** Well...because those that lives in the tropic region receive lots of sunlight to the point that they do not want to exposed from it. Additionally, due to the conservative dressing that covers everything, it also increases vitamin D deficiency risk.

When a patient have kidney failure, their active vitamin D content decreases which leads to a decrease in Ca^{2+} absorption in the gut. To compensate this, Ca^{2+} resorption from bone increases which lead to you having a condition called **osteomalacia**, which is literally translated as "soft bone"

due to low amount of mineralized Ca^{2+} .

3.3.4 Calcitonin

Calcitonin is a 32 amino-acid calcium-lowering peptide hormone that is made by parafollicular cells of the thyroid glands. It helps with lower plasma calcium by promoting transfer of Ca^{2+} from blood to bone, and increasing urinary excretion of Ca^{2+} . The regulation of calcitonin also dependent on $[Ca^{2+}]$ i.e. a rise in plasma $[Ca^{2+}]$ increases calcitonin while a decrease in plasma $[Ca^{2+}]$ will lead to decreases calcitonin release.

Nevertheless, compared to PTH and 1,25D3, calcitonin does not have much impact on the calcium homeostasis. This can be observed by the removal of the thyroid while leaving the parathyroid intact. What we would see is that in the absence of calcitonin does not compromise calcium homeostasis in man thus suggesting that **its biological importance is limited**.

3.4 The Adrenal Glands and Its Hormones

We will now shift away from the calcium cycle and look at the adrenal glands. The **adrenal glands** are located adjacent to the upper surface of the kidneys. Unlike the thyroid, the adrenal glands are heavier in male than female. The adrenal glands are made from 2 distinct tissues type: **cortex and medulla**.

Anatomically, the cortex is located in the core of the adrenal glands. They're made from large-lipid containing endothelial cells which is an important source to generate steroid hormones. These cells are derived from the **mesoderm**.

On the other hand, the medulla is located surrounding the adrenal glands. They're made from chromaffin cells-fine brown granules when fixed with potassium bichromate and is derived from the **neural crest**.

The cortex also differs from the medulla in term of function and hormonal production. In this case, the cortex produces steroid hormones such as **glucocorticoids** (the main one is **cortisol** for human), **mineralocorticoids** (such as **aldosterone**), and is a secondary sources for sex hormones e.g. progestins and androgens.

The medulla produces catecholamines, epinephrine, and norepinephrine.

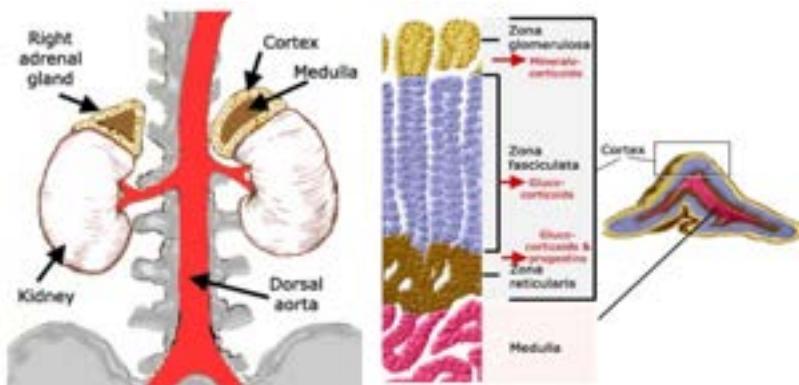


Figure 3.23: The adrenal glands and different layers of the cortex.

3.4.1 The Adrenal Cortex

The adrenal cortex is made from 3 different layers: **zona glomerulosa**, **fasciculata** and **reticularis**. These layers also differs in function because each of them has genes for different enzymes for their hormones biosynthetic pathway e.g. **18-hydroxylase** presents only in the zona glomerulosa which make it synthesize only mineralocorticoids.

The **zona glomerulosa** produces mostly mineralocorticoids (aldosterone); the **zona fasciculata** produces glucocorticoids (cortisol); and the **zona reticularis** produces glucocorticoids, progestins, androgens and estrogens.

You can see that each of these layers have the same underlying core structure of 4 steroid ring. The synthesis of adrenal steroids controlled by pituitary hormone **adrenocorticotropin (ACTH)**.

Just to remind ourselves of the purpose of steroid hormones, it functions to regulate the transcription of hormone/receptor-specific target genes.

3.4.2 Aldosterone

Aldosterone is an important steroid hormones to for Na^+ metabolism by increasing the reabsorption of Na^+ in the kidney. This also means it can control blood pressure. The problem is that you cannot simply uptake Na^+ alone due to electrochemical balance i.e. if you take in 1 cation, you have to either uptake an anion or release back a cation. In this instant, re-

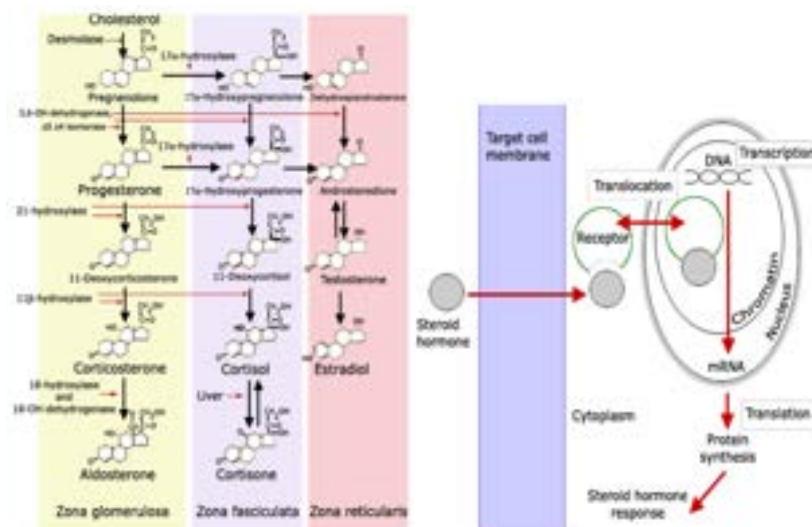


Figure 3.24: Different hormones biosynthesis in layers of the adrenal cortex and mechanism of steroid hormones.

absorption of Na^+ is coupled along with Cl^- or... it has to release K^+ or H^+ in urine.

Essentially, aldosterone affects the $Na^+ - K^+$ balance in blood as well as $Na^+ - H^+$ balance hence also affect pH.

3.4.3 Glucocorticoids

The main glucocorticoids produced by humans is cortisol while that of rodents are corticosterone. Now...glucocorticoids can act like aldosterone in salt retention only under pathophysiological condition e.g. **Cushing's disease**.

Glucocorticoids can affect metabolic processes like protein synthesis, blood sugar levels, and lipid metabolism. It increases the synthesis of **gluconeogenic enzymes** which is important for **gluconeogenesis** (synthesizing glucose) in the liver. Glucocorticoids increase the release of amino acid due to stimulation of protein degeneration, which can be used to fuel other processes.

When glucocorticoids levels deviates too much, glucose levels remain elevated which lead you secrete more insulin. This is a form of **adrenal diabetes**. If this condition is prolonged, it can lead to destruction of β -cells hence you would end up with **diabetes mellitus** or **type I diabetes**.

Glucocorticoids main/increase the action and level of **lipolytic enzymes** that are essential to breakdown lipids to be used as fuel in muscles. Essentially, excess glucocorticoids lead to **hyperlipidemia** and **hypercholesterolemia** (high lipid and cholesterol in blood).

Glucocorticoids can decrease the protein matrix of the bone through their protein catabolic effect. As a result, there is an increase loss of Ca^{2+} from the bone leading to **osteoporosis**.

Glucocorticoids can act as an anti-inflammatory that can reduce inflammation response to an injuries. In this case, when immune cells are activated, their metabolism changes; glucocorticoids can come and block these changes hence reduce amount of activated immune cells. It also decreases histamine formation thereby decreases allergic reaction.

Control of Glucocorticoids Secretion

The adrenal glands are 1 of the end-organ of the hypothalamic-pituitary-end organ axis i.e. hormones from the pituitary can affect the release of adrenal hormones, in this case, glucocorticoids.

The secretion of glucocorticoids is controlled by pituitary hormones: ACTH, which is a 39 amino acid polypeptide, synthesized as part of larger protein known as **proopiomelanocortin (POMC)**. Additionally, **stress response** that feed into the hypothalamus can increase glucocorticoids production. When hypothalamus is stimulated, it release **corticotropin releasing hormones (CRH)** that stimulates ACTH secretion of the pituitary glands, which ultimately increases glucocorticoids production. This is done through a G-coupled proteins pathway. Like other enzymes there is a double negative feedback loop made by glucocorticoids that inhibit the release of CRH and ACTH.

Under certain genetic disorders where there are missing enzymes that are essential for glucocorticoids biosynthesis, there would be a reduce in

glucocorticoids production. This also means the negative feedback loop is broken which means that ACTH level is not controlled and lead to over-stimulation of the adrenal glands. This subsequently lead to **congenital adrenal hyperplasia**. Note: *congenital* means "presented at birth".

To treat this, we simply administration of glucocorticoids that can: 1) correct the deficiency and 2) re-establish the negative feedback to ACTH.

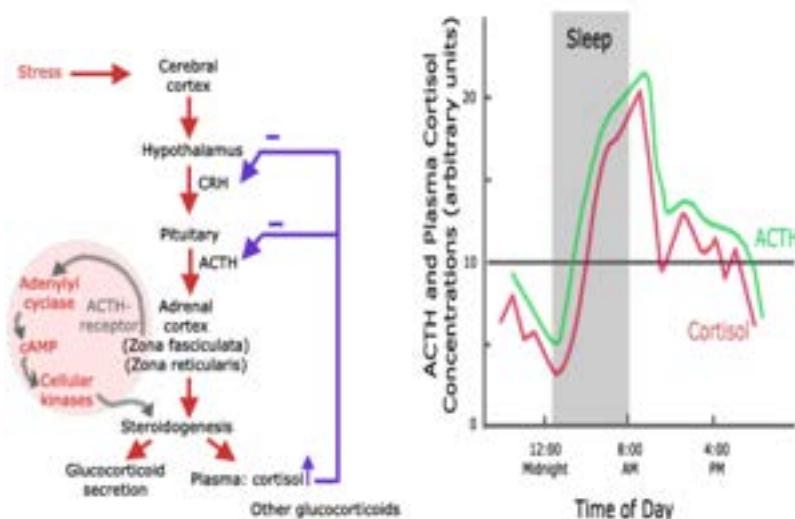


Figure 3.25: Control of glucocorticoids release and circadian rhythm.

Action of ACTH and Diurnal Rhythm

Circadian (diurnal) rhythm can control the release of ACTH i.e. [ACTH] is at its minimum at midnight while at its minimum. Because of this, there's also the same fluctuation (with slight delay) in glucocorticoids (cortisol).

Remark 3.8. *Circadian* derives from *circa diem* which means "about a day".

This rhythm may be independent of sleep and abolished by stress and Cushing's disease.

Glucocorticoids and Stress-Response

Stress stimuli, either psychological or physical (e.g. fear, pains, hunger etc.), can induce a significant increase in synthesis and release of CRH,

ACTH and cortisol.

This release of cortisol can be advantageous as it can provide energy and amino acids through the breakdown of tissue proteins, especially under conditions where normal feeding is not feasible.

Nevertheless, there could also be disadvantages to this since **cortisol can inhibit wound healing**. This also means prolonged stress can maintain a high level of glucose due to high level of glucocorticoids i.e. higher risk of type I diabetes. Furthermore, knowing the effect of glucocorticoids on active immune cells, its increase lead to lowering immune response.

In this lecture, we will look at the pathophysiology of the adrenal glands. Then, we will turn toward the pancreas and its hormones, growth hormones and finally is reproduction.

Pathophysiology/abnormalities can arise when there's either a **hypo-** or **hyperfunction** of the adrenal glands.

3.4.4 Addison's Disease

Addison's disease is characterized by the hypofunction of the adrenal cortex due to the failure of the adrenal cortex to produce adrenocortical hormones. This maybe caused by the total destruction of adrenal glands that is mostly due to autoimmune attack, but also by **tuberculosis**.

Essentially, you have a low production of cortisol and aldosterone. A low cortisol leads to **glucocorticoids deficiency** which decreases blood sugar, lipolysis and gluconeogenesis. Symptoms arises from this deficiency can be lack of energy and muscular weakness. You can also have **mineralocorticoids deficiency** which leads to loss of Na^+ in circulation called **hyponatremia**. These electrolytes imbalances can be fatal if not controlled.

To treat this disease, administration of cortisol and aldosterone is required.

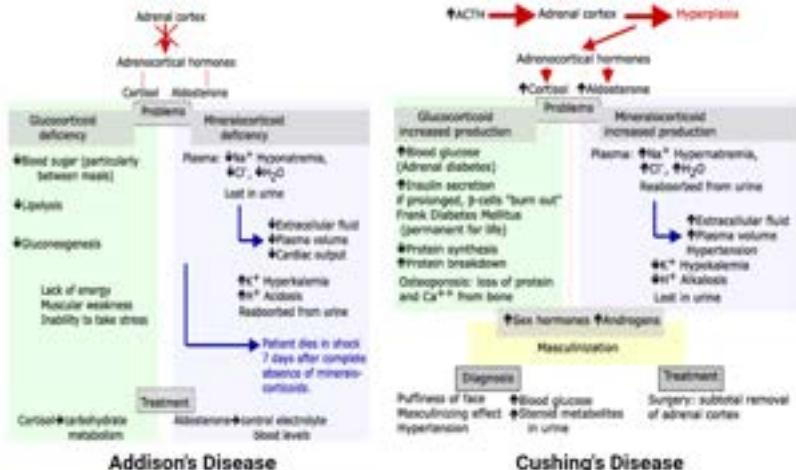


Figure 3.26: Addison and Cushing's Disease.

3.4.5 Cushing's Disease

Cushing's disease is the disease that has the opposite effect to Addison's. It is characterized by the hyperfunction of the adrenal glands due to the cortex **hyperplasia** (adrenal tumor) or hyperplasia in both pituitary and the adrenal cortex. This leads to an increase in circulating levels of ACTH that subsequently ends with excessive production of glucocorticoids as well as mineralocorticoids. In many cases, patient will end up with **masculinization**, increased extracellular fluid and thus hypertension.

A way to treat this is through the subtotal removal of the adrenal cortex.

Case Report

Female, early 30s, was first diagnosed with hypertension but did not respond to blood pressure medication. She developed **moon face** (fluid retention in the face). Her initial diagnosis was Cushing's disease which is confirmed when we measured an extremely high level of circulating cortisol while ACTH was undetectable. This is caused by **adrenal adenoma** (benign) which is removed through surgery.

Once the tumor was removed, we observed severe atrophy of other adrenal while **there's no detectable cortisol which lead to a second diagnosis of Addison's disease post-treatment**. The reason she developed this disease is because the original adrenal adenoma was left for 3 weeks straight; additionally, because of a low level of ACTH, the other adrenal begin to atrophy which leads to low cortisol production. To help with this, she was prescribed with synthetic glucocorticoids and mineralocorticoids.

3.5 The Pancreas and Its Hormones

The **pancreas** is located behind the stomach. 99% of the pancreas is **exocrine** (release substances to the outside or ducts, opposite to endocrine) and secretes the digestive enzymes. Nevertheless, the rest of the 1% are endocrine.

Remark 3.9. *Majority of pancreatic cancer is caused by the cancerous tumor of the 1%*

This endocrine part of the pancreas includes the **islets of Langerhans**, which are compact mass of cells with good vascularization. 60% of them

are known as β -cells that synthesize **insulin**. 25% are α -cells that synthesize **glucagon** (similar to calcitonin). Both insulin and glucagon are peptides hormones that control glucose concentration in blood.

Remark 3.10. *Insulin is more important than glucagon as its deficiency can compromises individual's well-being that lead to death.*

3.5.1 Insulin

Insulin is the only hormone that acts primarily to decrease blood glucose. The insulin level of a non-diabetic person (just waking up, pre-eating) is about 80mg/100ml, ~5mM. Glucose is a very hydrophilic molecules which means it will be diffuse along a cohort of water. This is also bad since hydrophilic molecules are very hard to be diffuse into cells.

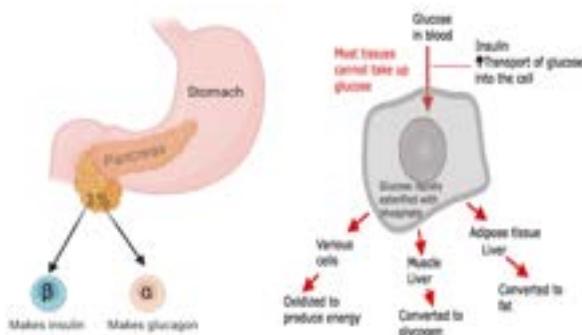


Figure 3.27: Insulin and the pancreas.

Insulin can help with this problems by transporting it into cells. In the liver and muscle cells, glucose molecules are converted into glycogen. In the adipose tissue, glucose is converted to fat and stored for later use. And in other cells, glucose can be used during glycolysis and the **Tricarboxylic acid (TCA) cycle** that is important to produce energy (ATP).

Insulin stimulate such transportation by binding to its cellular membrane **insulin receptors**. This binding **stimulates insertion of glucose transport proteins stored in cytoplasm into plasma membrane** which increases the uptake of glucose.

Insulin Deficiency

When β -cells are destroyed, other cells cannot uptake glucose anymore due to loss of insulin, which will lead to **diabetes mellitus** that is characterized by high glucose in circulation. This can occur even without any glucose in diet because of a process known as **gluconeogenesis** that uses amino acids to produce more glucose.

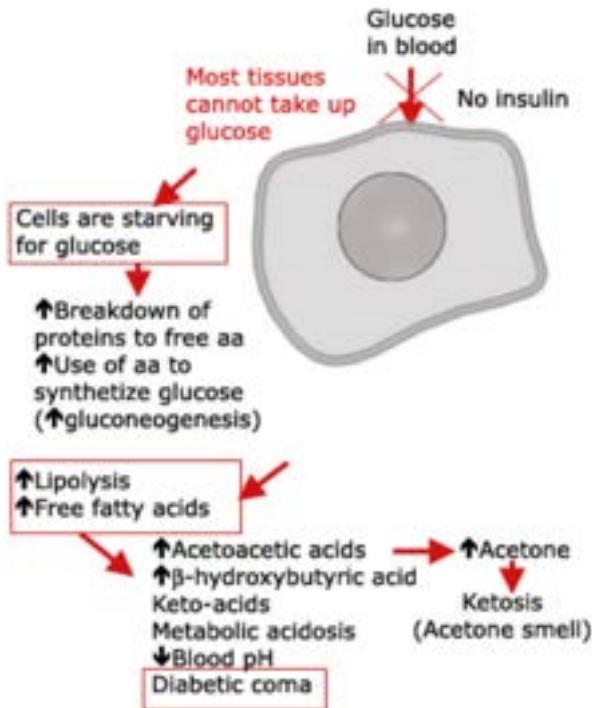


Figure 3.28: Insulin deficiency pathway.

Patient with this condition tends to make energy through **free fatty acid (FFA)** oxidation. The problem is that FFA oxidation is inefficient which can lead to build up of **acetoacetic acid**, **β -hydroxybutyric acid**, and acetone in circulation. This is characterized through the acetone smell in the breath of patient with uncontrolled diabetes. This can then decrease blood pH and lead to **diabetic coma**.

Diabetes Mellitus

Other symptoms of diabetes mellitus includes a high glucose spill over to urine ($> 180\text{mg\%}$, fasting is around 80) which causes **glycosuria**. Remember that glucose is hydrophilic so high glucose spill over also means higher water loss in urine hence causes **polyuria**. Because of high water loss, diabetes mellitus patient experiences dehydration and increased **thirst (polydipsia)**.

A treatment for this is injection of insulin (because it's a peptide hormone). In diabetic comas, acidosis and associated electrolyte imbalance must be corrected in addition to insulin administration.

Diabetes mellitus was coined by the ancient Greek where *diabetes* means "running through" and *mellitus* means "sweet" (indeed patient urine would be sweet due to high glucose concentration). Another disease that is not similar but is similar in name called **diabetes insipidus** which is caused by anti-diuretic hormones deficiency. In adults, diabetes mellitus may be due to a deficiency of insulin (**type 1 insulin-dependent diabetes mellitus**, an autoimmune disease) or hyporesponsiveness to insulin (**type 2 or insulin-independent diabetes mellitus**).

In type I diabetes, we can either treat it with injection of insulin if β -cell can no longer synthesize insulin with a proper diet. If it's due to defective insulin release, they can use drugs to stimulate its release along with good diet and exercise.

Remark 3.11. *The dosage of insulin administration is very important because a high dose can lead to low circulating glucose. If $[\text{glucose}] \leq 20 - 30\text{mg}/100\text{mL}$, glucose is not enough for brain which leads to **insulin shock** or **hypoglycemic coma**.*

If this is not treated with immediate administration of glucose, patient might die or have permanent brain damage.

In type II diabetes, insulin is at an abnormally high level which leads to reduce responsiveness from cells (decrease number of receptors in cells). This is typically associated with obesity due to overeating thus prolonged high insulin level which decrease the amount of insulin receptors (down-regulation). If you have high concentration of something, it's wasteful to have more receptors for that thing hence you downregulate it to be less. This can be treated through proper exercise and diet. It was determined that **an increase in endurance exercise increase insulin receptors response**

and is independent of body weight changes.

Majority of **Juvenile diabetes mellitus** (diabetes mellitus in children) are associated to type I diabetes. However, in recent years, there are more reported case of type II diabetes in children.

Measurement of Glucose Tolerance

Glucose tolerance is the ability of dispose glucose load. It is decreased in diabetes (low or absence of insulin) and is increased in **hyperinsulinism**.

Procedure: After an overnight fast, patient given 0.75 to 1.5g of glucose/kg body weight. Blood is taken before administration then at 30-60 minute intervals thereafter for 3-4 hrs, and glucose is measured.

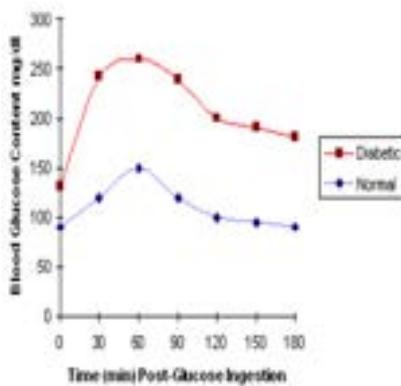


Figure 3.29: Measurement of glucose tolerance test of a normal and diabetic patient

In normal individual, within an hour interval, blood glucose goes from 80mg/100ml to 130mg/100 ml; and after roughly 2-3 hrs, it returns to normal. In diabetic patient, blood glucose changing is larger while rate of return is slower.

Control of Insulin Secretion

There are many feedback control for insulin to avoid hypoglycemia. The most important is β -cells responses according to the level of circulating glucose i.e. when blood glucose is low, insulin secretion is low or none at all; when blood glucose is high, insulin secretion is high.

Also, there's a release of gastrin and vagal impulses to the β -cells to induce insulin release. As a result insulin starts to leave the pancreas even before the blood glucose begins to rise during meals.

3.5.2 Glucagon

Glucagon is peptide hormone that is synthesized and released by α -cells. Its metabolic functions are opposite of insulin's i.e. it raises blood sugar by promoting **glycogenolysis** (breakdown of glycogen) and **gluconeogenesis** (synthesis of glucose) in the liver. In adipose tissue, glucagon increases rate of lipolysis leading to increased concentration of FFA in circulation.

Glucagon secretion is also controlled by concentration of glucose in circulation i.e. Low blood glucose stimulates pancreatic α -cells to increase synthesis and release of glucagon, while high blood glucose content decreases release and synthesis.

Like we've said, glucagon is not important like insulin. This is because other hormones like cortisol, epinephrine, and norepinephrine can increase blood glucose.

3.6 Growth Hormones

Growth hormones (GH) are single chain polypeptides produced by anterior pituitary gland. They're responsible for growth (**somatotropin (STH)**). It helps to increase protein synthesis in many tissues such as bone, muscle, kidney, liver by enhancing amino acid uptake by cells and accelerating the transcription and translation of mRNA. Additionally, it increases the rate of lipolysis and utilization of FFA as a source of energy.

Remark 3.12. *This is a direct effect of GH and not through the activation of factors (e.g. somatotropin).*

3.6.1 Somatomedins

GH can stimulate the production of factors called **somatomedins** in the liver. These factors have another name called **insulin-like growth factors (IGF) 1 and 2**. The reason for this is because it has similar structure to insulin but also insulin and IGF can bind to each other's receptors at high concentration. What IGFs can do is increase protein synthesis and stimulate growth.

3.6.2 Control of GH Secretion

The control of GH falls on the hand of the hypothalamus-pituitary-end organ (liver) axis. First, in the hypothalamus, you can get either a release of **growth hormone releasing hormone (GRH)**, AKA **somatolibrin**, or a release of **growth hormone inhibiting hormone (somatostatin)**. Exercises and sleep can low somatostatin while boost GRH to be released to the anterior pituitary gland. Then the pituitary gland release GH which can perform its own function as well as stimulate the production of IGFs. The IGFs in plasma can come and inhibit the production of GRH and GH.

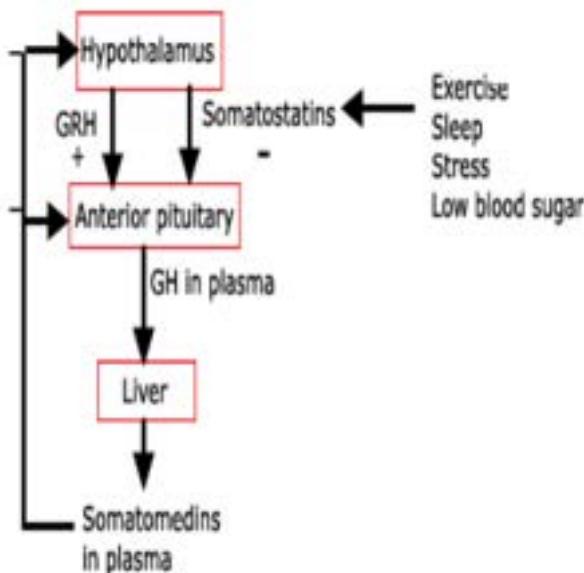


Figure 3.30: Control of GH secretion

3.6.3 Pathophysiology of GH

GH deficiency is characterized by the absence of growth hormone leads to decreased physical growth (muscle, bones, etc.). On the other hand, **excess GH** is characterized by having too much GH that lead to **gigantism** in the young. In the older population, excess GH can lead to **acromegaly** where many bones (particularly at the cartilaginous regions of the bones) get longer and heavier.

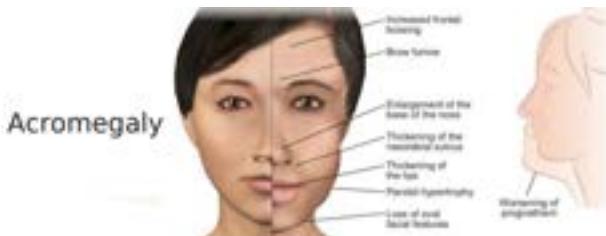


Figure 3.31: Acromegaly.

3.7 Reproduction

The primary reproductive organs are the gonads; more specifically, **testes** in male and **ovaries** in the female. The gonads in general serve 2 functions: **gametogenesis** and **sex hormones secretion**. Gametogenesis is the process of producing reproductive cells: **spermatozoa** in male and **ova** in female. Sex hormones secretion that helps with sex differentiation such as **testosterone**, **progesterone** and **estrogen**.

Remark 3.13. *Both male and female make these hormones, the differences is the amount of each e.g. testosterone is produced more in male than female, similarly but opposite for progesterone.*

It's not about a qualitative aspect but quantitative. This can be seen through a case study.

A 20-years-old male, standing at 6'10", suffers from abnormal continuous growth post-puberty as well as have joints problems and fracture. Upon X-ray analysis, we found that his bone density is way below average (comparable to an 85 years old). More testing using DNA sequencing found that he has a mutation for the aromatase gene which disrupt it from

producing estrogen from testosterone. Further analysis showed that the parents both carry this mutation (only 1 copy of each) because they were first-cousin.

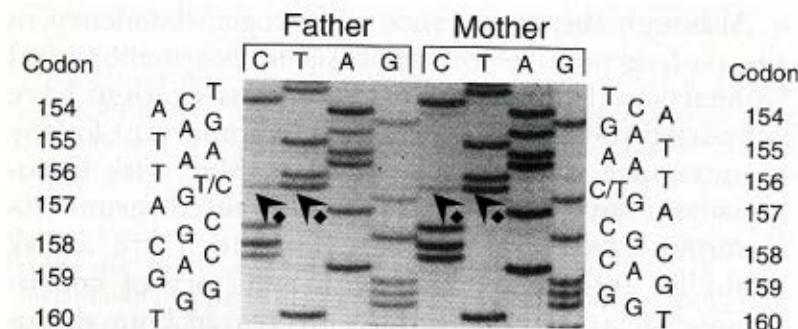


Figure 3.32: DNA sequencing of the patient's mother and father.

What we're more interested is the fact that estrogen has something to do with growth in male (we always thought it was in female only). Essentially, in male, estrogen was found to have an impact in body fat, sexual desire and erectile function.

3.7.1 Control of the Reproductive System

The control of reproductive system signalling is similar in both male and female. Like before, we're going to have that negative feedback on the hypothalamus-pituitary-end organ (gonads) axis.

Mechanism of Action (Control of Reproductive System): 1, **Gonadotropin releasing hormone (GnRH)**, secreted by hypothalamus, travels to anterior pituitary via hypothalmo-pituitary portal vessels. 2, GnRH stimulates the release of **follicle-stimulating hormone (FSH)** and **luteinizing hormone (LH)**. 3, FSH and LH stimulates the development of spermatozoa, ova and sex steroid secretion. 4, sex steroid can affect the gonads and other tissues as well as inhibit GnRH, FSH and LH release. **Inhibins** are also produced by gonads for the negative feedback.

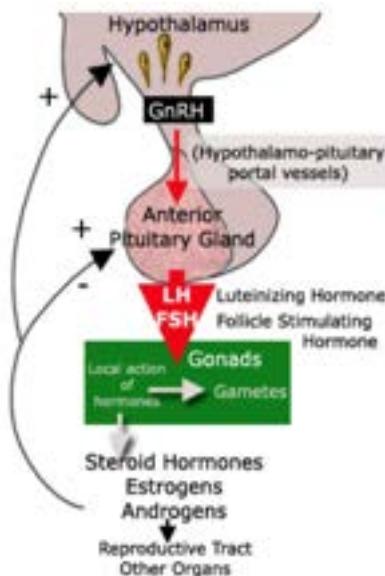


Figure 3.33: Control of the reproductive system.

3.7.2 Male Reproductive System

The principal function of testes is production of mature germ cells or **spermatogenesis** (takes place in the **seminiferous tubules** of the testes), and steroid hormones or **steroidogenesis**. Unlike females, who at birth has her whole life's supply of ova, the male continually renews his pool of **precursor germ cells (spermatogonia)** so that a relatively constant supply is available throughout life. The process of spermatogenesis all the way till maturation of spermatozoon takes around 60 days for human.

There are 2 vital cells for maturation of spermatozoa: **Leydig and Sertoli cells**. **Leydig cells** are located outside the seminiferous tubules that can be stimulated by LH to make synthesize androgens. **Sertoli cells** are located within the seminiferous tubules. They are intimately involved with the sperm maturation process - envelop the germ cells throughout their development. FSH can stimulate sertolic secretion of **androgen binding protein (ABP)** and inhibin.

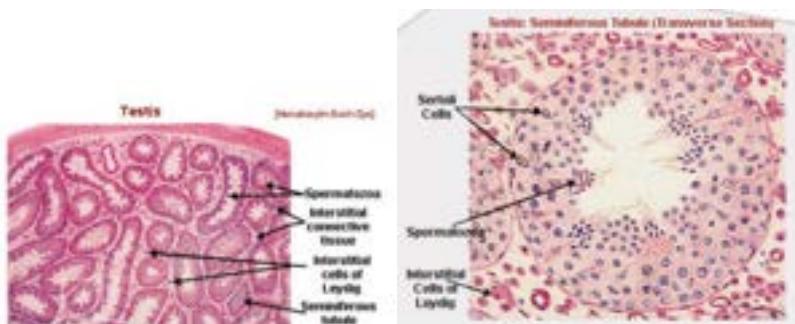


Figure 3.34: Histological slide of testes cross-section.

Spermatogenesis

The process of spermatogenesis critically dependent on androgen concentrations within seminiferous tubules, which must be approximately 10 times higher than androgen concentration in circulation otherwise spermatogenesis ceases. The presence of ABP synthesized by Sertoli cells ensures that high androgen concentration within seminiferous tubules.

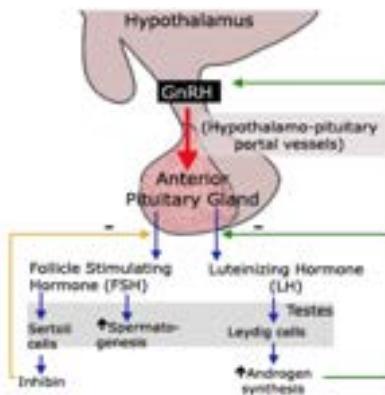


Figure 3.35: Regulation of androgen synthesis.

Testicular androgen synthesis regulated by two negative feedback loops. First, GnRH stimulates the release of LH and FSH that stimulates Leydig cells and Sertoli cells. Leydig cells produce androgen, which inhibit the release of GnRH, LH and FSH. Second, non steroidial inhibin, secreted by

the Sertoli cells, inhibits FSH release only.

Remark 3.14. Contrary to females, there is no positive feedback control in males.

3.7.3 Female Reproductive System

The principal functions of the ovaries is the production of mature eggs, and steroid hormones, which regulate the reproductive tract and influence sexual behavior. At birth ovary contains non-proliferating pool of germ cells or **oocytes** (about 2 million), which are its whole life supply of ova. At puberty only around 400,000 ova left (**we have no clue why**).

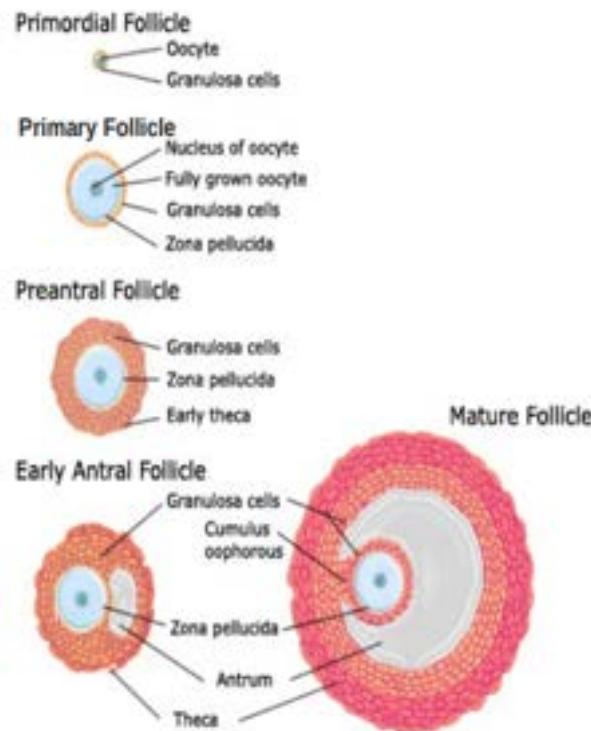


Figure 3.36: Development from the primordial follicles to a mature follicle.

The oocytes are surrounded by a single layer of **granulosa** cells and a basement membrane making up the structures called **primordial follicles**.

follicles which are fundamental reproductive units of the ovary. Growth of primordial follicles into **primary follicles** begins by an unknown initiating event (independent of pituitary). Once initiated, growth controlled by gonadotropins and steroid hormones until the follicles either ovulates or degenerate (**atresia**)

Remark 3.15. *There is only 1 ovulation event for every menstrual cycle regardless of the fact that female have 2 ovaries.*

Mechanism of Action (Follicular Growth): 1, there's an enlargement and differentiation of the oocyte, which grows and develops the **zona pellucida** (an acellular layer rich in glycoproteins surrounding the oocyte).

2, **Granulosa cells**, surrounding the oocytes, divide and increase to 2 or more layers thus forming **primary follicles**. They're influenced by FSH and estrogens. Estrogens important for expression of LH receptors on granulosa cells.

3, under the influence of FSH and LH, primary follicle develops into a **secondary follicle** which expresses receptors for FSH, estrogens and LH. Also, there would be the appearance of the **follicular antrum** which contains secretions from the granulosa cells.

4, Under the combined influence of FSH and LH, granulosa cells develop follicular fluid in the atrum, which takes up the larger portion of the **preovulatory follicle** (also known as late secondary follicle or Graafian follicle or mature follicle).

Remark 3.16. *As follicles matures from primary to secondary, outer most layer cells surrounding the follicles become steroid-producing cells called theca interna.*

Together, the theca interna and granulosa cells can boost high estrogen production.

At the end, majority of follicles will experience follicular atresia thus lead to degeneration. There would be only 1 follicle that fully mature and begin **ovulation**, which is the process of rupturing the mature follicle and release the oocyte for fertilization. This mechanism is poorly understood though there are suggestion that it's due to increase intrafollicular pressure and proteolysis of the wall.

In this lecture, we will continue from previous lecture on female reproductive system: menstrual cycle; fertilization, implantation and post-implantation. Then, we will turn our interest on vitamin D effect on physiology.

Luteinization

We begin where the mature follicle (only 1) ruptures and releases its oocyte and this process is called ovulation. This ruptured follicle transforms into **corpus luteum**, which is a temporary endocrine structure that can produce progesterone and estrogen. This transformation is also contributed mainly by theca and granulosa cells. 1 thing to note is that the amount of progesterone and estrogen produced by the corpus luteum is **massive for a few days but then rapidly drop unless implantation of the fertilized ovum occurred**.

If there's an **implantation** event occurred, the corpus luteum transforms into the **corpus luteum of pregnancy**. This new structure can synthesize progesterone and estrogen until the *placenta* takes over to create such endocrine environment for pregnancy.

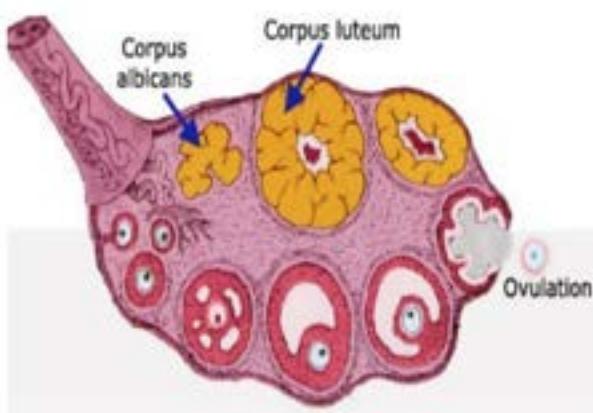


Figure 3.37: The corpus luteum.

On the other hand, if there's no implantation, the corpus luteum will experience **luteolysis** where its life-span is limited, triggered by **prostaglandin**. This can further decrease LH binding and thus steroidogenesis. Ultimately, the plasma progesterone and estrogen level drops which trigger initiation

of the next/new reproductive cycle.

3.7.4 Menstrual Cycle

What we've said above and the last bit of previous lecture can be summed up as the **menstrual cycle**.

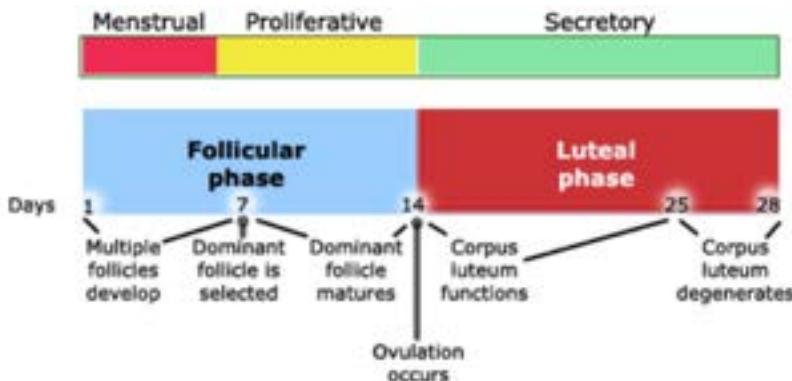


Figure 3.38: The menstrual cycle.

Before menstrual cycle begins, we have estradiol causes the thickening of the **endometrium**, which is important glandular structure for implantation.

On the first day beginning the **menstrual phase**, if no implantation occurred, low circulating progesterone and estrogen reduce blood flow to the endometrium causing it to deteriorate. The deterioration of the endometrium causes **bleeding (menses)** that flow through the cervix to the vagina ad last roughly 5 days.

At the same time, the multiple follicles begin to develop at the same time (follow the mechanism of follicular growth discussed in previous lecture). Then by day 7, only 1 follicle mature and will be release on day 14 (ovulation) then enter the luteal phase.

Graphical Representation

We can look at the levels of different hormones involved in this cycle. At the beginning (day 1-14), we can see there's a low level of estrogen and progesterone which means the negative feedback is lacking thus FSH and LH

is secreted more. Also, there's also a low production of inhibin thus lower inhibition of FSH.

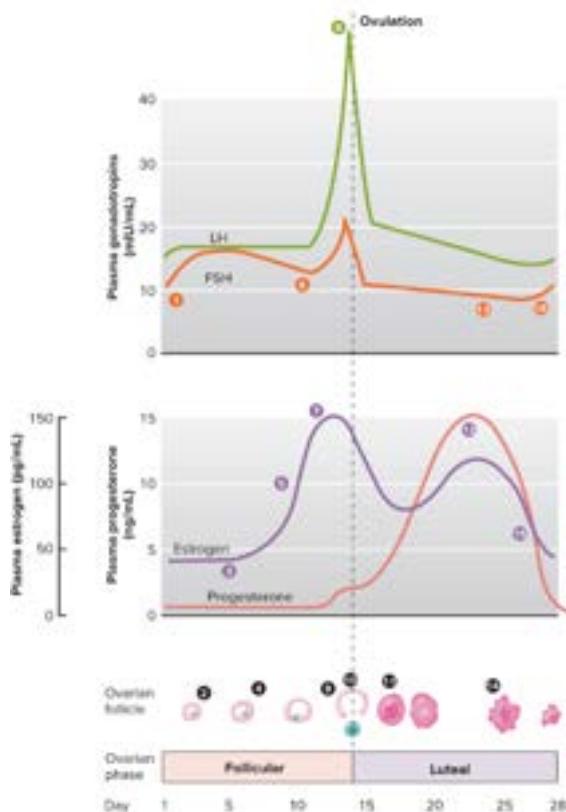


Figure 3.39: Different hormonal level in the menstrual cycle. Also ignore the circled numbers, it's the textbook's explanation.

With the rise in FSH, multiple follicles develop up until day 7. Not only that, FSH stimulates the proliferation of granulosa cells on the follicles, allowing it to synthesize more estrogen which further stimulate granulosa cells proliferation. On Day 7-8, 1 follicle becomes dominant and further develop while the other follicles experience atresia. The dominant follicle release more estrogen, specifically **estradiol**, that can induce endometrium thickening. Estradiol can also induce production of endometrial progesterone receptors making it sensitive to progesterone.

LH surge event

Estrogen can also create a negative feedback to FSH secretion. Furthermore, it can stimulate the synthesis of LH and increases the pituitary's sensitivity to GnRH that further stimulate LH synthesis. Now, **moderate concentration of estrogen may induce LH synthesis but inhibit its release i.e. there's LH accumulation in the pituitary.**

As the dominant follicle develops, the amount of estrogen rises rapidly. The high concentration of estrogen induces a massive surge in GnRH which releases the accumulated LH out of the pituitary. This event is called **LH surge** which is around day 14 of the menstrual cycle.

What we can conclude from this is that estrogens exert negative feedback that decreases GnRH and LH release and positive feedback that increases sensitivity of anterior pituitary cells to GnRH and increased LH synthesis.

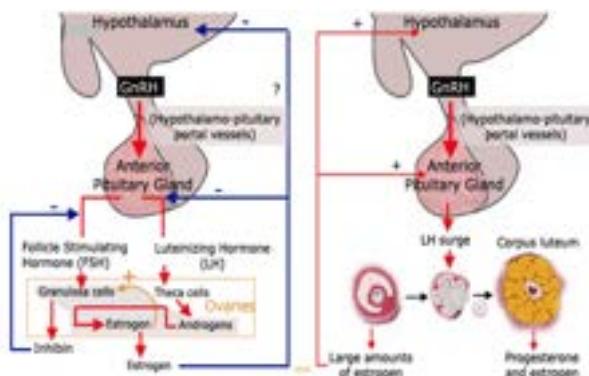


Figure 3.40: Feedback mechanism of estrogen

Oral Contraceptives

Oral contraceptive pills contain estrogen and progesterone which maintain moderate circulating levels of estrogen and progesterone. This suppresses the release of LH and FSH from the pituitary thus preventing ovarian follicles from maturing and being ovulated. These pills have a 99% success rate, provided that the pill is taken daily for 21 consecutive days with 7 days of no medication that would induce menstruation.

Luteal Phase

Under the influence of LH the follicle becomes corpus luteum that produces large amounts of estradiol and progesterone that lead to endometrium thickening. In addition, under the influence of progesterone the endometrium becomes glandular. The endometrium is now fully prepared to receive and support the development of a growing embryo.

The **luteal phase** lasts a constant 14 days where steroids produced by corpus luteum dominate. After 14 days, if there's no implantation or fertilization, oocytes and corpus luteum degenerate which induce a drop in steroid. The endometrium will also deteriorate and thus menstruation begin, FSH is secreted more by the pituitary and the cycle restarts.

3.8 Fertilization, Implantation and After

Upon ovulation, unfertilized egg (oocyte) is taken by the **fimbria** of the **oviduct (fallopian tube)** and is being propelled towards the lumen of the uterus. If (unprotected) sexual intercourse occurs, spermatozoa deposited in the vagina will travel as far as the oviduct and 1 of which will fertilize the egg.

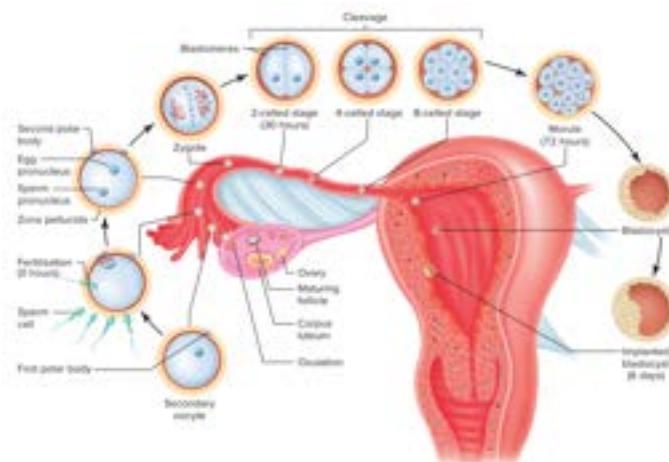


Figure 3.41: From ovulation to implantation.

After **fertilization**, the egg will undergo rapid cellular division (no growth yet) leading to a structure called **blastocyst**. After which, blastocyst will differentiate into: 1, **trophoblast**, that will become the placenta; and the **inner cell mass**, that will become the embryo. At the same time, it moves through the oviduct toward the uterine lumen.

Implantation occurs when the trophoblast "invades" the uterine mucosa and implant itself there. Around this time, trophoblast starts to produce **human chronic gonadotropin (HCG)** that is similar to LH, which promotes corpus luteum to continue secreting gonadal hormones. After the 12th week of pregnancy, the placenta takes over the endocrine function of the corpus luteum and together with the developing fetus, it forms the **feto-placental unit**.

If we measure the hormonal level, we can see that estrogen and progesterone is kept rising all the way till **delivery (parturition)**. Another thing is a sharp overshoot of HCG at around 1-2 from the last menses and it forms the basis for pregnancy test.

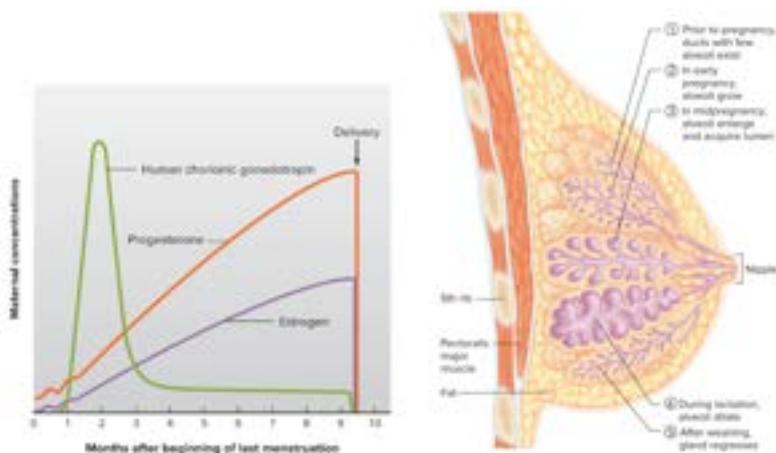


Figure 3.42: Hormonal level during pregnancy and lactation.

The secretion of milk by the breast (mammary glands) is called **lactation**. The mammary glands growth is under the control of endocrine. With onset of puberty under the action of increasing levels of estrogens, marked enhancement of duct growth and duct branching but relatively little development of the **alveoli**. Progesterone can stimulate these alveoli.

However, most breast enlargement is due to fat deposition under the glandular tissue.

Under influence of several hormones, including estrogen, progesterone, prolactin, human placental lactogen, both the ductal and alveoli structures fully develop. Prolactin helps with milk production however high estrogen inhibit its secretion.

After parturition, estrogen level drops while prolactin remains high i.e. milk production is high and is allowed to be released. During **nursing (breast-feeding)**, the suckling action of the baby stimulate the hypothalamus that lead to production of oxytocin and prolactin in the pituitary gland. Prolactin will cause the alveoli to produce milk while oxytocin stimulate its contraction leading to **milk ejection**.

Remark 3.17. *Oxytocin is important for parturition because it induces uterine contraction due to high oxytocin receptors expression there.*

Milk consists of water, protein, fat and carbohydrate lactose and antibodies. However, infectious agents such as viruses and drugs may be transmitted from the mother to infant through breast milk.

Lactational Amenorrhea

Lactational amenorrhea is the way for the body to be temporarily infertile through nursing. Essentially, the constant suckling during nursing from the baby stimulates prolactin production and this can inhibit FSH and LH i.e. blocks reproductive cycle.

In fact, nursing is a used natural method of contraception. However, it must be noted that frequency and intensity of this suckling are important parameter to induce contraceptive effect i.e. if suckling is not as frequent, pregnancy may occur.

3.8.1 Menopause

At the end of reproductive period, most ovarian follicles have disappeared by atresia and a few hundred have been ovulated during successive menstrual periods. This depletion of follicles results in loss of capacity for steroid (estrogen and progesterone) hormone production by the ovary. Lack of estrogens often induces number of symptoms such as: **hot flashes, dry vagina, restlessness, bone loss (osteoporosis - long term), etc.**

Because production of steroid hormones ceases, FSH and LH rises in the plasma due to the negative feedback loop. The constantly high FSH level is indicative of **menopause**. Symptoms caused by low estrogen can be treated with **estrogen replacement therapy** however it does not restore fertility as the main cause to menopause is follicular depletion.

3.9 Vitamin D Effects on Physiology

Here's the schematic of how active vitamin D is made in the body

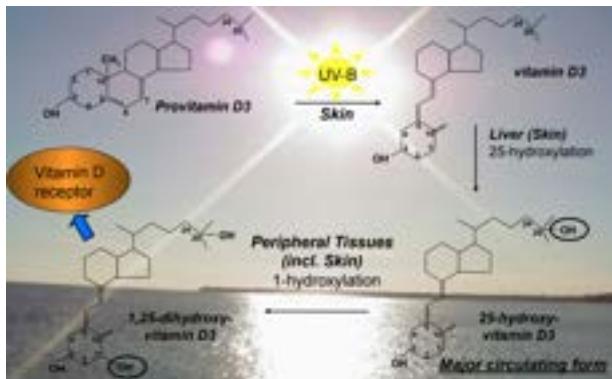


Figure 3.43: Scheme of vitamin D synthesis.

We begin with the provitamin D3 that has the distinct 4 ring cholesterol structure. The main thing to note here is there's an enzyme called **7-dehydrocholesterol** that reduces the single bond at position 10 into a double bond. The conjugated double bond combination is sensitive to UVB which can cause it to rearrange into vitamin D3.

There are vitamin D supplement that can be plant-based or animal-based. In animal-based, the compound is called **cholicalciferol** while in plant-based, it is **ergosterol** that lead to vitamin D2 instead of D3 but is just almost as good.

Back to the vitamind D3, after its synthesis it will be 25-hydroxylate in the liver to form the 25-hydroxy-vitamin D3 intermediate. In fact, in vitamin D test, doctors will test for these intermediate since its half-life is a few weeks. Then this intermediate is 1-hydroxylated by an enzyme **that func-**

tion independently of calcium homeostasis to form the active form 1,25-hydroxy-vitamin D3 (1,25D3)

3.9.1 Affect on Vitamin D Synthesis

What we can see from the map below is as you move toward the 2 poles, the intensity of UVB decreases which also lead to decrease in sufficient vitamin D synthesis. With that logic, we expected that vitamin D insufficiency to be near the poles but turns out it's mostly in the Middle Eastern region. The reason is high heat and humid push the population to stay indoor that outside + conservative dressing.

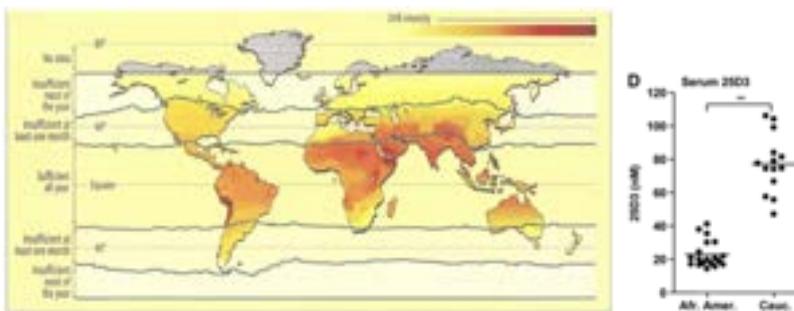


Figure 3.44: Vitamin D winter map and circulating vitamin D due to skin colour.

Skin colour can affect the amount of vitamin D will be synthesized in the body. A serum test showed that there's a 6-fold difference in serum vitamin D in Caucasian than in African American. Nevertheless, a compensate affect that the body made is that African American will tend to have higher bone density than Caucasian.

3.9.2 Vitamin D and the Immune System

Children with rickets tend to have a higher risk for infections, autoimmunity, allergies, and even cancer. This is because ricket is characterized with the deficiency in vitamin D (maybe a mutation that lead to decrease synthesis in the child) which links directly toward the immune system.

3 disease that demonstrated NS gradients are certain types of cancer, autoimmune disease and infectious disease (e.g. tuberculosis myobacterium)

and they're linked with vitamin D deficiency.

In the study, the production of an enzyme called cyp27B1 that is responsible for the 1-hydroxylation is tracked. What happened is that they exposed macrophages to bacterial cell wall (BCW) which induce them into releasing infection signal to the body. When this happened, we detect an increase in active 1,25D3 in circulation.

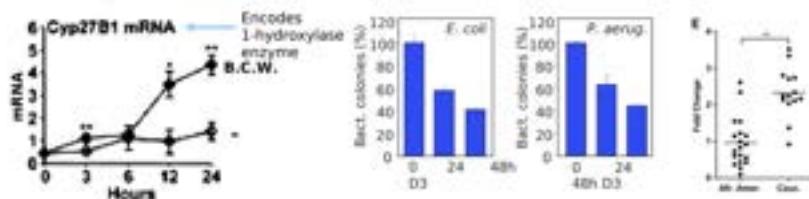


Figure 3.45: 1,25D3 level in circulation with macrophage BCW exposure (left); increases 1,25D3 level induces higher release of antimicrobial peptides (middle); and antimicrobial peptide level differences between African American and Caucasian (right).

In our lab in 2004, we searched for genes whose transcription is regulated by 1,25D3. It turns out that major genes we found was that for **antimicrobial peptides** and they can poke holes on the surface of bacteria. So, we decided to treat cells with 1,25D3 and exposed them in an environment of *E. Coli* (less strong strain than the actual outbreak). What we found is over a period of 48 hours, the amount *E. Coli* decreases. A repeated experiment was done on *Pseudomonas aeruginosa* (pathogenic in cystic fibrosis patient) and it yields a similar result.

Now if we look at the amount of these antimicrobial peptide in African American and Caucasian, we can also see that difference due to vitamin D differences.

Chapter 4 Gastroenterology will cover all of lectures on digestive system spanning from February 28th to March 25th, 2024.

Definition 4.1. The **digestive system** is a system of organs (main and accessory) in order to breakdown and absorb nutrients from food.

The organs that contributes to the digestive can be divided into 2 branches: **Gastrointestinal tract (GIT)** and **accessory organs**. The **GIT** includes the mouth, esophagus, stomach, small and large intestine and the anus i.e. it's the main continuous "tubes" going from the mouth to the anus. **Accessory organs** are organs connected to the GI tract and secrete substances to facilitate with digestion and absorption. They include the salivary glands, pancreas, liver and gallbladder.

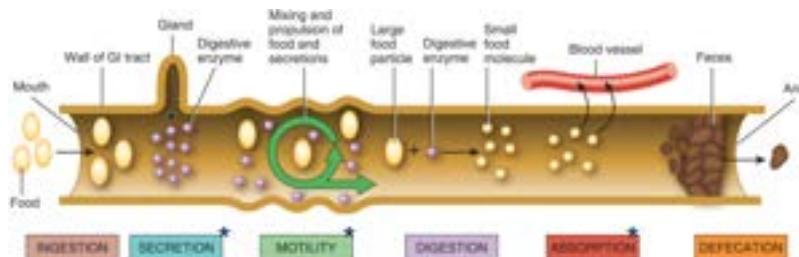


Figure 4.1: Activities made by the GIT.

The GIT's function is to break food down into smaller molecules that the body can absorb. It does so through 6 different activities. First is **ingestion** where food enters the mouth. **Secretion** is when glands secrete its enzymes to chemically break down food. **Motility (propulsion)** is when food moves through the GIT as well as being mechanically broken down. **Digestion** is the broad term include breaking down food mechanically and/or chemically. After it is broken down into smaller molecules, GIT does **absorption** which is transferring those molecule into bloodstream. Finally,

any part of food that wasn't absorbed will be released back to the environment via **defecation**.

In this course, we will look at mainly: secretion, motility and absorption.

The GIT is important for maintaining the body homeostasis as it helps to breakdown nutrient sources from external environment into absorbable nutrient in the internal's. These nutrients provide fuel for our cells to grow, repair and perform the daily functions. The GIT is very efficient in term of absorption i.e. **it can absorb 99% of carbohydrate, 95% fat and 92% proteins from food**. Its efficiency is thanks to the high coordination of propulsive, secretory and absorptive activities that are mediated by neuronal and hormonal control. We shall begin with some anatomy.

4.1 General Anatomy and Control of the GIT

To look at the GIT, we can simplify it by looking at that of worms. Our GIT is almost exactly like that of worms that it is tubular in nature. Not only that, we also realized that both of the tubules' ends are in contact with the external environment. And if you think about it, the content of the **central luminal cavity** is also part of the external environment.



Figure 4.2: Simple GIT of worm.

The GIT was set up in this way so that bacteria and toxin that might be in the food to not get into the bloodstream but also absorb nutrients.

Evolutionary speaking, we can see that our GIT was built from that of the worm. One of the main changes is through growth and development. If we look at the worm GIT, it has almost the same length as the worm. However, for us, GIT's length is almost 3x their height (a 1.5m person have 4.5m GIT).

Remark 4.1. There could be some discrepancy in length measurement due to muscle tone between a live human and a dead cadaver

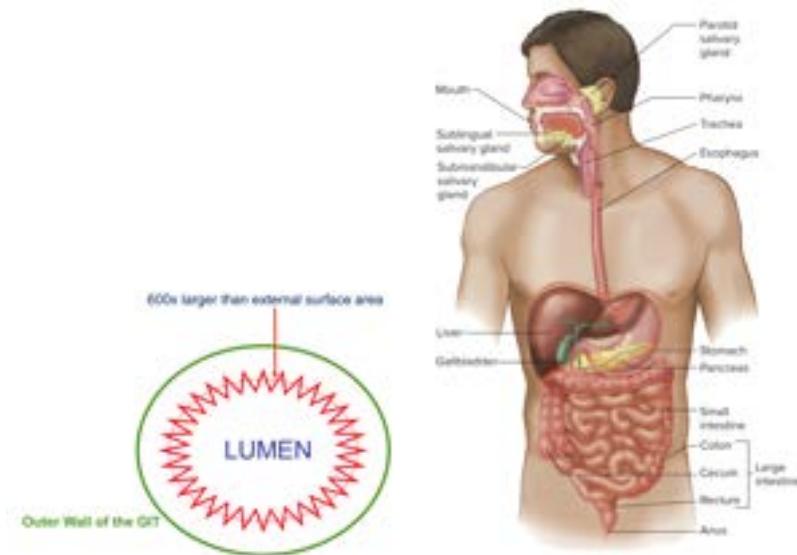


Figure 4.3: Internal surface's invagination, finger-like projection (left) and differentiation of the GIT.

Not only we have growth in length, we also have growth in the internal surface area. The internal surface area have invaginations and finger-like projection which make its area is almost 600x larger than the external surface. The total area covered by the internal surface is almost $200-250\text{m}^2$ (around a tennis court). With this large surface area, the efficiency in nutrient absorption.

We also have differentiation of the GIT i.e. different section of the GIT performs different function

4.1.1 GIT Tubules Structure

We will now look at the cross-section of the GIT we see that it's made from 4 different layers. Starting from the interior lumen, we have the **mucosa** which is where the majority of secretory and absorptive cells are located (**epithelial layer**). This layer also consists of the **lamina propria** which are

loose connective tissue, and **muscularis mucosae** which are smooth muscle. We then have the **submucosa** which is a layer of loose connective tissue containing lymphatics and blood vessels that provide nutrients to the GIT cells.

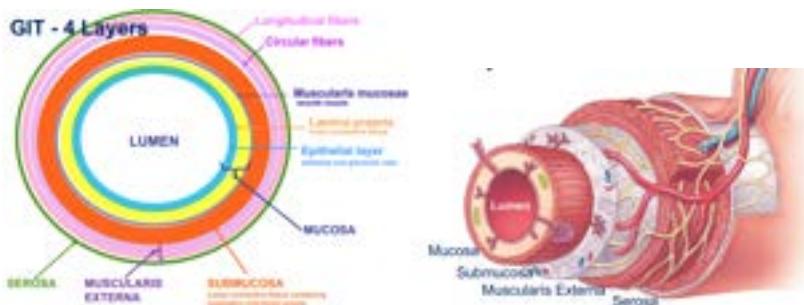


Figure 4.4: Layers of the GIT

We then have the **Muscularis externa** which consists of 1 layer of **longitudinal fibers** and **circular fibers**. The longitudinal fibers are parallel to the length of the GIT i.e. when it contracts, it shortens the GIT. The circular fibers run perpendicular to the length of the GIT i.e. when it contracts, it decreases the aperture (diameter) of the GIT lumen.

Remark 4.2. *The striation of these fibers depends on its location e.g. near the mouth and anus it's striated while in the stomach it's smooth.*

Finally, the outer most thick layer is called the **serosa** which is in contact with the **peritoneum** that is the serous membrane that lines the abdominal cavity.

4.1.2 Enteric Nervous System

The **enteric nervous system (ENS)** is the nervous system that controls the motility, secretion and absorption of the GIT. It consists of neurons located in the GIT that can function independent from the CNS and ANS, though it can be affected by them. Essentially, it's integrative that is **it can initiate, program, regulate and coordinate activities of muscular and secretory and absorptive elements of the GIT**.

We can zoom in on to the walls of the GIT, we can see that there are 2 layers of the ENS called **myenteric plexus** (between the circular and lon-

gitudinal fibers) and **submucosal plexus** (between circular fibers and submucosa). **Plexus** is a collection of nerves cell bodies. Anatomically these 2 plexuses are distinct but for the sake of simplicity, we will treat them as 1 functional unit.

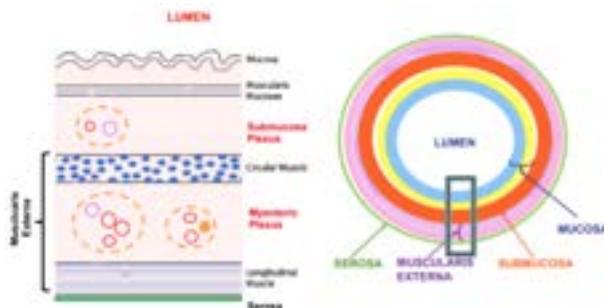


Figure 4.5: Plexus layers of the GIT.

These plexuses contain elements for the reflex arcs: **sensory, motor (effector) and interneurons**. Sensory neurons have receptors located at the level mucosa and musclurasis that can sense chemical environment (chemo- and osmoreceptors), stretch of the gut (mechanoreceptors). These sensory neurons can then communicate with effector neurons via interneurons that can lead to contraction of the GIT or activation of secretory cells.

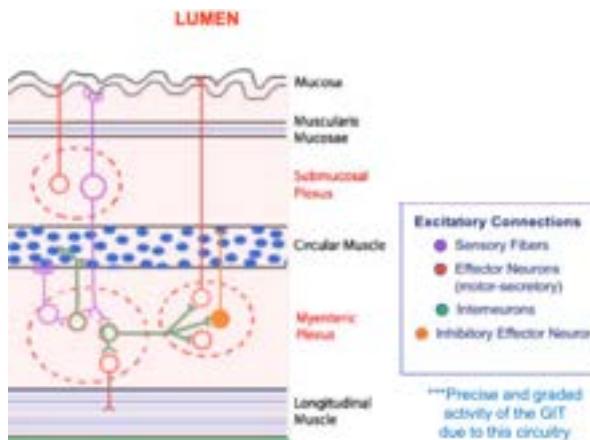


Figure 4.6: GIT wall innervation.

Looking at the better illustration above, we see the sensory neurons have extensions toward the lumen and muscle to detect the change. Once a change is induced, sensory neurons send afferent to interneurons. Interneurons then communicate with effector neurons which make them send efferent to either smooth muscles or secretory cells. Secretion would change the environment again and could activate inhibitory response by effector neurons. Because we have all of these neurons and connections in the gut via ENS, it gives us a very precise and graded activity of the GIT.

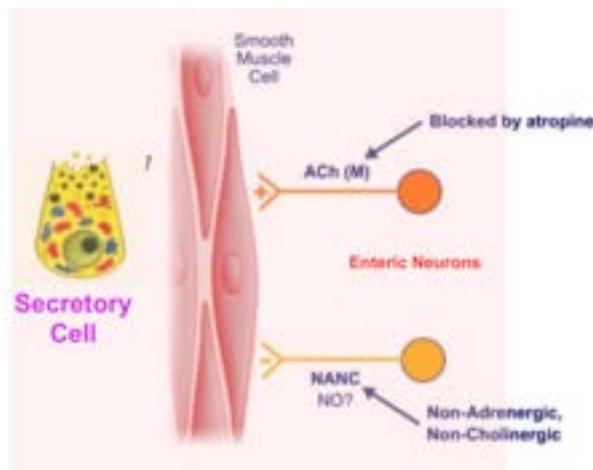


Figure 4.7: Inhibitory and excitatory ENS neurons.

Effector neurons can be either inhibitor or excitatory. If excitatory effector neurons, they will release **acetylcholine (ACh)** on to target cells' muscarinic receptors (that can be blocked by **atropine**). On the other hand, upon activation of inhibitory effector neurons, they will release **NANC** (e.g. nitrous oxide) onto target cells' receptors. The NANC are non-cholinergic and non-adrenergic.

Now the ultimate enteric activity is dependent on the sum of input that it receives, e.g. if 5 excitatory signals and 1 inhibitory signals are sent to the muscle, the muscle will be excited.

So to sum up the pathway from stimulus to response we've said above, when stimulus comes in, it will be detected by receptors. These receptors send signal through the nerve plexus which activate effector neurons that induce a response in the form of contraction or secretion. Together, this is

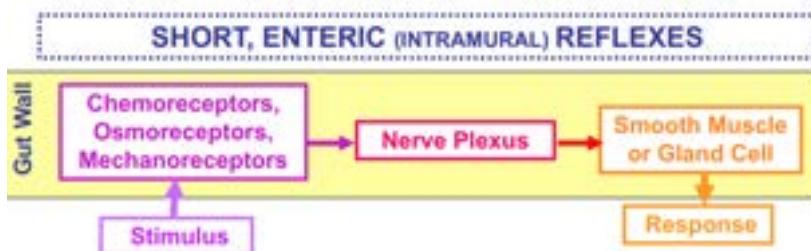


Figure 4.8: Stimulus to response of ENS

called the **enteric reflexes**.

4.1.3 ANS Innervation of the GIT

Though the ENS is independent from the CNS and ANS, it can be modulated by them. The ANS does not affect directly the target cells like muscles and glandular cells, however it can affect the ENS neurons.

On the parasympathetic branch of the ANS, it has **preganglionic fibers** from CNS that will release ACh onto the ENS neurons' receptors (nitrotnic-ACh) which leads to its excitation thus promotes gut motility and secretion. On the sympathetic branch, it first start from the CNS then sent ACh to excite the sympathetic ganglia. This excited sympathetic ganglia will send signals through the **post-ganglionic fibers** that synapse to the ENS neurons. This synapse is characterized by the release of **noradrenaline (NA)** that inhibit them.

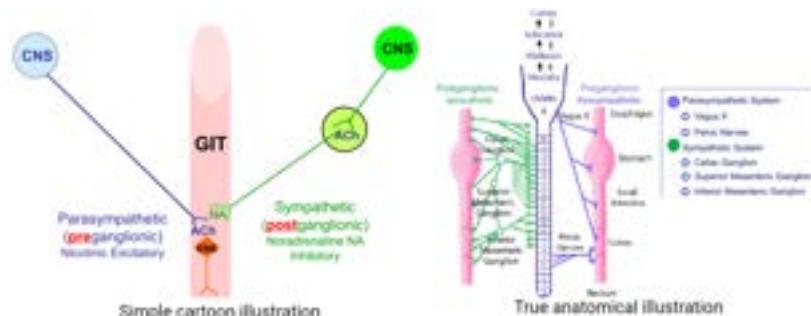


Figure 4.9: ANS innervation of the GIT.

Upon a closer inspection of the parasympathetic branch, we can see that it originates from the medulla and travels to the GIT via the **vagus nerves**. The only exception is the innervation via **pelvic nerves**. On the other hand, we can see the sympathetic originates from the spinal cord that synapse first to a ganglion chain. These ganglia will innervate the GIT via the post-ganglionic nerves.

We put this new knowledge with the cartoon that we had. Within the wall of the gut, we have the enteric or short reflexes mediated by the ENS however beyond the wall, we have the **long reflexes** mediated by the ANS modulation on the ENS. The parasympathetic system can send ACh to either inhibitory or excitatory ENS neurons to activate them. Similarly, the sympathetic system can send NA from the chain of sympathetic ganglia to inhibitory or excitatory ENS neurons.

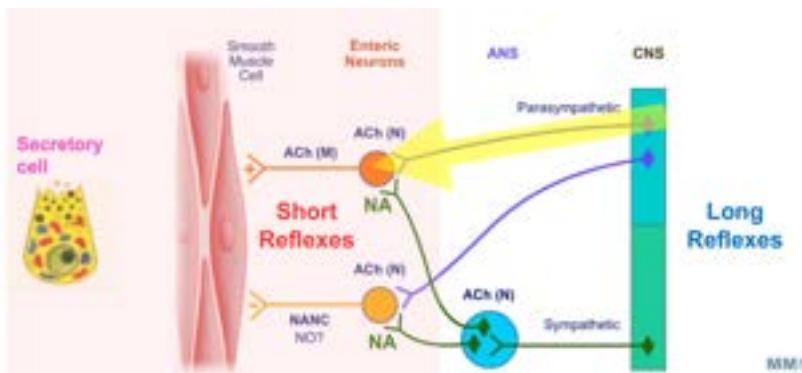


Figure 4.10: ANS long reflexes and ENS short reflexes illustration.

Another thing we should know is that parasympathetic input can also lead to blood vessels dilation while sympathetic input does vasoconstriction. Notice on the diagram that there's a big yellow arrow. The reason it is there because the majority of parasympathetic signals are excitatory.

In previous lecture, we talked about different layer of the wall of the GT which includes: muscosa, submucosa, muscularis externa and each of them serve different purposes. We also said that GIT have many different functions, 3 of which we will be focusing on: motility, secretion and absorption.

These activities are made possible by the GIT own enteric nervous system (ENS) which is a branch of the autonomic nervous system (ANS). Nevertheless, the ENS can function independently from the ANS. It can perform integrative innervation and regulate the GIT via short, intramural (in the wall of GIT) reflexes. On the other hand, the ANS can modulate the activities of the ENS via long, extrinsic (beyond the wall of GIT) reflexes.

4.1.4 ANS Activation from the GIT

We can look over these innervation. Essentially, we have signals coming receptors in the mucosa and muscularis to the ENS sensory neurons. These neurons can then synapse with interneurons which then relay these signals onto effector neurons. Effector neurons can be either inhibitory and excitatory; and they both can be modulated by the sympathetic or parasympathetic branch of the ANS. But now if you think about it.

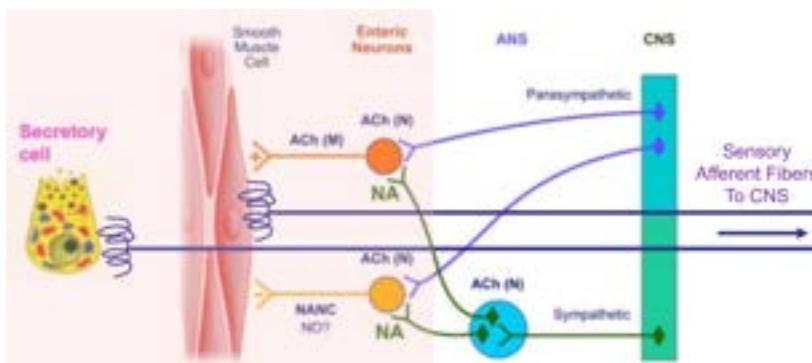


Figure 4.11: Sensory afferent from the GIT travels to the CNS which induce an ANS response.

What causes the activation of the ANS into modulating the ENS?

Well...it's due to signals coming from the GIT itself. There are sensory fibers that send afferent toward the CNS instead of the ENS, which can activate the ANS to feedback onto the ENS.

Here we can see there are sensory afferent coming back to the medulla or spinal cord. Then sensory efferent will be sent back to activate the ENS neurons to induce a response.

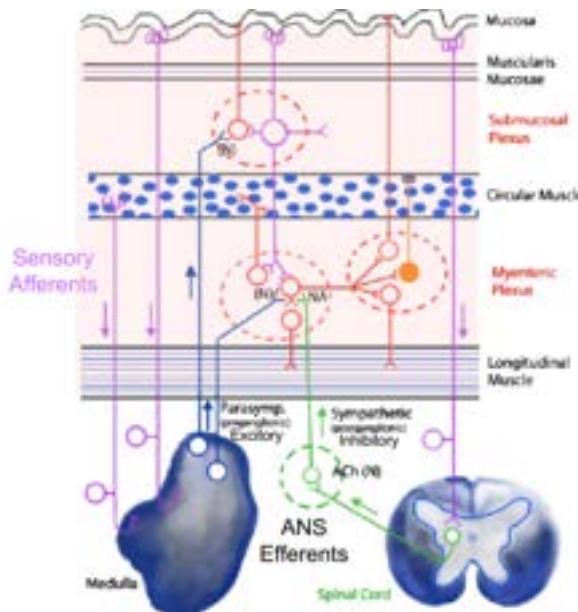


Figure 4.12: Sensory afferents from receptors of the GIT travel either toward the medulla or the spinal cord. This in turn, produces efferents travel back down the GIT.

We can sum up the control as the following diagram. What we have are afferent neurons receiving signals from the receptors, they then send afferent to the CNS. The CNS can send back efferent to the GIT plexus via the sympathetic (mainly inhibitory) or parasympathetic (mainly excitatory) branch of the ANS, and this makes up the long, extrinsic reflexes.

Interestingly, we can also activate this directly by the CNS e.g. see food,

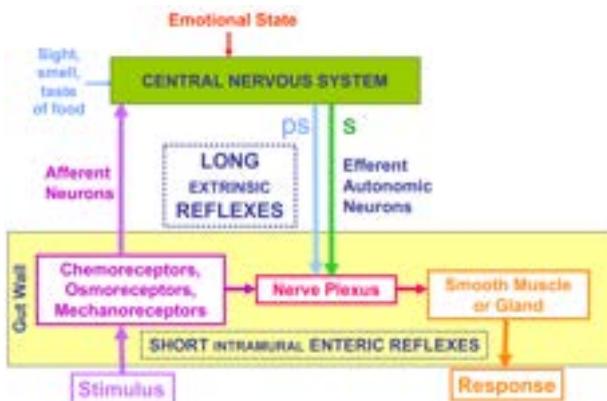


Figure 4.13: ANS modulation of the ENS via long, extrinsic reflexes.

smell food, chew it. Emotional pathway can have an affect e.g. food that you know delicious will activate the gut.

4.1.5 Hormonal Influences on GIT Activities

There are non-GIT hormones that have an effect on GIT (regarding to growth and development) however, we will only look at those in the GIT. These GIT hormones can also induces an effect on outside of the GIT.

Example 4.1.1. During starvation, glands in the stomach can release **ghrelin** that can enter the bloodstream and target the hypothalamus which produce a hunger response. On the other hand, those same cells can release **leptin** in response of overeating that decreases appetite.

The GIT have the largest and most diverse endocrine system in the body. Together, the cells that release hormones in the GIT are called the **diffuse endocrine system (DES)**. This is because they're not collectively found at 1 place but diffuse all through out the GIT. There are only 5 GIT hormone that we will focus on out of 200+: **gastrin, CCK, secretin, GIP and VIP**.

Brief Revision on Endocrine

Autoendocrine cells release hormones that have an effect on itself. **Paracrine cells** release hormones to induce an effect on neighbouring cells. The most

common are **endocrine cells** that release hormones into the bloodstream that induce an effect on later cells.

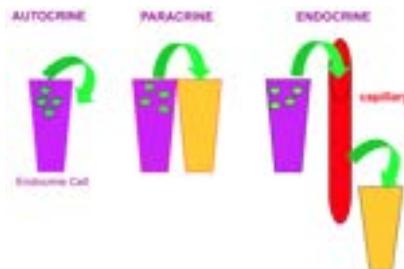


Figure 4.14: Different mode of hormonal regulation.

Regulatory hormones of the GIT

Most GIT regulatory hormones are peptide hormones. They're released from mucosa into the blood of the GIT that travel through the **hepatic portal veins** (in the liver), before reaching the systemic circulation and then induce an effect on target cells. **Why does it need to travel through the liver?** Well...because the liver plays an important role to trap any toxin absorbed by the GUT via the hepatic portal veins. Essentially, all of the blood vessels that come out of the GIT and other "absorptive organs" need to go through the hepatic portal veins for processing by the liver.

These hormones can have multiple targets that lead to different effects (e.g. excitatory vs inhibitory). They can also interact with other hormones and neurotransmitters to have a **synergic effect (enhance each other)** or **antagonistic effect (inhibit each other)**.

4.2 Motility of the GIT

The motor activity of the GIT is mediated by the muscularis externae. They're either made from the striated (upper third of the GIT) or smooth muscle. The importance of it is for mixing and propulsion. **How does this propulsion work?** Well...you can think of the CVS in terms of blood flow that's made by pressure gradient. Similarly, the GIT muscle can produce these coordinated contractions that create such gradient.

There are 2 types of motility that GIT's circular muscle can induce: **segmentation** and **peristalsis**. **Segmentation** movement is the rhythmic contraction at different segment along the GIT, this is mainly for mixing. **Peristalsis** is the continuous contraction along the GIT, this is mainly for propulsion.

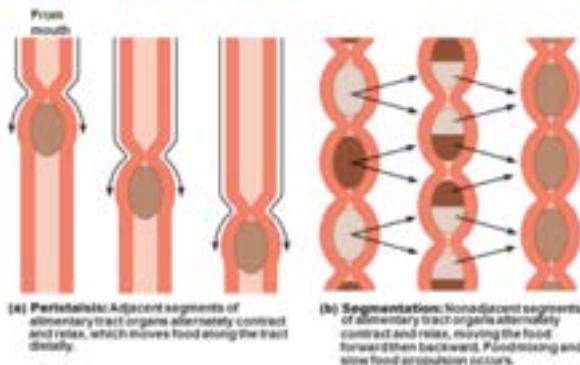


Figure 4.15: Peristalsis and Segmentation.

There are very little resistance in the GIT so the main driving force of it is pressure gradient. Nevertheless, because of the low resistance, we need to have a structure to differentiate different compartments of the GIT, such structure is called **sphincter**. These sphincters close at rest and only open when food is moving from 1 compartment to the next.

Example 4.2.1. The **lower esophageal sphincter (LES)** separate your esophagus from the stomach. At rest, the LES is closed which prevent your stomach acid from going up. When the LES fails to do its job and stomach acid rise to the esophagus, you will experience a condition known as **heart burn**.

In general, the flow in the GIT is very slow, is in the *aboral* direction (movement away from the mouth) and has little resistance.

4.2.1 Swallowing: Mouth and Pharynx

The first motility is **swallowing (deglutition)**. Swallowing is a very fast process, complex (up to 20 muscles involved) and is highly regulated (since we do not want food up the nose nor in the airway).

We divide deglutition into 4 different phases: **oral, pharyngeal, esophageal**

and **gastric**, in that order. In today's lecture, we will only look at the first 2.

Before that, we will look a bit about the anatomy. The **pharynx (throat)** is a connection between the nasal and oral passage cross. It conveys food from the mouth to the **esophagus** known as deglutition. As food moves through to the stomach via the esophagus, 2 sphincters must relax: **upper esophageal (UES)** and **low esophageal sphincter (LES)**. UES closes off the esophagus from the pharynx while the LES closes off the stomach from the esophagus.

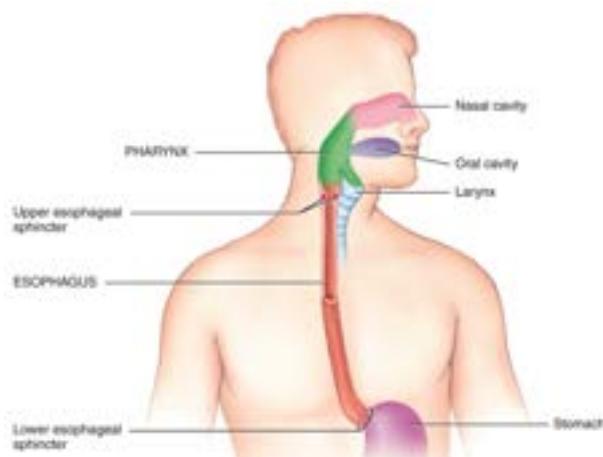


Figure 4.16: Anatomy of the throat

Remark 4.3. We typically don't refer to food when they're swallowed but a **bolus** which is chewed up foods covered in saliva.

Oral Phase

Oral phase is the transport from mouth to pharynx, and it is the only GIT motility voluntarily controlled by us. As soon as the decision to swallow is passed, there's no more voluntary control. First, our lips are closed while the tongue pushes up against the hard palate. This squeezes the bolus to move to the back of the tongue. At the same time, the soft palate closes which blocks the access through to the nasal cavity. At the pharynx, as the bolus moves down, it pushes on the **epiglottis** which blocks the passage that lead to the lung.

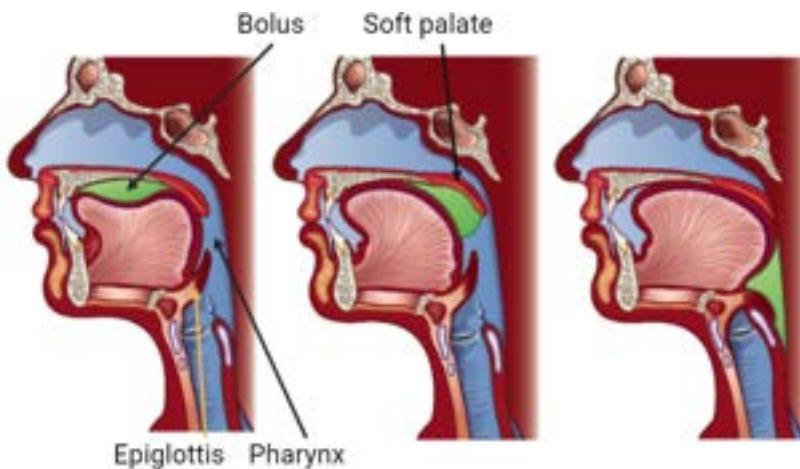


Figure 4.17: Deglutition: oral Phase

The voluntary aspect of the oral phase is the ability to chew and initiate swallowing which happens via **cortical processing**. During the initiation to swallowing, you'll activate the **deglutition center** in the medulla to produces a series of involuntary reflexes for us to swallow.

So to sum it up, oral phase allow us to transport the bolus from the anterior to the posterior portion of the mouth. This process involves a series of involuntary reflexes coordinated in the deglutition center in the medulla oblongata.

Pharyngeal Phase

Bolus at the level of the pharynx stretches its **pharyngeal receptors** and that's going to produce a reflex that lead to swallowing. As it moves downward, it presses and closes the epiglottis. At the same time, the **larynx** contracts and further closes off the **glottis** which stop bolus from going into the airway.

Remark 4.4. *Patients who suffer from stroke tend to have troubles swallowing.*

After protecting the bolus from entering the nose and trachea, the UES relaxes while the pharyngeal muscle contracts which pushes the bolus into the esophagus.

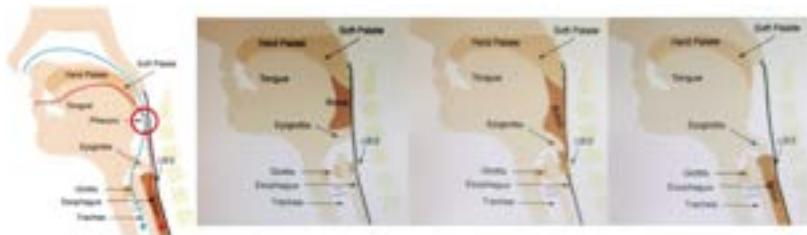


Figure 4.18: The pharynx is where the respiratory and digestive tract meet (left), and the pharyngeal phases (3 right).

Essentially, we have all of these involuntary control that are: passage from nose to mouth and trachea is blocked, **apnea (brief stopping of breathing)**, UES relaxes and Pharynx muscle contracts. **All of these processes need to follow in order!**

In summary, stretches of pharyngeal receptors sends afferent toward the deglutition center. Here, it will send efferent that lead to protective reactions and propulsion like we've said above.

To begin this lecture, we first summarize what we've talked about from last time. We've talked about GIT hormonal regulation and the mechanism of propulsion. Then, we begin with deglutition which is basically swallowing and it is divided into 4 phases: oral, pharyngeal, esophageal and gastric phases. We mentioned that in the oral phase, it is voluntarily initiated by us in the cortex and is governed by the deglutition center and the medulla. Then, we enter the pharyngeal phase which is an involuntary process dictated by the deglutition center that induces a protective reaction by blocking the airway temporarily (apnea). At the same time the upper esophageal sphincter (UES) relaxes and the pharyngeal muscle contracts which move the bolus down to the esophagus and begin the esophageal phase.

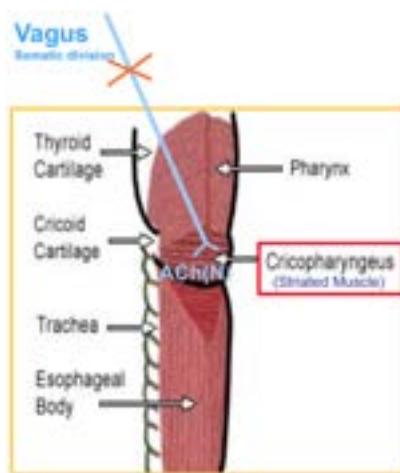


Figure 4.19: UES is closed due to the release of ACh onto its cricopharyngeal muscle. If this release is inhibited, UES opens.

Before talking about the esophageal phase, we will look at the UES and its mechanism. The UES is made from the **cricopharyngeal muscle** that are striated which is indicative of it being controlled by the somatic division. At rest, the UES is always closed (tone) due to the constant release of **acetylcholine (ACh)** by the **vagal somatic nerve** directly on its musculature. **How can we open the UES then?** Well...we can send inhibitory impulses that stop the chronic release of ACh, which allow the musculature to relax and open up the UES.

To summarize the pharyngeal phase, we said that it is involuntary, rapid (takes only roughly 1/5 of a second), stereotyped (same sequence of action every time) and is **temporospatially coordinated** (coordinate in a space and timely manner) so that we do not choke.

4.2.2 Swallowing: Esophagus

We're now in the **esophageal phase** where the bolus move down a long muscular tube called the **esophagus** via peristaltic activity. 1/3 of the esophagus is made from striated muscle, which is also where the pharynx ends. Furthermore, it lies in the thoracic cavity, which we've discussed before in pulmonology, **it has negative pressure** and this is why having 2 sphincters closing it off is important.

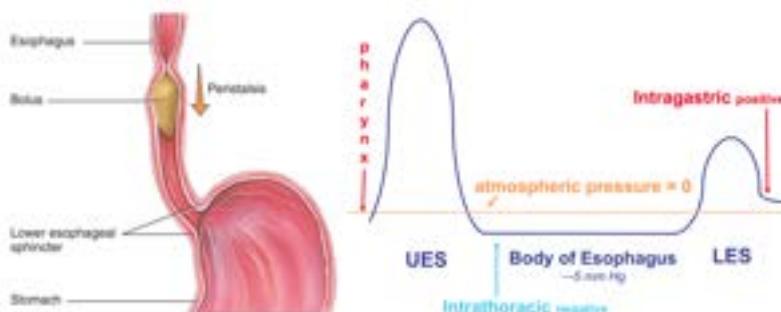


Figure 4.20: Esophageal phase and pressure gradient within the esophagus.

But how come? Well...the pressure acting on the body of the esophagus is roughly -5mmHg while atmospheric pressure is 0 and pressure from the stomach or **intragastric pressure** is always positive. In other words, if there are no UES nor LES, the content from the stomach and air from the outside will be pulled into the esophagus due to the pressure gradient.

There are 2 major forces that come to play in the movement of bolus in the esophageal phase: **gravity and peristalsis**. Gravity have very minor importance and induce small effect on liquid. This can be observed with astronaut that can perfectly drink in space. On the other hand, peristalsis is this wave of contraction moving down the esophagus that generates the pressure gradient to move bolus aborally.

Each time we swallow, we generate 1 **primary peristaltic wave** that takes 8-10s to propagate the entire esophagus' length. This primary wave is part of the deglutition reflex. There's a problem...we've said that 1/3 of the esophagus is striated while the rest is smooth muscle so **how can we create an uninterrupted peristaltic wave from striated to smooth muscle?** Well..the deglutition center will send down efferent on 2 separate fibers: **vagus somatic and autonomic fibers.** The vagus somatic fibers will synapse directly to the striated muscle **in a sequential manner from proximal to distal muscle** i.e. it will send efferent to the muscle closest to the UES then further and so on to generate the wave of striated muscle activity. On the other hand, vagus autonomic fibers will synapse to the ENS and activate it synchronously, **however there will be an increase in latency from proximal to distal ENS neurons** i.e. proximal ENS neurons will activate sooner than distal to generate a wave of smooth muscle activity.

Definition 4.2. **Latency** refers to the delay between the onset of stimulation and the response (activation).

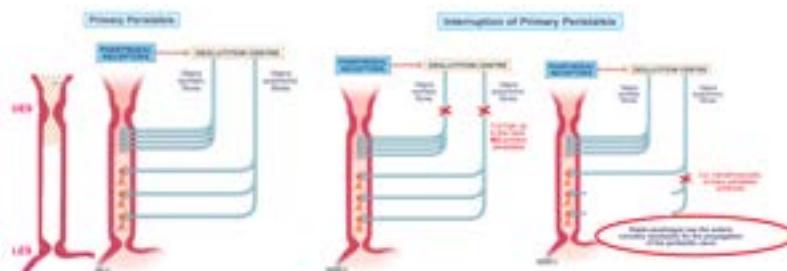


Figure 4.21: Primary peristalsis and interruption of the fibers generating peristalsis.

What if we cut the vagus nerve?

Well...if we cut it high up in the neck, we would disrupt the primary peristaltic wave, meaning that we cannot swallow. However, if we cut lower in the transthoracic portion, we might have the primary peristalsis. The reason is that we did not disturb the efferent toward the striated muscle but also we left some efferent in the proximal. These efferent/signal are enough to propagate through the ENS and thus allow primary peristalsis to continue till distal portion.

So just to summarize the regulation of primary peristalsis, you first have the stretch of the pharynx by the bolus which would activate the pharyngeal receptor and subsequently the deglutition center. The deglutition center will send efferents via the somatic and autonomic vagus nerve to activate the mainly proximal striated muscle of the upper esophagus and the ENS of the lower esophagus (which will later activate its smooth muscle).

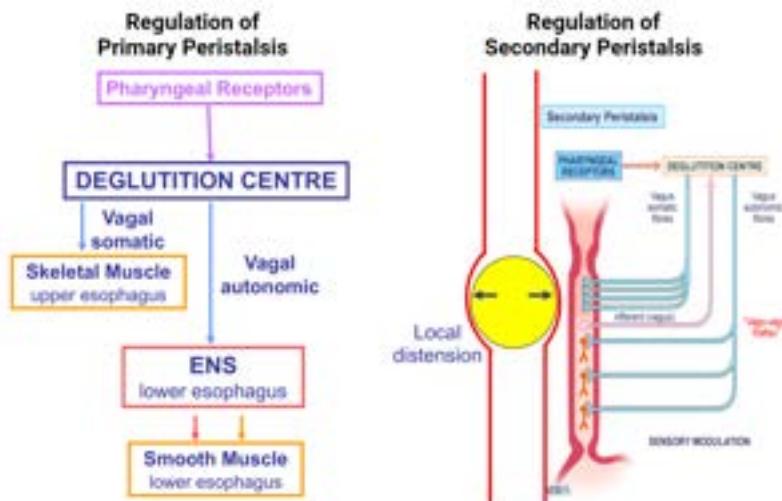


Figure 4.22: Regulation of primary and secondary peristalsis.

Secondary Peristalsis

Sometimes, the bolus can get stuck in esophagus (not the same as **choking** which is when the airway is blocked). In this case, 2 things can happen: first, the bolus will create a local distension on the esophagus smooth muscle which lead to the activation of the ENS. Second, we have afferent fibers (vagal nerve) in the ENS that will pick up the distension and travel to the deglutition center. The deglutition center will send down efferent via the vagal nerve to activate ENS. Together they make up the **vagal-vagal reflex**.

Remark 4.5. *The vagal-vagal reflex is excitatory since it comes from the vagus nerve which is via the parasympathetic system (excitatory for the GIT).*

In this reflex, there maybe multiple secondary peristaltic wave generated to move the bolus. **Why is it called vagal-vagal reflex?** Well...because

it has afferent and efferent come in and out of the vagus nerve respectively.

Lower Esophageal Sphincter

Covering the last 4cm of the terminal portion of the esophagus that lead to the stomach is the **lower esophageal sphincter (LES)**. Half of the LES sits above while the other sits below the diaphragm. Its job is to separate the acidic environment of the stomach from the neutrality of the esophagus.

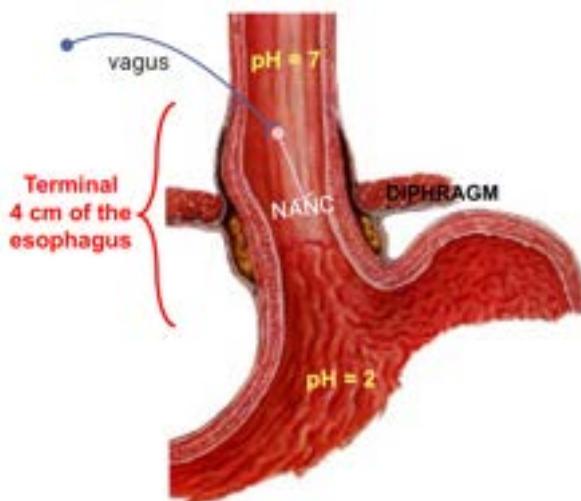


Figure 4.23: LES relaxation and neural control.

Interestingly, due to its property and residual resistance, the LES musculature has a constant tone at rest without any neural input i.e. it always closes and we call this closure **myogenic**. On the other hand, its opening or relaxation is said to be **neurogenic** i.e. there's an neural input. In this case, deglutition center send signals via the autonomic vagal nerve to excite the local inhibitory ENS neurons. They can then release inhibitory NANC and the LES relax.

We can summarize all of the function of the deglutition center as the following figure (See Figure 4.24).

You might ask now **why does LES has half of it in the gastric and thoracic cavity?** Well...because the gastric cavity is always high in pressure and

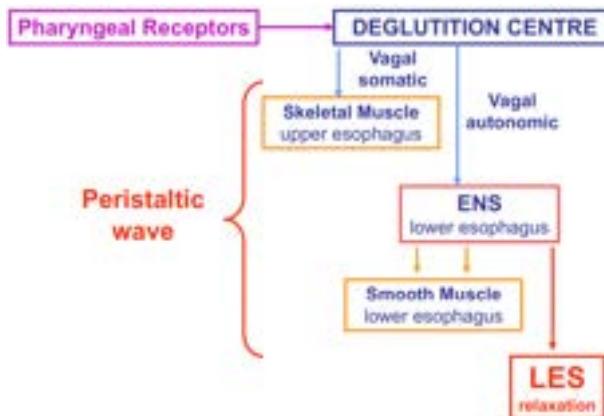


Figure 4.24: Deglutition center and its effect on LES.

LES need to feel that to modulate accordingly. Normally, we would have the thoracic cavity's pressure to be -5mmHg while that of gastric is +5mmHg, we can say that the pressure of the LES produced is 20mmHg which prevent the contents movement from either direction. **What if the intraabdominal pressure increases?** Well...the pressure of the stomach increases equally with the intraabdominal LES i.e. if intragastric pressure increases by 100mmHg, the intraabdominal LES increases by the same amount.

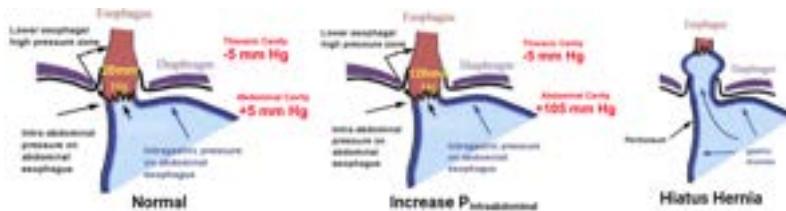


Figure 4.25: LES contraction at normal, with increase intraabdominal pressure and hiatus hernia.

In a **hiatus hernia**, the LES is pushed up all in the thoracic cavity. So if there's an increased in intraabdominal pressure, the pressure will increase in the stomach but not in the LES i.e. the LES fails to do its job and stomach content pour into the esophagus.

So to summarize the characteristics of the LES, it is an intrinsic physiologic sphincter i.e. it's tonically contracted in the absence of swallowing. It serves as an **anti-reflux** mechanism (preventing the upflow of gastric acid to the esophagus) thanks to its intraabdominal portion. If the LES fails to do its job (incompetent), it will lead to **pyrosis (heartburn)** which is characterized as burning sensation, radiating upwards in the chest towards the neck, due to acid reflux into the esophagus.

GIT hormones and LES

You might ask yourself that **is there GIT hormones that regulate LES action?** Well...it turns out, gastrin does increase contraction of LES, **however** it only happens at a very high level (not the typical physiological level). This is pointless since the more gastrin there is, the more gastric acid is produced. Another hormone can modulate LES is progesterone which can induce its relaxation. This is also why pregnant women tend to have more acid reflux than normal.

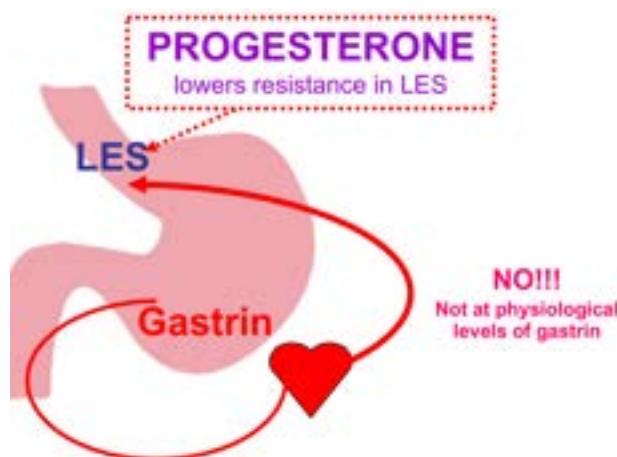


Figure 4.26: GIT hormone regulation of LES

4.3 The Stomach

After going through the first 3 phases of deglutition (swallowing), the bolus will now end up in the stomach which begin **gastric phase**. Before talking

about gastric phase, we will look briefly about the stomach.

The stomach is an organ to temporary store the food we ate which can be up to 1-2L. It's going to be used in the physical disruption of food (breaking it down); at the gastric level, the bolus will be churned and mixed with gastric juice to form **chyme**. After this, chyme will be propelled into the duodenum in a regulated manner since we do not want to let 2L of acidic chyme to be in the small intestine all at once.



Figure 4.27: Anatomical and physiological division of the stomach.

Normally without any food, the stomach only hold around 50mL of volume. Anatomically, it is divided into 3 parts from top to bottom: **fundus**, **body** and **antrum** which is next to the **pylorus** (where the **pyloris sphincter** is). Physiologically (musculature-wise), it is divided into the **proximal and distal portion** which is used for storage and mixing + propulsion respectively. These 2 portions have the same circular and longitudinal muscle, however the distal portion have thicker for obvious reason.

The stomach wall have the same composition as the rest of the GIT. However it has some modification e.g. the gastric mucosa have folds called **ruga** to increase surface later on; it also have pits and glands to secrete gastric juice. The muscularis externa has an extra layer of the **oblique muscle** along with the longitudinal and circular.

4.3.1 Swallowing: Gastric Phase

We said that at rest the stomach is 50mL in volume so **how can the stomach accommodate the meal we ate?** Well...you can think of a balloon, as the pressure build up inside, its volume increases greatly. For the stomach, it's going to experience **receptive relaxation** which is part of the deglutition reflexes. In this case, **the proximal stomach will increase its volume without a significant increase in pressure (at around 5mmHg)**. We do not want high intragastric pressure or else chyme will move very rapidly to the duodenum.

In the deglutition gastric phase, pharyngeal receptors send afferent to the deglutition center, which in turn send a vagal efferent to local inhibitory ENS neurons. These neurons release NANC to relax the musculature of the proximal stomach. Amazingly, this can happen before the arrival of the meal (you can look or smell food to activate it). The relaxing of the proximal stomach musculature allow it to increase in size.

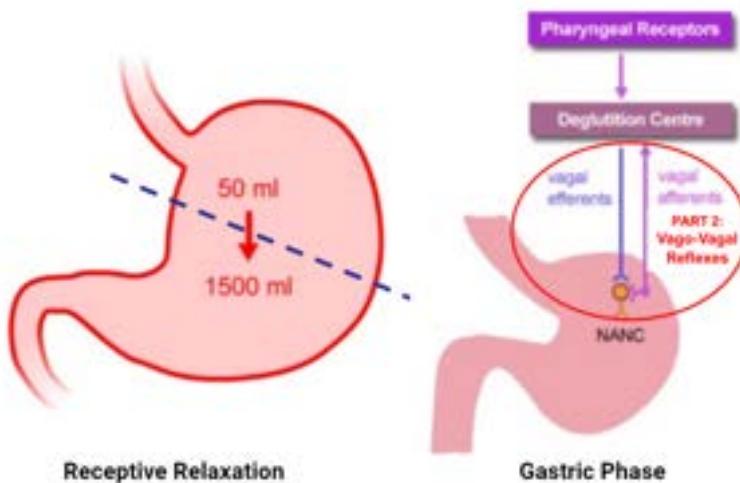


Figure 4.28: Receptive relaxation and deglutition gastric phase.

Now, this is not complete relaxation until food arrives. Once food arrived in the form of bolus, it will cause distension leading to activation of sensory ENS neurons which can recruit more inhibitory ENS neurons to have more relaxation. Even this is not enough to induce receptive relax-

ation, and this is where vagal-vagal reflex will come into play. The sensory ENS neurons can also send afferent to the deglutition center, which will send back efferent to relax the musculature more.

Receptive relaxation requires all of these 3 factors. In fact, if we cut the vagus nerve of the proximal stomach, receptive relaxation is limited which limit the expandable gastric volume hence increases intragastric pressure.

To sum up all of the phases in deglutition, with the intake of the meal and the stimulation of the deglutition center you have a wave of activation and relaxation appropriate for carrying the bolus along the upper GIT and allowing it to be accommodated in the stomach.

To summarize from previous lecture, we talked about regulation of primary peristalsis and its difference from secondary peristalsis. We also touched upon the functionality of LES and its mechanism of anti-reflux by having half of it in the intra-abdominal. We then shifted into talking about the stomach as a storage unit in its proximal portion that have thin musculature. The stretching of the proximal stomach is mediated by *receptive relaxation* which is a series of activation of inhibitory ENS neurons to inhibit the stomach proximal muscles. Receptive relaxation, which is 1 of the deglutition reflexes, only occurs if all 3 stages of activation is met: activation before food arrive, after and when food is in (vaga-vagal reflex).

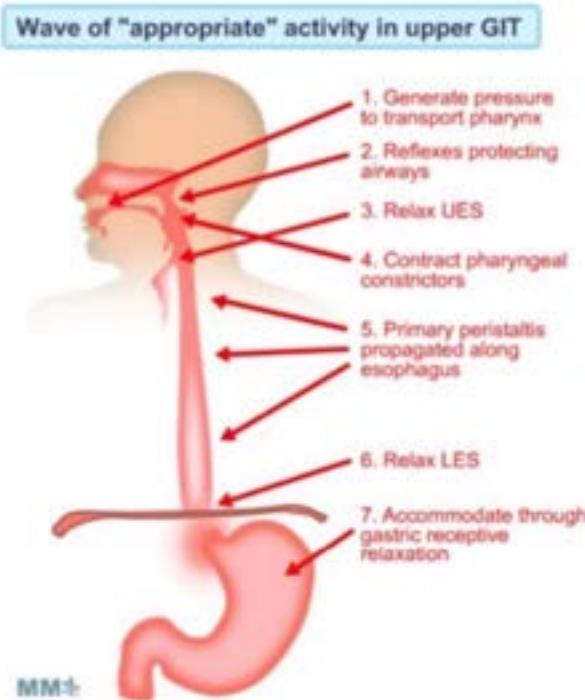


Figure 4.29: The complete temporo-spatial coordination of deglutition.

Finally, we ended it with concluding on deglutition by saying that all of the processes we've touched upon are **coordinated temporal-spatially** i.e. they happens in a sequence 1 after the other and in the aboral direction

(moving away from the mouth).

4.3.2 Motor Activity of Stomach

Now we will look at the stomach motor activity which mainly focuses on the distal stomach. The distal stomach has much thicker muscle which is ideal for physical disruption and propulsion of chyme. The main type of muscle activity in distal stomach is peristalsis **and none in the proximal**. The wave of contraction move from the **midpoint** (separating proximal and distal) toward the pylorus region.

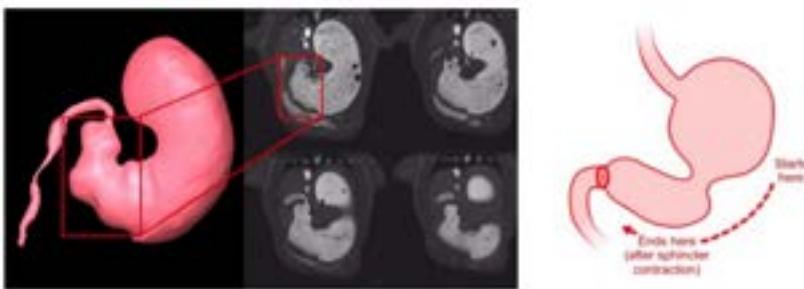


Figure 4.30: Peristalsis in the distal stomach for mixing and propulsion as seen on medical scan and cartoon representation.

Peristalsis in the stomach happens due to local ENS reflex in response to local distension i.e. stretch of the stomach wall lead to its contraction. The magnitude of the stimulus (the amount of stretch and ACh released) will have an effect on the **amplitude of the contraction**. Additionally, electrical characteristics of smooth muscles also changes the **contraction frequency, velocity and direction**.

Electrophysiology of The Distal Stomach

Supposedly, we make a physiological measurement using electrode in the stomach. If we measure in the proximal stomach, we would record only a constant potential level of -55mV. However, if we look at the distal stomach, we will always see a rhythmic wave of partial depolarization that is not enough to cause muscle contraction. These on-going wave of depolarization is called **basic electrical rhythm (BER)** which is 10-15mV in amplitude, lasts around 1-4s and occurs at an interval of 3 per minutes.

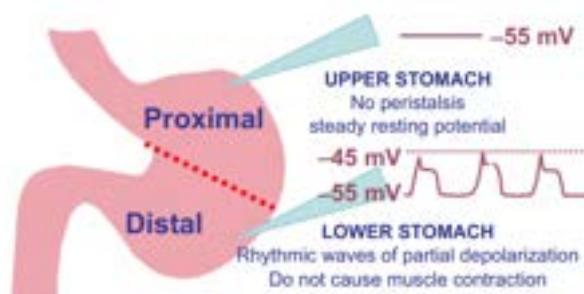


Figure 4.31: Electrode measure of the distal and proximal stomach.

If we do this measurement for each region until the sphincter, we can see the depolarization is synchronous circumferentially but it delays as it moves toward the pylorus. Once again, these depolarization waves do not cause contraction.

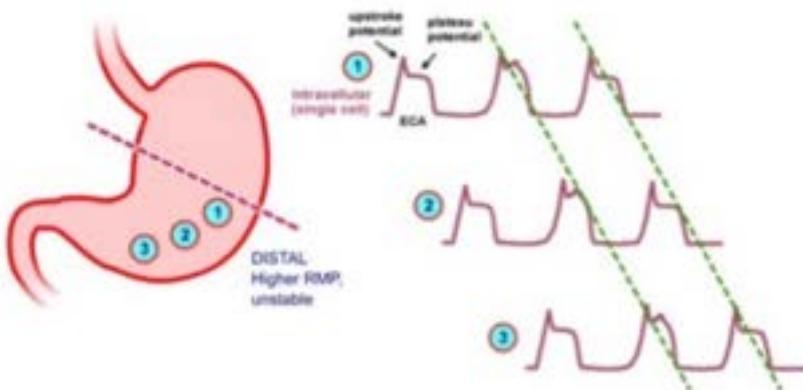


Figure 4.32: Depolarization wave is synchronous circumferentially along a stomach segment, while it delays as we move away from each segment toward the pylorus.

When food comes in, it will trigger more stretch and ACh release which lead to generation of spikes at the peaks of the BER called **second electrical signal** or **electrical response activity (ERA)** that passes threshold and generate muscle contraction. Just like before, these spikes are delayed as we move toward the pylorus creating that peristaltic contraction. To drive this

point home, the only time we have muscle tension/contraction is when the second electrical signal is generated atop the BER.

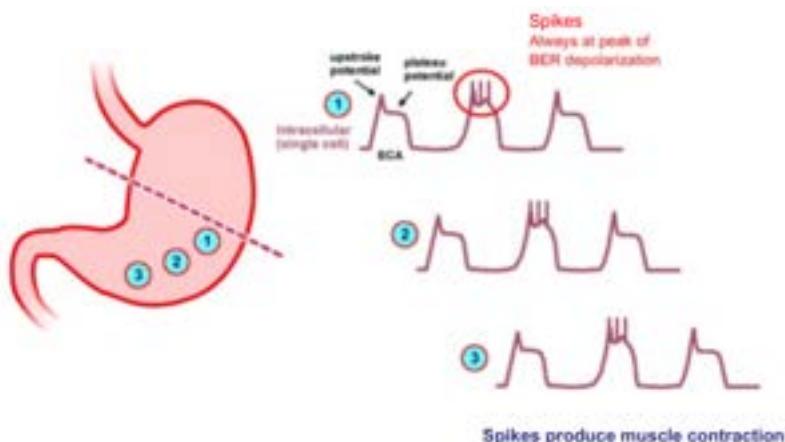


Figure 4.33: The delay of the ERA as it moves toward the pylorus.

Furthermore, the more stretch and the more ACh is released the more depolarization occurs and thus higher contraction i.e. more spikes, the larger the muscle contractions. Because the depolarization frequency is 3 per min, the contraction frequency would be maximally 3 per min.

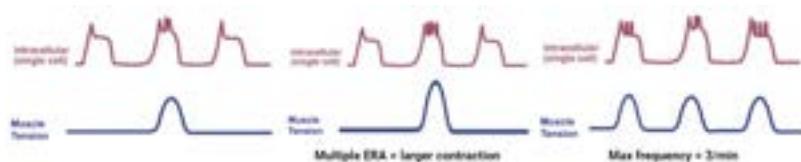


Figure 4.34: Muscle tension and spikes (ERA).

To summarize about BER, it's constantly present that propagate from cell to cell but does not activate contraction. The frequency is constant at a given region of 3 per minute. It is detectable in both longitudinal and circular muscle. The BER originates from non-neuronal non-ENS pacemaker cells called **interstitial cell of Cajal (ICC)**. ICC is a network of star-like pacemakers located between smooth muscle layers and the enteric pulses. They extend circumferentially and longitudinally, and they may act as an intermediary between the neurons and the smooth muscle and can

coordinate a groups of muscle cells.

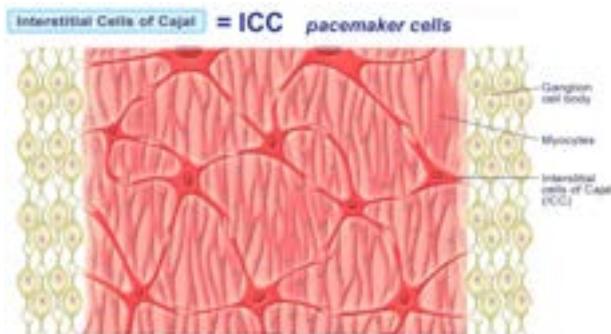


Figure 4.35: ICC of the stomach.

As for the spikes or ERA, they're intermittent, phase-locked to BER and is trigger by stretch or ACh release. They're Ca^{2+} dependent and found in longitudinal and circular fibers, and propagate via *gap junction*. The number of spikes is proportional to the magnitude of the stimulus while the amplitude of contraction is proportional to the number of spikes. The maximum frequency of contraction is limited by the frequency of BER.

Peristaltic Action of The Distal Stomach

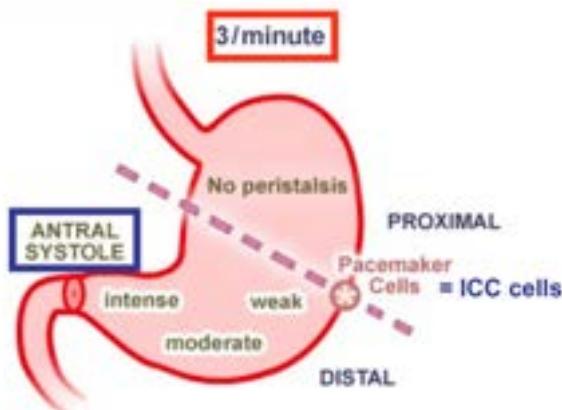


Figure 4.36: Musculature of the distal stomach.

The musculature of is different in the distal stomach also. What we found is that the musculature become increasingly thick from the mid-line toward the pylorus. What this suggests is that the contraction near the midline to the pylorus is increasing in intensity. Peristalsis wave will move down to the sphincter with increasing intensity and once it got there it will generate **antral systole** which is a very strong contraction the closes the stomach antrum and the pyloric sphincter. **Why is would we need to close the pyloric sphincter?** Well...because it's opened all the time which means the only time it closes is antral systole. Then **how does it work as a barrier?** Well...the lumen of the sphincter is very small (1-2mm) so it serve as a filter to allow only small particles to come through.

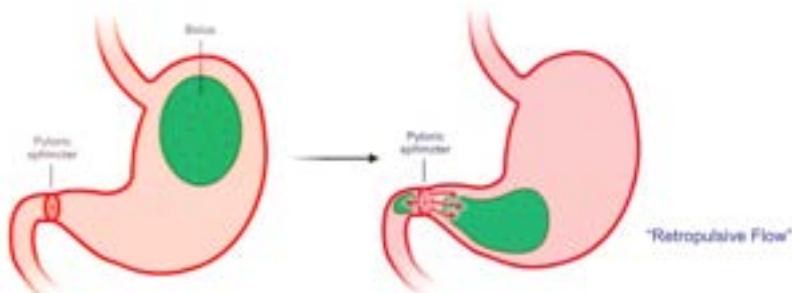


Figure 4.37: Peristalsis is used for mixing in the stomach instead of segmentation.

Antral peristalsis does not only move food but is also important for mixing. At first, the bolus comes in and enter the distal stomach. Here, peristalsis initiates and the bolus moves very quickly through the antrum toward the pyloric sphincter. Then **antral systole** happens but still allow **little amount of bolus to enter the duodenum while the rest hits the sphincter at high velocity**. This hitting action create a bounce back reaction and the bolus mixes to produce chyme. This creates **retrorepulsive flow** that effectively disrupt the bolus into suspension particles of diameter < 1mm.

To sum this up, antral peristalsis is important regulate the movement of content to the duodenum and ultimately the small intestine.

Gastric Emptying

Propulsion is what lead to gastric emptying and it differs between liquid and solid. The emptying of liquid is due to the ΔP between proximal and

duodenum. If $P_{\text{proximal}} > P_{\text{duodenum}}$, then it moves toward the duodenum. Typically, we have receptive relaxation which can decrease ΔP and this is fine since because we need gastric emptying to be slowly and not rushing through. If we interrupt this communication of receptive relaxation through **vagotomy** (cutting of vagal nerve) in the proximal stomach, we would get large ΔP which means a large amount of liquid will flow to the duodenum uncontrollably. However, if we do this in the distal stomach, not much would change because liquid does not require peristalsis but ΔP between the 2 compartments.

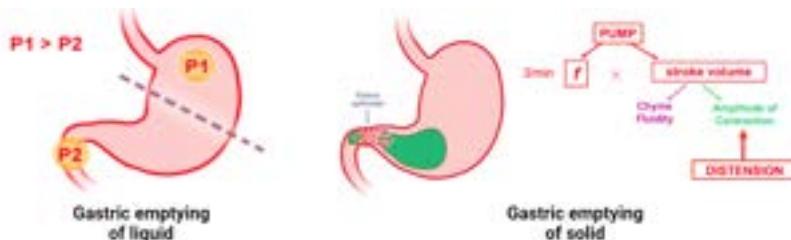


Figure 4.38: Gastric emptying of solid and liquid illustration.

On the other hand, the emptying of solid is due to antral peristalsis i.e. pumping action of the stomach. The pumping action of the stomach is dependent on the frequency and stroke volume. The stroke volume depends on the chyme fluidity and amplitude of the contraction (which depends on distension).

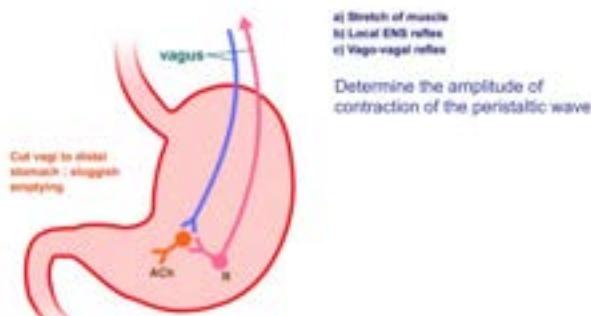


Figure 4.39: Factors controlling antral peristalsis which lead to gastric emptying.

Distension of the distal muscle is the main factor that lead to antral

peristalsis. However, we can also have the local ENS reflex that receive these afferent and then activate excitatory ENS neurons; as well as, the vagal-vagal reflex. So if we cut vagal nerve to the distal stomach, gastric emptying will be suboptimal.

Interestingly, there are factors from the duodenum that can control the rate of antral peristalsis and gastric emptying. First is distension of the duodenum lower peristaltic rate, this is self-evident since the stretch of the duodenum is indicative of it having lots of chyme (it takes time to break down) and also duodenum does not like to be stretch. **Low pH, high osmolarity and chemical composition of chyme can change lowers the rate of gastric emptying.** These factors are relayed by the duodenum to the stomach in the form of hormones (endocrine communication) such as **secretin** and **CCK** that inhibit gastric emptying.

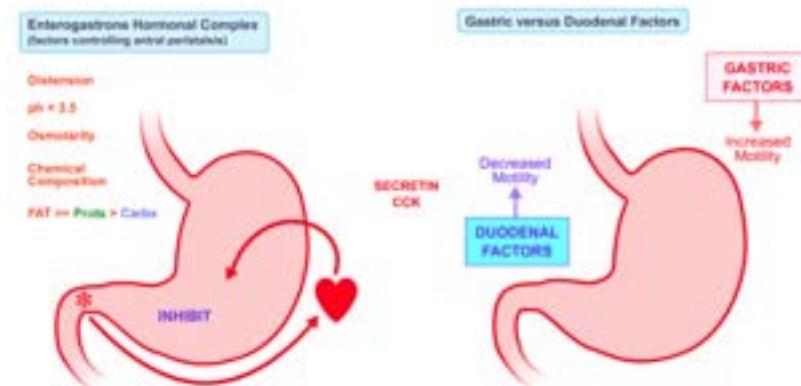


Figure 4.40: Duodenal factors that inhibit gastric activity via hormones (left) and summary of duodenal and gastric factors.

So, to summarize what we've said, we have gastric factors (mainly stretches and ACh release) that lead to an increase of its motility. This motility via peristalsis does not only move the bolus but also mix it with gastric juice to produce chyme. Meanwhile, there are duodenal factors that have an opposing effect which decrease its motility.

We will begin this lecture with summarizing last lecture. Basically, the smooth muscle of the distal stomach has electrical activity called *BER*. This *BER* is not enough for contraction but with enough stimulus, it can produce spikes that lead to contraction. This contraction propagates from the midline with increasing intensity till the pylorus. The contraction reaches its maximal called *antral systole* which closes the pyloric sphincter. There are 2 ways the stomach empties its content, if it's liquid, then the emptying action is dependent on ΔP between the proximal stomach and the duodenum. If it's solid, then the emptying action depends on the frequency and the amplitude of antral peristalsis.

There are factors that can contribute to this emptying actions. Gastric factors, such as distension and ACh release can trigger antral peristalsis which induce gastric emptying. On the other hand, to slow down the release of chyme depending on the level of distension, pH, osmolarity, and chemical composition of the chyme in the duodenum; it will release its own factor to inhibit gastric emptying.

* Factors in the duodenum also control the rate of gastric emptying/ antral peristalsis

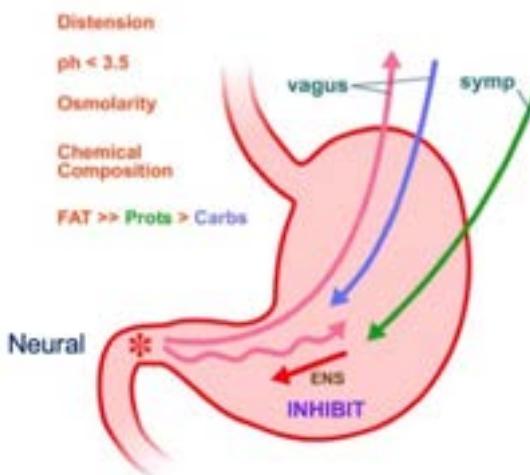


Figure 4.41: Factors from the duodenum mentioned above contribute to the **enterogastric reflex** which can control the rate of antral peristalsis and gastric emptying.

4.3.3 Vomiting

We will begin our lecture today with talking about vomiting then we will move on to the motility of the intestine.

Definition 4.3. **Vomiting** is the emptying of the upper GIT content in the oral direction.

Vomiting is a passive process that is a result of increase in intraabdominal pressure due to action of the diaphragm and the abdominal muscle. By passive we meant that it doesn't need **reverse peristalsis** to propels the content in the oral direction.

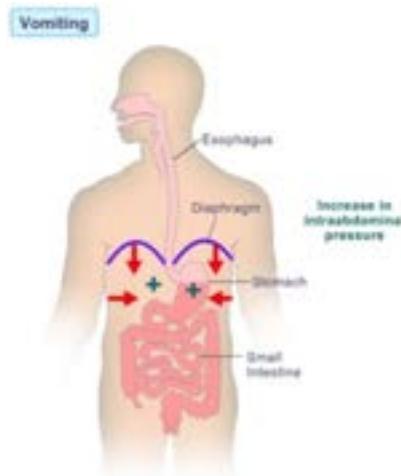


Figure 4.42: Vomiting illustration.

Mechanism of Action (Vomiting) First, the proximal stomach and everything above relax. Then upper duodenum and distal stomach both contracts together. At the same time, the diaphragm moves down thus exposing all of the LES to the thoracic cavity instead of half-half; and the abdominal muscle contract altogether. The contraction along with the upper duodenum and distal stomach create a pressure gradient favours the oral direction. The combined intraabdominal pressure will then overcome the tone of LES and vomiting occurs.

Regulation of Vomiting

Vomiting is regulated by the **vomiting center** lies at the 4th ventricle in the medulla. It can receive afferent from different sources like pharyngeal stimulation, over-distension of the GIT, pain, biochemical disequilibrium, vestibular and psychogenic factors, etc. Once it is activated, it will send efferent that activate component that is essential for vomiting.

To begin with, it will create a widespread autonomic discharge i.e. **it will turn on both the sympathetic and parasympathetic activities**. This is probably why you feel sweating, vasoconstriction, salivation, an alternating between fast and slow HR that all accompany vomiting. Next, it will lead to a sensation of **nausea** (a feeling of unease), **retching** (the feeling on vomiting but without any content expulsion), then finally **emesis (vomiting)**. During emesis, you have all of the event we mentioned in the mechanism of action occur.

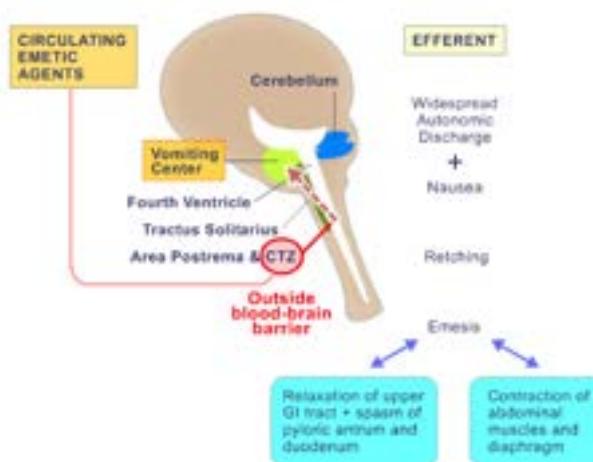


Figure 4.43: The regulation of vomiting.

There's another area to trigger vomiting and it is called the **chemoreceptor trigger zone (CTZ)**. The CTZ located outside of the blood-brain barrier to detect toxins or **emetic agents** in circulation that many not cross the barrier. Once the CTZ is activated, it will then activate the vomiting center, etc.

Remark 4.6. *CTZ and vomiting center are distinct, and vomiting center does not require CTZ to be activated. It can activate itself through the mentioned afferents above.*

As for vomiting, like we've mentioned above, it's divided into 3 stages: nausea (a psychic experience), retching (abrupt, uncoordinated respiratory movements with glottis closed) and emesis (actual expulsion of contents of upper GIT). Individual who initiate vomiting will first take a deep breath and closes off their glottis. Then, they will have concerted abdominal muscles and GIT contraction, along with the diaphragm moving downward. Finally, emesis is completed when the thoracic pressure goes from negative to positive which forces the diaphragm to move upward which forces the esophageal content to be expelled through the mouth.

Like deglutition, all of these steps need to be temporal and spatially coordinated to have a complete emesis.

4.4 Motility of the Intestine

The **small intestine (SI)** is where most digestion and all absorption of nutrients occur. It is divided into 3 regions: **duodenum, jejunum and ileum**. Majority of digestion and absorption happen in the duodenum because of its high efficiency at doing it. Ileum, as we will later see, is important for the absorption of vitamin B12 and iron.

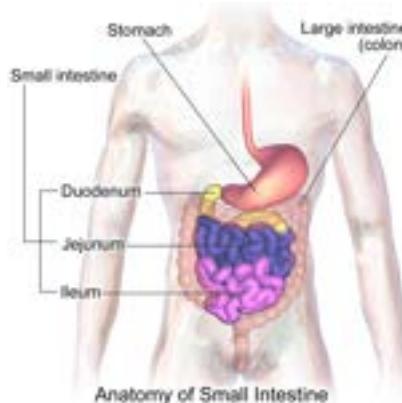


Figure 4.44: The small intestine.

The upper portion of the SI is used to rapidly neutralize the acidic chyme from the stomach. This is because the sSI does not have a mucosa that's well-protected from acid than the stomach. Not only that, it will "isotonize" the chyme. And of course it will also do digestion and absorption.

4.4.1 Motor Activities and Contractions of the Small Intestine

The motor activities of the small intestine is effective for mixing but not only that, it forces contacts between the foodstuff to mucosa absorptive cell. Because it's creating contact for absorption, it's best to maximize the time for the meal to be adequately digested and absorbed hence it takes around 2-6 hours for the propulsion.

The contraction of the intestine is dependent on the electrical characteristics of the smooth muscle. Like the stomach, its contraction frequency is governed by the *basic electrical rhythm (BER)*. The contraction is initiated by spikes that are initiated by stretch and ACh release and they're phase-locked with BER. The amplitude of the contraction will depend on the number of these spikes found on the BER i.e. more spikes = stronger contraction.

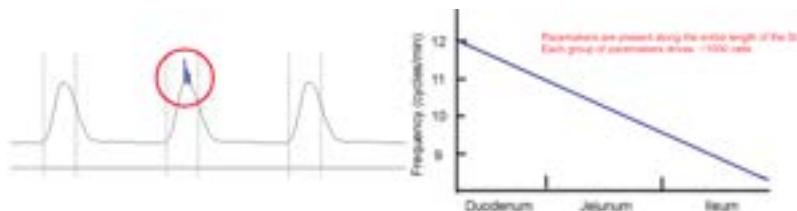


Figure 4.45: BER, spikes and its frequency along the SI.

The main thing that differs BER is different in SI than in the distal stomach is its frequency. BER in the stomach has a range of frequency that goes from **12/min (duodenum)** to **8/min (ileum)**. Each pacemaker along the entire length of the SI control roughly 1000 cells (100 of which are muscle cells). Not only the frequency is different but also the intensity is stronger in the proximal while become weaker in the distal SI. This is due to a much more excitable, thicker smooth muscle in the proximal than distal SI.

Remark 4.7. *The maximal contractile activity in the SI cannot exceed the BER frequency of that gut segment.*

The common type of contraction in the SI is **segmentation**. Segmentation is initiated by distension on the SI that lead to circular muscle contracting. ENS are also important to coordinate these contraction over the length of the SI. You also have ANS and hormones to modulate the level of contraction (parasympathetic increases while sympathetic decreases).

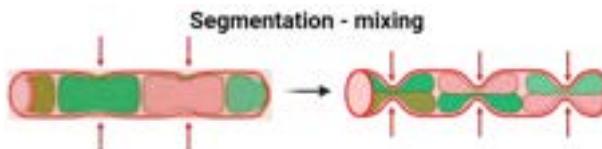


Figure 4.46: Segmentation used for mixing SI content.

So we can clearly see that it's good for mixing but we also said it's used for slow propulsion...but **how can segmentation do propulsion like peristalsis?** Well...it's not that segmentation lead to propulsion, it's the fact that contraction in the proximal SI is stronger and more frequent than the distal SI. This ultimately creates a slow, net aboral propulsion of the content.

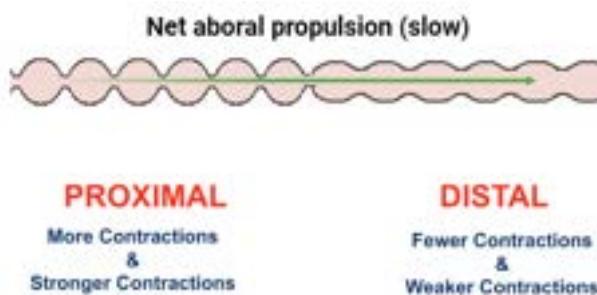


Figure 4.47: Different segmentation frequency and intensity between proximal and distal SI lead to slow net propulsion.

SI do have peristalsis but it's infrequent and irregular, weak and shallow; and is used only to travel a small distance of a few centimeters.

In general, intestinal peristalsis (better to say "motility") is mediated by a series of local reflexes. It involves interaction of longitudinal and circular muscle and its contraction frequency cannot exceed that of BER's. It requires the integrity of ENS and can be modulated by ANS and hormones.

4.4.2 Law of the Intestine

The interaction of longitudinal and circular muscle to help move content forward is dictated by the **law of the intestine**. Basically, radial stretch (stretching outward from the lumen center) of the SI section will activate stretch receptors via the ENS. This is going to lead to muscle activation and move the content ahead.

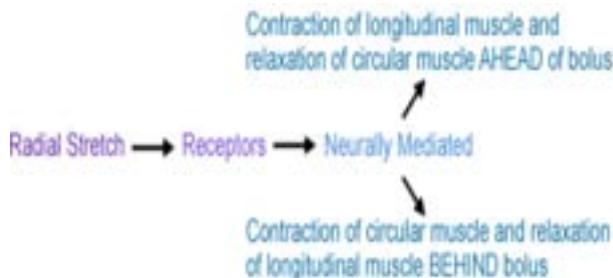


Figure 4.48: Law of the intestine.

We have to look at this in term of bolus. When the bolus sit a location in the SI, it will activate stretch receptor and thus lead to muscle contraction. To the front of the bolus, longitudinal muscle contracts while circular muscle relax. This makes the length of the SI shortens while muscle ahead of it opens up and allow the bolus to move forward. At the same time, to the back of the bolus, the opposite action happens (longitudinal relaxes, circular contracts). This muscle contraction forces the bolus to move forward.

4.4.3 The Large Intestine

The end of the SI (terminal ileum) will merge into the **large intestine (colon)**. Between the terminal ileum and the beginning of the large intestine (**cecum**) is the **ileocecal sphincter** that is normal closed. From the cecum, you will move up to the **ascending colon**, then **transvers colon** and finally is the **descending colon, sigmoid colon** and **rectum**.

The motility of the colon is similar to that of the SI however, it is now much slower, sluggish and more irregular. Here in the colon, it is also used for absorption, wait...**didn't the SI do majority of absorption already?** Well...yes, but the absorption of the colon is mainly for water and ions. Every day, around 1.5L will travel through the ileocecal sphincter but by the

time it exits the colon, only 200mL is left.

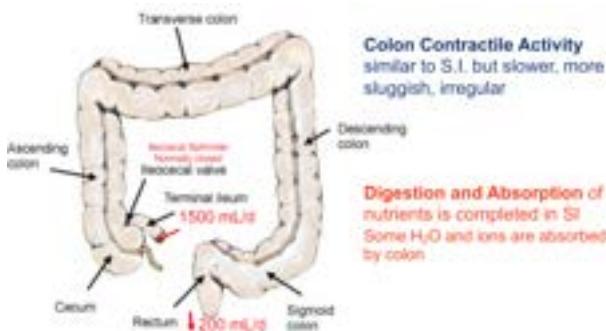


Figure 4.49: The colon.

The function of the colon is for mixing which is a way to promote water and ions absorption. It also performs propulsion to move contents forward and converted into feces and stored over a period of 50-60h.

The motor activity of the colon will be mainly segmentation and peristalsis that is governed once again by BER. However, there's no pattern in the BER and the frequency changes irregularly from 1 end to the other. Essentially, it's going to produce some mixing, some propulsion and of course storage.

How often does the large intestine empty its content

Well...on average, it's around 2-3 times per day but it corresponds mostly to the intake of new meal. When we ingest a new meal, the **gastroileal reflex** will be activated which will activate the stomach while increasing the activity of the ileum to make room for new meal. We will also have **gastrotrocolic reflex** which will increase the activity of both the stomach and sigmoid colon. The increase of sigmoid colon activity will push its content toward the rectum. When there's enough content in the rectum, **defecation reflex** will activate. There's also a small reflex called the **ileocolic reflex** where there's an increase in ileum and distal colon activity.

From previous lecture, we talked about vomiting (which is not reverse peristalsis). Upon the activation of the vomiting center near the 4th ventricle via different stimuli, efferent would be sent out and lead to a widespread of ANS discharge, nausea and finally emesis. The vomiting action is due to concerted contraction of abdominal, distal stomach and duodenum while the upper most GIT relaxes. Not only that, we have *chemosensory trigger zone* located outside the blood-brain barrier to detect emetic agents that can then signal to the vomiting center and activate emesis.

We then switch to motility of the small intestine where we have both segmentation and peristalsis but most common is segmentation. Segmentation helps with mixing but also create slow net movement. For the colon, we have similar mixing, propulsion and storage but at a longer pace and more irregular. We then described 3 reflexes that help us make room for the next meal which are **gastroileal, ileocolic and gastrocolic**. These reflexes move contents in the go fast through the colon into the rectum. Once enough pressure by contents in rectum, defecation reflex activate.

4.4.4 Migrating Motor Complex

In the past, we thought that when we're sleeping, there will be an absence of a meal (this period is also called **interdigestive period**) thus the GIT will be relaxed. Turns out, during this period, the GIT motility will organize into intense pattern of cyclic myoelectric motor activity called the **myoelectric motor complex (MMC)**. It occurs at **regular intervals in the interdigestive period of every 90min**. The MMC will be present and move sequentially from the distal stomach to the small intestine at a rate of 2-10cm/min.

The MMC has a cycle of 90 minutes which is divided into: **phase I, II and III**. In phase I, it lasts around 60 minutes and nothing happens i.e. no spikes on the BER thus no muscle contraction. Phase II would last around 20 minutes and have irregular spikes on BER thus producing irregular contraction. Finally, the most important time for MMC is phase III that last 10 minutes. Here, there's a regular maximum amount of spikes on the BER as well as the BER frequency is at its max in accordance to whichever region it lies (3/min for distal stomach, 12/min for duodenum, etc.).

Now the reason it's called MMC is because the 3 phases occurring at an SI segment will eventually move down stream e.g. Phase I occurs at 1 segment of the SI will move down to another segment and then at then

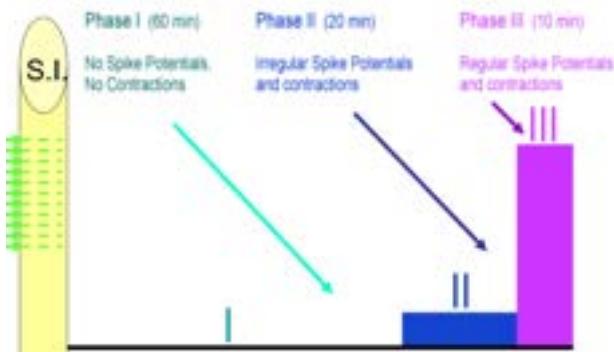


Figure 4.50: Period of the MMC.

phase II occurs at the previous segment then etc. If we look at only phase III as it propagate down the SI, we can see the 90 minutes delay between each segment during sleep. We can also see that by having meal, the MMC is disrupted but then return when there's no new meal coming in.

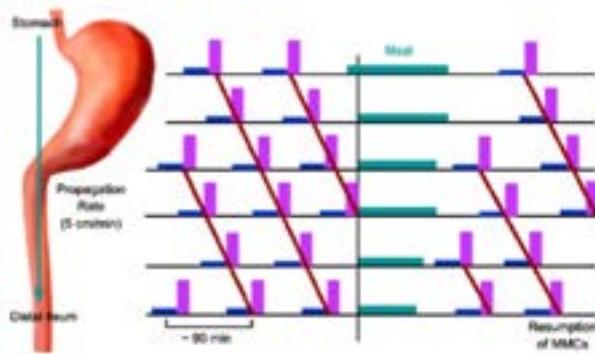


Figure 4.51: Propagation of phase III of MMC down the SI.

What's the purpose of generating an MMC? Well...it's mainly for house-keeping i.e. sometimes we have contents in the body that's yet to move at other time so we need to clear it by the time the next meal come.

Example 4.4.1. You ingested a penny or something that is non-digestable and non-absorbable by the body. First it passes through the pyloric sphincter via the antral systole. Note that anything beyond 1mm will be trapped

in the stomach since the sphincter can only open to 1mm. If the penny gets through,

The MMC is initiated by a hormone called **motilin** in the interdigestive phase. It requires the ENS to function because its signals will propagate through it; this also means that the MMC can be modulated by the ANS and gut peptide. Its only interruption is the intake of a new meal.

4.5 Secretion of the Upper GIT

Secretion is a function of glandular cells where it releases substances (e.g. enzymes) that's important for chemical breakdown of food. Secretion can be either exocrine or endocrine: in exocrine secretion, the substance is released to the external environment; in endocrine secretion, the substance is released to the blood stream/internal environment. Now, we said many lectures ago that the lumen of the GIT is continuous with the external environment, which means that the secretion we'll be looking at is exocrine.

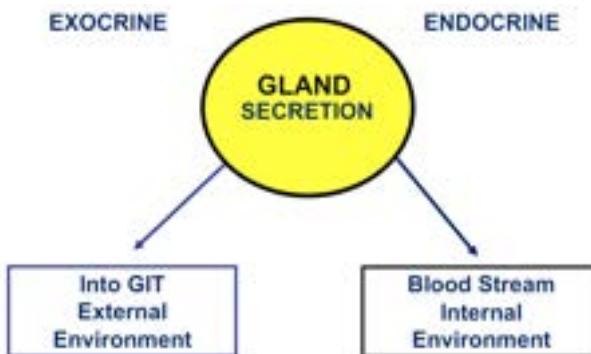


Figure 4.52: Secretion types.

4.5.1 General Consideration

Secretion of these substances plays an important role in digestion. Digestion itself is due to a series of interdependent steps i.e. it takes us multiple step before completely breakdown food material e.g. we breakdown proteins down to polypeptide then eventually amino acid that is absorbable. This also means that we would probably require different enzymes

A little revision that enzymes are proteins and they're absorbable. These enzymes may have duplication activities i.e. multiple enzymes may act multiple different ways on different steps. Lastly, these enzymes can only be secreted into a specific environment that is most optimal for it e.g. pH and ionic composition of the medium.

All in all, digestion is the chemical breakdown of food into smaller absorbable molecules. It is the result of the secretory activity (into GIT lumen) of a large number of exocrine glands found within and in association with the GIT.

Secretion is an active, energy and blood flow dependent process i.e. these exocrine glands and secretory cells require lots of energy and sit near capillaries to get the raw materials for secretion of ions and a variety of enzymes. There are 3 main types of enzymes: **amylases, proteases and lipases** and they break down carbohydrates, proteins and fat respectively.

Regulation of Secretion

The regulation of secretion in the most proximal (apical) part of the GIT is through the nervous system i.e. nervous system will have the highest regulation at the mouth and decreases as it moves down the GIT length. On the other hand, at the regulation of secretion at the most distal part of the GIT is through hormones and decreases as it moves up the GIT length. So therefore, midway through at the stomach, we would have both hormonal and neuronal inputs.

4.5.2 Secretion in the Mouth

The mouth has 3 glands for secretion called **salivary glands**: **parotid, submandibular and sublingual glands**. They secrete **mucin** which is a component of mucus to protect the mouth and lubricate the bolus. They can also secrete **salivary amylase** to digest carbohydrate and **lingual lipase** to digest lipid.

Remark 4.8. *salivary lipase is active at neutral pH hence it works in the mouth while lingual lipase is only active in the stomach since its activity is at acidic pH.*

The mentioned glands can coalesce into ducts which then secrete to the mouth. Normally, we produce around 0.5-1.5L of saliva per day that

consists mainly of Na^+ , K^+ , Cl^- and HCO_3^- . Saliva is the only secretory substance that is hypotonic (the rest will be isotonic), and it has a pH of 6.5-7.0. So at the level of the mouth, you can breakdown polysaccharides (such as starch) by an amylase called **Ptyalin** into disaccharides (maltose). Another component we have in the saliva is **lysozyme** which is used to breakdown bacterial cell wall.

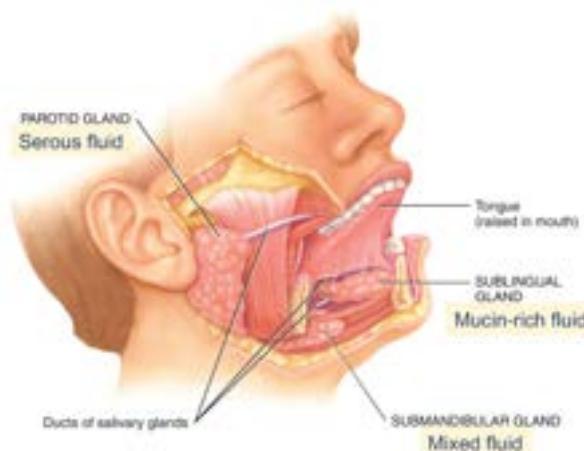


Figure 4.53: Salivary glands.

Glands Regulation

Like we've said before glands and cells located in the proximal GIT will be regulated by the nervous system, to be specific, it is the autonomic nervous system. If the parasympathetic branch of the ANS is activated, there will be an increased in ACh released which lead to increase glands activity and therefore secretion. When glands is more active, we also need to have the raw materials for it to use therefore we also have vasodilation. On the other hand, sympathetic branch will inhibit secretion and increase vasoconstriction.

Salivary Secretion Regulation

Secretion of the salivary gland is obviously neuronal. First, you can activate sensory receptor in your mouth by having food in it. This will trigger a

release of afferent that travel to your **salivary center** in the medulla. The medulla will send back efferent that cause salivary glands to secrete. We also have regulation via other stimulus e.g. stimulus from the eyes, nose, etc. in seeing food will activate higher center which then communicate to the salivary center and finally lead to secretion.



Figure 4.54: Glands and salivary secretion regulation,

This leads to different phases of secretion: **psychic, gustatory, gastric and/or intestinal**. Secretion at the level of the mouth is mainly in the psychic and gustatory phase which is both group together as the **cephalic phase**.

4.5.3 Secretion in the Stomach

The stomach secrete a substance called **gastric juice** at a rate of 1.5-2L/day. The fluid is isotonic and is included ions such as Na^+ , K^+ , Cl^- but most importantly it's H^+ . This is because the main component of gastric juice is **hydrochloric acid (HCl)** that has a pH of 1-2. There's **pepsinogen** which is a **zymogen** (inactive enzyme precursor) to **pepsin**. There are also intrinsic factor (helps with vitamin B12 digestion), mucin and alkaline secretion.

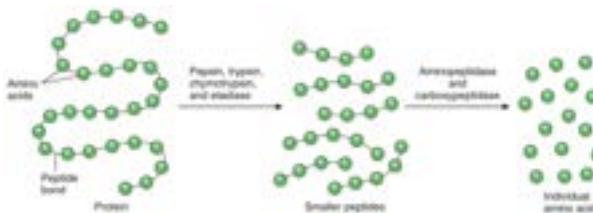


Figure 4.55: Enzymes for protein digestion.

The epithelial cell of the mucosa will secrete mucous and alkaline fluids to protect the stomach lining from its own acid. Along this lining, we

will find invaginations called **tubular glands**. These tubular glands are located throughout the stomach but will have different role e.g. cardiac and pyloric tubular glands will secrete mucus and enzymes while fundus and body tubular glands have specialized cells that secrete acid, enzymes and intrinsic factor.

Specialized Cells in Body and Fundus Tubular Glands

We first begin with the **parietal (oxyntic) cells** and they're going to release HCl into the lumen of tubular gland that will enter the gastric lumen. The other cell is called **chief cells** and they produce pepsinogen which will become pepsin in acidic pH to breakdown proteins.

Another type of cells is **mucus neck cells** which produces mucus and alkaline fluids even though they're not in the cardiac nor pyloric region.

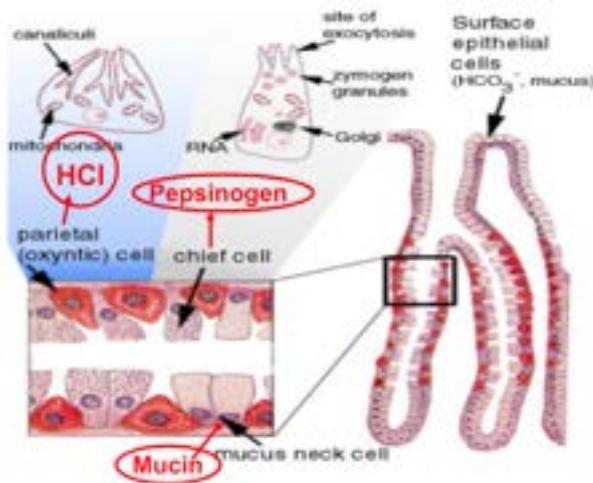


Figure 4.56: Specialized gastric cells in tubular glands.

Parietal Cells

Upon a closer inspection, we see that the parietal cells also have its own invaginations called **canalliculi**. These invaginations are to increased the surface area which increase HCl released to the tubular gland lumen and subsequently gastric lumen. The production of HCl require lots of energy

which is why we can find many mitochondria in the parietal cell.

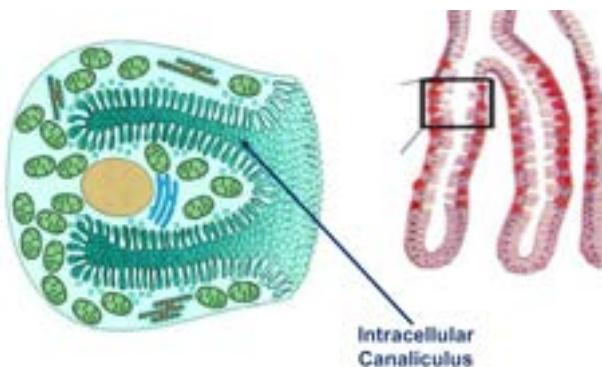


Figure 4.57: Structure of parietal cells.

So How do they actually produce HCl? Well...we will follow this schematic. First, we need to know that the parietal cells releases an equal amount of H^+ and Cl^- into the tubular lumen of around 150mEq each (isotonic). We can also see that the capillaries near it have $[H^+]$ of only 4×10^{-5} mEq; this means that in order to transport HCl out, it requires a lot of energy. At the same time of releasing H^+ and Cl^- , parietal cell releases HCO_3^- into the capillaries i.e. when we're acidifying the lumen, we're alkalinizing the blood (postprandial which means after a meal).

Mechanism of Action (HCl Production): First, water is catalyzed into H^+ and OH^- in the cell. Then, **carbonic anhydrase** inside the parietal cells will take CO_2 and H_2O to turn it into H_2CO_3 which can react with OH^- forming HCO_3^- . The H^+ will enter the lumen via pumps while HCO_3^- will enter the capillary via diffusion. The H^+ can move out the lumen via a pump called **H^+/K^+ ATPase** on the parietal cells' apical side. On the basolateral side, you have Na^+/K^+ ATPase to help with ionic balancing. Chloride will be pumped out at the same time with the same contraction hence the HCl is isotonic.

Remark 4.9. H^+/K^+ ATPase is a special type of pump found only in the apical side of the parietal cell.

This makes them a good pharmacological target e.g. when patient have

acid reflux, they're overproducing HCl so they can use a drug called **proton pump inhibitor** to reduce HCl production.

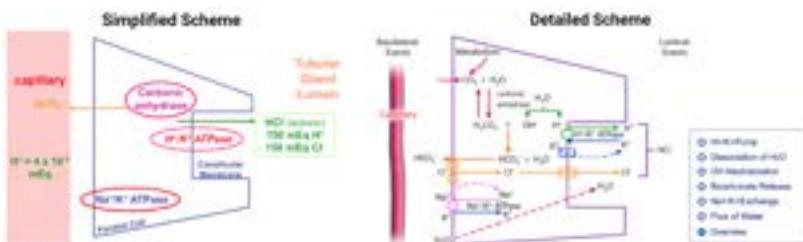


Figure 4.58: HCl production schemes.

Because the blood is getting alkalinized, urine would be more basic than usual. This phenomenon is called **postprandial alkaline tide**.

So in total, parietal cells secrete pure HCl fluid that has the acidity of pH 0.8 and this secretion is independent to the type and strength of magnitude. Mixed gastric juice, on the other hand, has pH of 1-2 because it's HCl mixed with other components from non-parietal alkaline secretions. Even so, **pH of gastric juice depends on the number of active parietal cells.** HCl has many functionalities. This includes precipitating soluble proteins i.e. allow proteins to form globs and junks which makes them stay longer in the stomach for digestion. HCl can also denature proteins for better digestion, activates and provides an optimal environment for pepsin activity.

Remark 4.10. Parietal cells also secrete intrinsic factor (a glycoprotein) for vitamin B12 digestion and absorption in the ileum. Without it, patient will develop **pernicious anemia**.

This is the only secretion by the stomach that is essential to life.

Chief Cells

Chief cells can produce granules that are filled with pepsinogen called **zymogen granules**. Once the pepsinogen interact with H^+ in acidic pH environment ($pH < 6$), it will turn into pepsin. Interestingly, **pepsin** can auto-catalyze pepsinogen to produce more pepsin. Pepsin has its optimal pH at around 2-3 to cleave protein into polypeptides.

Mucin Secretion

Mucin, as we said before, is secreted by all surface epithelial cells. It's also produced by cardiac and pyloric tubules, and mucous neck cells in the stomach fundus and body.

End of Lecture —

To begin this lecture, we'll first summarize previous lecture. First, we talked about MMC which is the GIT activity during interdigestive period to clear its lumen. Then we shifted toward secretion which requires energy and blood flow. The action is mediated by glands and cells in the mucosa. Then we talked about the secretion at the level of the mouth with salivary glands. These glands produce saliva which is the only secretion that is hypotonic in the GIT, along with ptyalin (salivary amylase) and mucin (mucus). Secretion at this level is regulated neuronally without any hormonal intervention. Finally, we ended with gastric secretion with different glandular cells and its production of mixed gastric juice.

4.6 Secretion of the Upper GIT II

We finished off previous lecture with mucin secretion in the stomach that's important to protect it, so **how does mucin really protect the stomach?** Well...if we look at a cross section of the layer of the stomach, we can see the capillaries, surface epithelial cells and mucous gel layer. If we were to probe between the lumen and the mucous gel layer, we would see a clear difference in pH (2 vs 7); this shows that the mucous gel layer has some degree of protection. Not only mucin is released into the layer but also HCO_3^- . This is because H^+ can enter the gel layer and react to form CO_2 and H_2O .

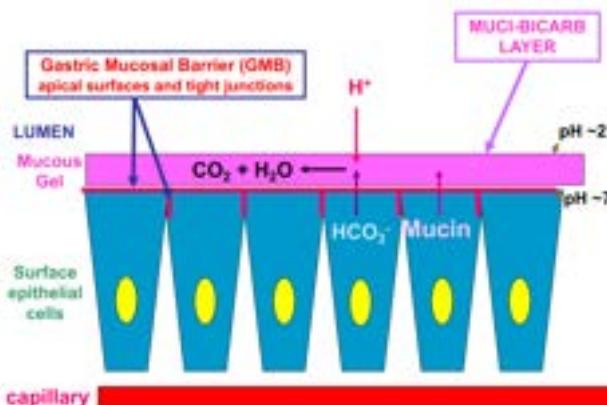


Figure 4.59: Different layers of the stomach contributing to protection.

But now, we realized that there's not much that prevent H^+ from penetrating the gel layer so **is there other protection methods?** Well...yes and there's 2 others. First, the main thing that protect the epithelial cell mucosa is the **gastric mucosal barrier (GMB)** that cover the apical side of the mucosa (face the stomach lumen) and it's impermeable from H^+ . Second, there's a high cell turnover (**reepithelialization**) in the GIT, especially in the stomach and small intestine because they're constantly damaged by acid and enzymes.

Even so, there are pathological conditions that can lead you to develop an **ulcer**, which is soreness on the lining of the stomach and small intestine.

Example 4.6.1. Patient with normal HCl output but have weak can develop an ulcer. Drugs that contribute to the weakening of this barrier include aspirins and NSAIDs (Non-steroidal anti-inflammatory drugs).

Remark 4.11. When aspirin said "enteric coated" meaning it has a coating protecting it from the stomach and small intestine.

Another factor contributing is a bacteria strain called *Helicobacter pylori* that burrows between the mucous gel layer and the epithelial cells, and release toxins.

Another way to develop ulcer is overproduction of HCl which can be due to **gastrin-producing tumors** for example.

4.6.1 Regulation of Gastric Secretion

The regulation of secretion in the stomach is due to both neuronal and hormonal input. So just to remind ourselves, ENS neurons can synapse to smooth muscle but also to secretory cells. Here, excitatory ENS neurons can release ACh to initiate secretion while inhibitory ENS neurons inhibit it.

Neural Regulation

First, when you see food or smell it etc, we initiate the cephalic phase that can communicate via the vagal nerve to the ENS neurons. ENS neurons is excited by the signal will also synapse to secretory cells such as parietal and chief cells, etc. and activate them and create vasodilation. You can also have sympathetic input that inhibit the secretion (we won't look into it much).



Figure 4.60: Neural regulation of gastric secretion.

That was the cephalic phase, during gastric phase when food entered the stomach. It creates distension which is captured by receptors that send afferent to local ENS and activate secretory cells. To enhance this signalling, we can have vagal-vagal reflex.

Hormonal Regulation

When proteins are broken down in the stomach, they'll produce products called **secretagogues** which are simply amino acid or partially digested proteins. They will act upon **gastrin-releasing G-cells** present in the stomach as well as some in the duodenum which lead to the release of **gastrin** (a hormone) into the blood stream. Gastrin will move from the hepatic portal vein back out to the stomach. In the stomach, it will act directly on parietal cell and increase HCl production.

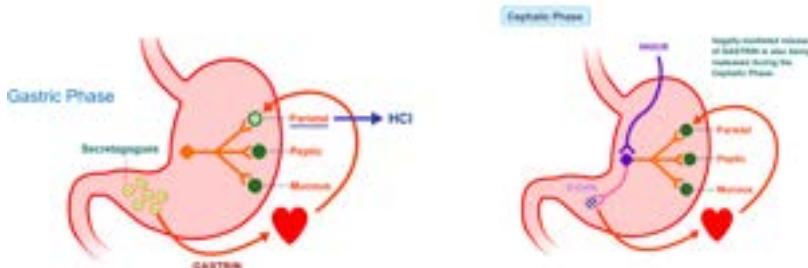


Figure 4.61: Gastric and cephalic phase of gastric secretion.

Not secretagogues can trigger the release of gastrin but there local ENS reflex due to distension and vagal mediated reflexes can also do trigger this.

During cephalic phase, afferent comes down from the vagal nerve which activate G-cells thus releasing gastrin which then increase HCl release. Like before, this can be reinforced by vagal-vagal reflexes.

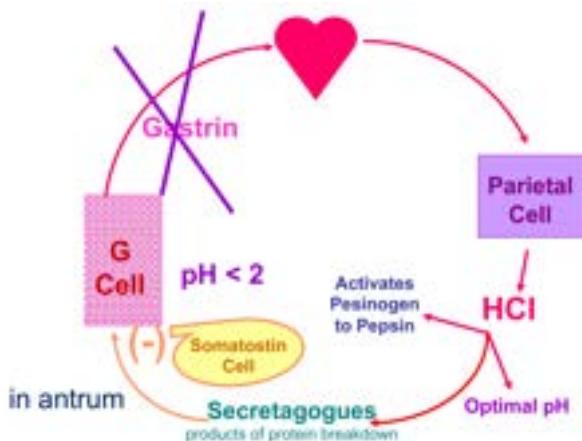


Figure 4.62: Gastrin release regulation.

So let's go through the production and action of gastrin once more. First secretagogues trigger gastrin release by G-cells into the hepatic portal vein. From there, it will move to the stomach and interact with parietal cells to produce more HCl. HCl will activate pepsinogen into pepsin as well as provide an optimal pH environment for it to perform. Pepsin thus breakdown even more proteins into secretagogues and the cycle repeat. Evidently, we can see that **this is a positive feedback loop**. Wait...so the stomach would get more and more acidic, that doesn't make sense! Well it doesn't because it won't get too much acidic...then **how can it regulate this?** Well...G-cells have receptor that detect the pH of its environment i.e. if $pH < 2$, G-cells will stop releasing gastrin. Not only that, we have **somatostatin cells** that response to low pH and release somatostatin that inhibit gastrin release from G-cells as well as HCl production from parietal cells. Therefore, we do have a negative feedback on gastrin production.

Histamine and HCl Secretion

Another hormones that plays an important role in HCl secretion is **histamine**. There are lots of histamine present in the gastric mucosa at all time but interestingly, when administer a person with histamine, we found

that their gastric juice has high concentration of HCl than normal. **So how does that happen?** Well...it used to be thought that parietal cells only have histamine receptor, and gastrin and ACh stimulate the stomach to produce histamine to bind to this receptor to produce HCl. This is the **common mediator hypothesis** and it is WRONG.

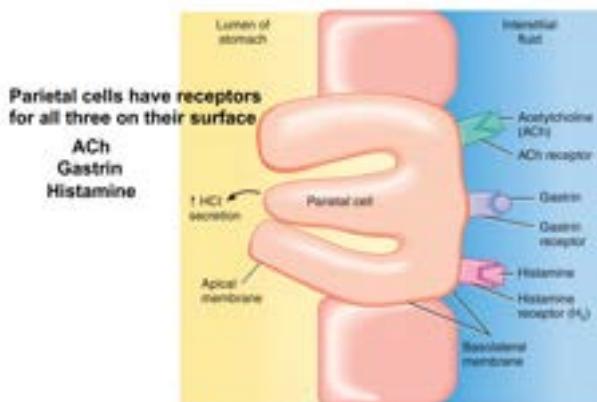


Figure 4.63: 3 receptors on parietal cells.

The parietal cells have 3 receptors for histamine , gastrin and ACh. What we think really happened is that these 3 receptors have cooperative binding effect i.e. when histamine bind to its receptors, it will increase the parietal cells ability to be activated by ACh and gastrin and this is called the **receptor-receptor interaction hypothesis**. In fact, a blockade in any of these receptors will change the properties of the rest. Using this fact, the histamine receptor has been the pharmacological target in treating ulcer i.e. a **histamine (H_2) receptor antagonist** will lower HCl secretion.

Remark 4.12. We can also use H^+/K^+ ATPase blocker to treat ulcer too.

Intestinal Phase and Gastric Secretion

Majority of intestinal feedback to the stomach is inhibitory however there's an existence of small burst of excitation. This excitation is caused by a small amount of secretagogues in the duodenum which lead to secretion of gastrin and so on. On the other hand, you have inhibitory signals like distension, acidic pH, chemical composition in the duodenum that produce

negative feedback to the stomach secretion. These signals are mediated by hormones and we will look at mainly CCK and Secretin.

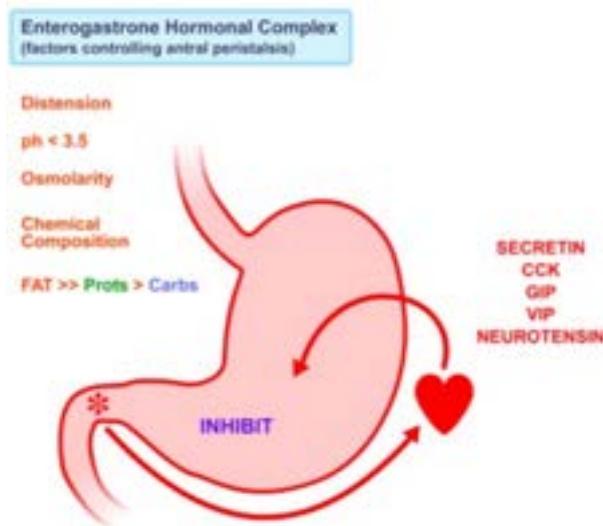


Figure 4.64: Gastric secretion inhibition.

What we've known till now is that motor and secretory activity of the stomach reflects a balance between excitatory and inhibitory influences on the muscular and glandular cells in the gastric wall.

Pre-Intestinal Changes

So before entering the small intestine, let's review what we've done so far. First, the meal we ate has been reduced to a semi-liquid which is called *chyme* and has low pH due to mixing with gastric juice. Nevertheless, its osmolarity remained unchanged and there's barely any digestion. We've only broken some polysaccharides into disaccharides via salivary amylase, proteins into polypeptides via gastric pepsin, and lipids into di-/monoglycerides and fatty acids via lingual lipase.

4.6.2 Secretion in the Small Intestine

The upper small intestine is used for chyme neutralization and osmotic equilibration. This is because the acidic chyme will damage the duodenum

and also by having osmotic equilibrium it will help with absorption (high osmolarity would push water into the intestine lumen). Here's where most of digestion and absorption take place.



Figure 4.65: Anatomy of the accessory organs and secretion.

There are lots of secretion at the level of the small intestine. These secretions are mostly from accessory organs like the liver, gallbladder and pancreas. All of them produce their own secretion and transport it via ducts and these ducts coalesce and pour their contents into the duodenum. To be more specific, the liver's **left and right hepatic duct** and gallbladder's **cystic duct** will transfer its secretion via the **common bile duct** which will merge with the **pancreatic duct** (carries pancreatic secretion) forming the **ampulla of Vater**. The ampulla of Vater can secrete into the duodenum and is controlled by the **sphincter of Oddi**.

Pancreatic Juice

We'll mostly talk about digestive enzymes found in the pancreas and pancreatic juice since it's the most powerful so far. **Pancreatic juice** is produced at a rate of 0.5-1.5L/day, it's isotonic with electrolytes such as Na^+ , K^+ , Cl^- and HCO_3^- (majority). Because bicarbonate is the major component, it will help with neutralizing the acidic chyme. There are also powerful enzymes (around 3g%) and they're amylases, proteases and lipases.

Although salivary amylase broke polysaccharides into disaccharides, this is still not absorbable in the body, which is why it requires pancreatic amylase to break it further into monosaccharides.

Interestingly, pancreatic protease will be released under its inactive form called **proenzymes (zymogen)** is **trypsinogen**. When released in the small intestine, trypsinogen will be converted into **trypsin** by an enzyme (released also by the small intestine) called **enterokinase (enteropeptidase)**.

The trypsin, an active protease, can autocleave trypsinogen to make more trypsin but also can turn other inactive proteases into its active form e.g. chymotrypsinogen into chymotrypsin, proelastase into elastase and procarboxypeptidase into carboxypeptidase. Once again, the reason it does this because these enzymes are very powerful and it would damage the tissues of the pancreas upon secretion. Additionally, pancreas also release **trypsin inhibitor** along the pancreatic juice as a second measure to prevent activation of the mentioned components.

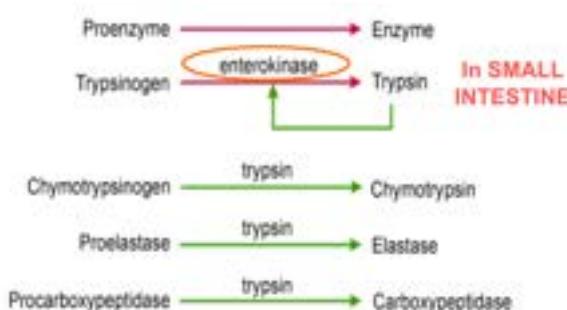


Figure 4.66: Pancreatic proteases.

Like usual, we will start this last lecture by reviewing what we did in the previous lecture. Last time, we talked about secretion at the level of the stomach along with its neural and hormonal regulation. We saw how phases of secretion linked to the stomach activity. The hormones that we saw controlling it is gastrin but also histamine. Then we shifted toward looking at the small intestine and its secretions (anatomically). Finally, we talked about the secretion of one of the accessory organ called pancreas.

4.7 Secretion in the Upper GIT III

We did not finished with talking about secretion by the pancreas into the intestine. Another component we would find in pancreatic juice, secreted in the small intestine, are **pancreatic lipase**. Due to their strength, they're regulated the same way that protease is: first, **pro-colipase** is turned into **colipase** by trypsin. The colipase can then activate pancreatic lipase to have its effect.

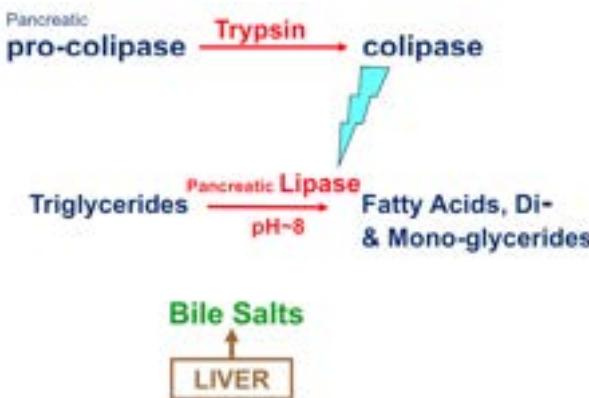


Figure 4.67: Pancreatic lipase and bile salt.

Another important secretion that will be important to breakdown fat is **bile salt** which is a secretion of the liver.

4.7.1 The Liver and Gallbladder

The **liver** is the largest gland in the body, it functions as a storage, place of synthesis, detoxification and even metabolism. Nevertheless, we will only

focus on its secretion of bile from the **hepatic ducts**. Like we've said before, bile will travel from the left and right hepatic ducts which then all merge together with the cystic duct (from the gallbladder) to form the **common bile duct**. This duct will fuse with the pancreatic duct at the **ampulla of Vater** which is regulated by the **sphincter of Oddi**.

Liver bile is secreted at a rate of 0.5-1.0L/day. It's a near basic isotonic fluid whose main ions is HCO_3^- (but also exist Na^+ , K^+ and Cl^-). Unlike other secretion, it do not have digestive enzymes but only solids and proteins (~ 3%). These solids consists of bile salt for breaking down fat, **bile pigment** for breaking down hemoglobin products, it also gives urine and feces their colour; cholesterol and phospholipids.

The secretion/production of the liver bile is continuous with the mentioned rate above. However, **its release into the duodenum is only when there's food** (~ 500 – 700mL/day) i.e. when you eat, CCK will be released and open the sphincter of Oddi to secrete bile into the duodenum. Wait...so **the liver is making more bile than it's releasing? How is that possible?** Well...the unreleased bile will be stored in the **gallbladder**.

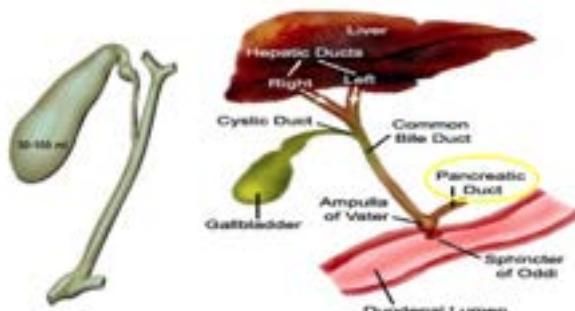


Figure 4.68: The gallbladder and liver.

The gallbladder is a small pouch that holds around 50-100mL of fluid. Its job is to store and concentrate the solid in the bile. This is made evident when we look at the solid composition of gallbladder's bile salt which sits at 10 – 20% (more viscous, water removed) but also it reduces pH down to 7.0-7.5.

Remark 4.13. *The gallbladder does not synthesize bile salt, they only store it.*

So what would happen when you remove the gallbladder in a cholecystectomy? Well...to answer this we need to know why would we need

to remove it? Well...sometimes, we can develop a condition called **gallstones** which is caused by the precipitation of phospholipids and cholesterol if not enough bile salt is present. The gallstone will block cystic duct and inhibit the release of bile to breakdown fatty food. Additionally, CCK can cause gallbladder to contract and with the present of gallstones inside, it will cause distension and pain. So to answer the original question, not much would happen if you remove the gallbladder since the liver can still make bile to breakdown fatty food. However, because of the lost of bile storage, patient cannot consume very fat and heavy meal.

4.7.2 Bile Salts

Bile salts are important components in bile. They're synthesized in the liver from cholesterol. The facilitate digestion, transport and absorption of fat by forming water-soluble complexes called **micelles**. They're also important in facilitating transportation and absorption of fat-soluble vitamin: **A, D, E and K**. The micelles can reduce surface tension of fat droplets and stabilize it which allow lipase to act upon them.

Bile salt are *amphipathic* which means they have a hydrophobic (non-polar) and hydrophilic (polar) side on their structure. They can coalesce together and have the hydrophilic side facing outward while the hydrophilic facing inward to the fatty acids, cholesterol and fat-soluble vitamin. These micelles can form droplets-like structure and the more bile salt there are, the smaller these droplets would be and the more easy the lipase can act on them.

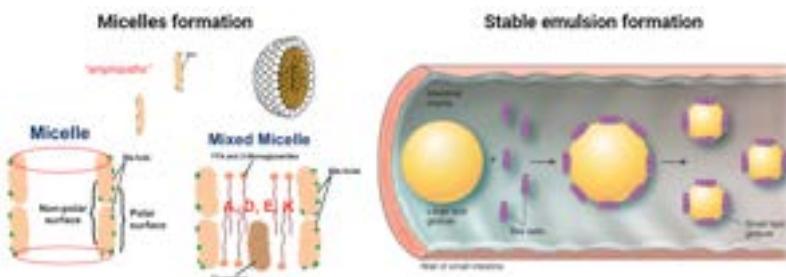


Figure 4.69: Bile salts help forming micelles and stable emulsions.

We said that it will form stable emulsions **what did we meant by that?** Well...if you take oil and water bring it together, they will separate into 2

layers, but if you mix them up, you would see these temporary droplets forming before they separate again. However, when you add in bile salt or detergent, the droplets will last longer and this is called a **stable emulsion**. We need to form the stable emulsion so that lipase has a chance to breakdown the fat. When the emulsion is smaller, there would be more of them thus increasing the surface area that the lipase can act upon.

The total bile pool in our body is 3.5g, the daily bile synthesis is 0.5g but we release 15-20g of bile salt, **how does that work?** Well...this works because we're constantly recycling bile salt. Most bile salt is absorbed in the hepatic portal vein which return to the liver. This is why we have smaller pool but high release of bile salt.

Enterohepatic Circulation

First, the liver required oxygenated blood to survive so some of the liver blood comes directly from the heart. Nevertheless, majority of its blood is from the **hepatic portal veins** or the **enterohepatic system**. The enterohepatic system consists of secretion of the liver into the small intestine but also all of the blood exiting the GIT into the liver for filtration and detoxification. This blood can ultimately return into the central circulation and back to the heart for oxygenation.

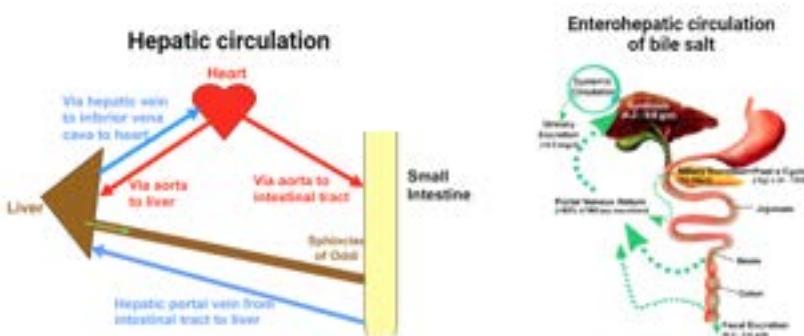


Figure 4.70: Hepatic circulation and enterohepatic circulation of bile salts

With this understanding, we can now look at the **enterohepatic circulation** of bile salts. So bile are made by the liver and some of it is stored in the gallbladder. Both can release its content into the duodenum. All along the GIT: small intestine and colon, there will be absorption of those bile

salts. These bile salts will return to the liver via the hepatic portal veins to be recycled and reused. The bile salts themselves have lots of function and not just only reacting micelle and emulsion.

In the liver, the amount of bile salts returning regulates the amount of bile salts release. For this case, **the more bile salts returning to the liver, the more bile salts will be released** (a positive feedback). This makes sense because if we're using lots of bile, that means there's lots of fat to breakdown hence upregulate the release. **what would happen to bile secretion when ileum is removed?** Well...the feedback will decrease because you have lower bile salts absorption.

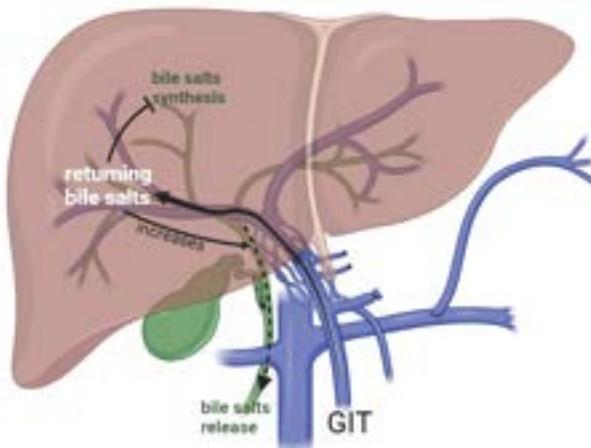


Figure 4.71: Intraportal function of bile salts.

Not only that, the amount of bile salts returning regulates the synthesis of new bile salts. In this case, **the more bile salts returning to the liver, the less synthesis of new bile salts would be needed** (a negative feedback). This also makes sense since it's wasteful to make more bile salts if you're already getting back a lot of them. Like before, when removing the ileum, the synthesis of new bile salts will increase since absorption decreased.

Bile salts can help emulsify cholesterol in the liver and make it stay in solution (since cholesterol is insoluble in water). We need to keep it in solution otherwise it can precipitate and form gallstones. Bile salts make cholesterol more soluble in water by 2×10^6 fold.

In the intestine, like we said before, it will help forming stable emulsions and micelles for the fat and fat-soluble vitamin so that lipase can break it down easier and the small intestine can absorb them easily. Finally, at the level of the colon, bile salts' main role is to absorb water and inhibit Na^+ transport. However, if too little bile salts are present we will absorb too much water and feces becomes too compacted lead to **constipation**. On the other hand, too much bile salts will lead to **diarrhea**.

Intraportal – regulate volume of bile secreted by liver
– regulate synthesis of new bile salts

Intrahepatic – keep cholesterol in solution

Intraintestinal (SI) – emulsify & transport fats

Intracolonic – prevent too much water absorption

Figure 4.72: Summary of bile salts functions.

4.7.3 Regulation of Pancreatic and Bile Secretion

Secretion in the small intestine (SI) will be regulated by both hormonal and nervous aspects.

There will be an increase of pancreatic and bile secretion in response to preparation of a meal as well as during intestinal phase but not much during gastric phase. The pancreas has 2 distinct cell types: 1 type produces a large volume of juice rich in HCO_3^- (for neutralization and osmolarity balance) while the other type produces a small volume of juice rich in enzymes. So the regulation would be differential i.e. depending what's in the duodenum, 1 type will be upregulated more than others e.g. more acidic chyme in the duodenum trigger high volume cell type to release.

Now we will look at the regulation of bile flow. Bile flow can be divided into 2 effects: **choleretics and cholagogues**. Choleretics are agents that cause the liver to secrete a larger volume of bile while cholagogues are

agents that promotes gallbladder emptying. The contraction of the gallbladder directly link to the **law of reciprocal activity** which simply states that contraction of the gallbladder will lead to the relaxation of the sphincter of Oddi and v.v.

We can summarize regulation of bile and pancreatic juice as the following table. This includes the secretion from the liver, contraction of gallbladder and relaxation of sphincter, and 2 pancreatic cells type.

	LIVER	GB Contracts Sphincter Relaxes	PANCREAS low vol/high enzyme/low pH	PANCREAS High vol/low enzyme/high pH
VAGUS	+	+++	+++	--
GASTRIN	+	+	+	+
CCK	--	+++	+++	--
SECRETIN	+ vol/ HCO_3^-	--	--	+++
BILE SALTS	+++	--	--	--

The vagus nerve in cephalic phase transmit its efferent toward these targets when you prepare, see or smell a meal. In this case, there will be small secretion from the liver, a large secretion of concentrated bile from the gallbladder and strong digestive enzyme from the pancreas. When food is in the stomach, it begins gastric phase and the release of gastrin. Gastrin has little effect on the secretion though still have a small increase. When fat and protein rich chyme enter the duodenum, they trigger CCK release. CCK will lead to a large secretion of bile from the gallbladder and strong pancreatic enzymes. **why?** Well...because we have lots of proteins and fat, so we would need lots of protease, lipase and bile to break it down. When highly acidic chyme enter the duodenum, cells release secretin which lead to a secretion of HCO_3^- from the liver and large volume for neutralization fluid from the pancreas. Lastly, when there's a lot of bile salt, then the liver will be triggered to released more bile salt.

4.7.4 Result from Upper GIT Secretion

As a result of all of the upper GIT secretion, polysaccharides are broken down into disaccharides which is not the form that's absorbable yet. Proteins are broken down into smaller peptide and similar to disaccharides, they're inabsorbable. Finally, fats are broken down into mono-, diglycerides and fatty acids which are all absorbable.

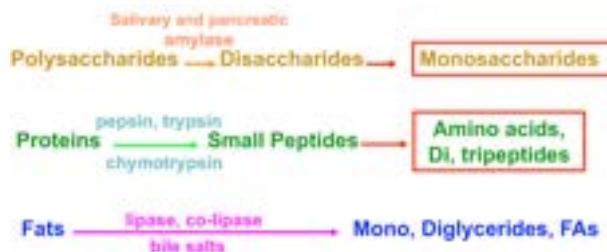


Figure 4.73: Secretion results by the upper GIT.

The last step of digestion will be mediated by *intestinal enzymes* which is produced by mucosa where absorption occurs.

4.8 Absorption and Final Secretion in the GIT

The **small intestine (SI)** secretes intestinal juices that consists of water, mucous and ions. It receives pancreatic juice enzymes to help with digestion. Nevertheless, it has its own enzymes called the **brush border enzymes** attach to the microvilli (long projection like cilia) of the SI epithelial cells. They perform segmentation which helps with mixing food as well as absorption. They also perform chemical digestion when chyme mixes with pancreatic juice and bile. After all of these, it perform absorption to uptake all the nutrients.

4.8.1 Secretion in the SI

The surface area of the SI is very large due to its all of the invagination and projection from the surface that it has. The invaginations of the SI surface is called **crypt region** while the finger-like projection are called **villi (villus region)** where digestion is completed and cells absorb its nutrient called

enterocytes. A closer inspection on the surface of these cells, they also have smaller finger-like projection which is called **microvilli** where the brush border (surface of the microvilli) enzymes are located.

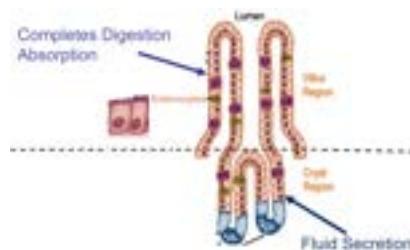


Figure 4.74: Crypt region and villi

Crypt region consists of **crypt cells** which produces a large volume of alkaline fluid (rich in HCO_3^- and have other ions too) called **succus entericus** (pH of 7.5-9) at a rate of 3L/day.

Remark 4.14. *The villi are not secreting the fluid, it's the crypt and once cells in the crypt region become a villi cells, they cannot produce fluid any more.*

The enterocytes in the villi synthesize digestive enzymes that stay in its brush border (hence the name). These enzymes include enterokinase which is what needed to activate trypsin hence turn on other strong enzymes. There are also **disaccharases** such as sucrase, maltase, etc. to help breaking disaccharides into monosaccharides for absorption.

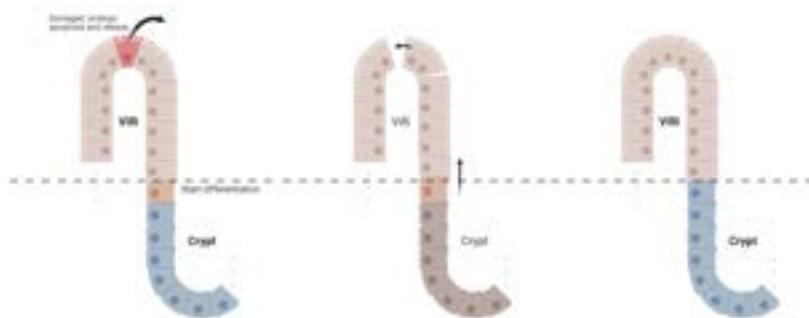


Figure 4.75: Simple illustration of villi turn over process.

Another important thing is that the villi has high turn over rate every 3-5 days starting from the crypt region moving upward. What happens is

that cells in the microvilli will get damaged by the enzymes which will ultimately die by apoptosis and released into the lumen. Then cells start differentiate from the crypts pushing each other upward becoming the next cells in the villi etc.

Another thing that's important is the blood flow into the villi. Each villi has a capillary loop surrounding a **lacteal** (lymphatic capillary). Blood flow coming in to provides cells nutrient and oxygen to perform the job. At the same time, enterocytes can absorb the nutrient from the lumen: fat and proteins are packaged together called a **chylomicrons** that will be absorbed at the level of the lacteal which later rejoin the central circulation. On the other hand, sugar and carbohydrates absorbed by the enterocytes will then be absorbed into the blood stream and return to the liver via the hepatic portal vein

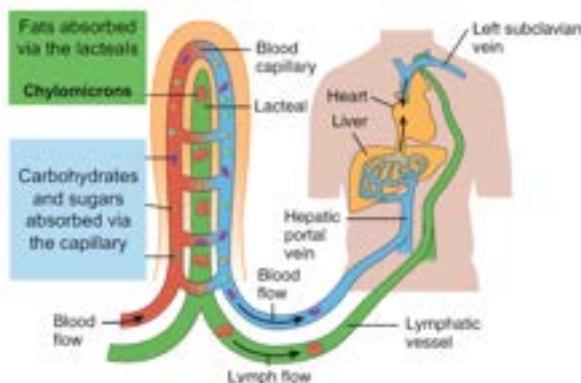


Figure 4.76: Blood and lymphatic flow in the villi

Now with the addition of intestinal enzymes, disaccharides are broken down into monosaccharides and peptides are broken into amino acids; all of which are absorbable.

4.8.2 Colonic Secretion

Before heading into absorption, we need to look at the final secretion in the colon. The colon do not secrete much fluid but it still secretes a small volume of fluid that is rich in HCO_3^- , K^+ (both around 100-150mEq/L) and lots of mucous. There won't be secretion of digestive enzymes nor nutrient

absorption. The most important thing is that there are lots of bacteria that contribute to the gut health as we learn about its microbiome. When we have an MMC, the ileocecal sphincter open and bacteria move into the SI allow the colon clear its content and not kill the bacteria.

So to end secretion of the intestine, its regulation is made by local ENS reflexes, vagal-vagal reflexes and hormonal factors.

4.8.3 Absorption

Everyday, you intake around 2L of fluid but only 100mL of fluid is excreted with 50g of solid. Within this excreted solid, there are bacteria, undigested fibers, lipids and inorganic matters. Not only that, we also have to consider 7L of secretion by the GIT which mean in total the body would need to reabsorb 9L of fluid in a day. As for the non-fluid component: we got ions which can be reabsorbed, proteins as enzymes and cells will be broken down into amino acid and reabsorb. As you can tell by now that **most absorption is reabsorption.**

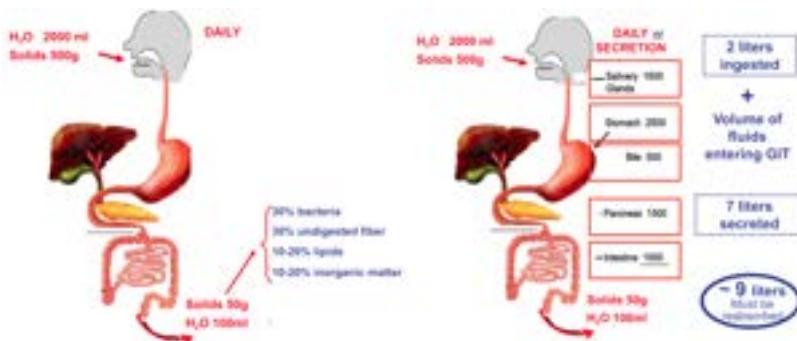


Figure 4.77: Ingestion, excretion and absorption of fluid.

Where is everything absorbed?

Well...absorption happens mostly in the SI of the GIT. The site of absorption is characterized by **large surface area and intimate contact with blood vessels.**

The SI makes a perfect job for this as it matches all the characteristics. First, looking at the intestine, you can see that it has circular folds along its lumen. Along these circular folds are projections called villi and on top of these villi there are cells with its own projection called microvilli. As you can see, we have this fractal pattern of projections as you shrink down to cellular level and this rapidly increases the total surface area. Villi also have these rapid blood flow in its capillaries at rate of 1-2L/min and also lymphatic flow of 1-2mL/min.

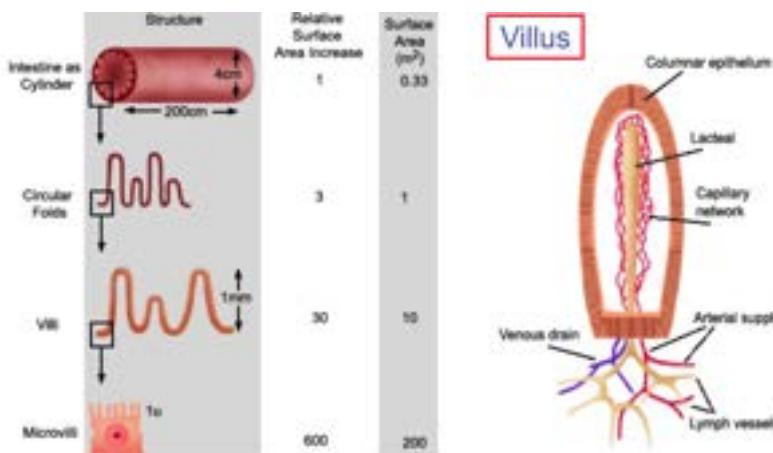


Figure 4.78: Surface area and circulation in the villi

Majority of absorption happens in the duodenum of the SI however there are still absorption at the jejunum and ileum which are equal in efficiency. The ileum however has the highest absorption efficiency with bile salt (increasing efficiency from duodenum) and vitamin B12.

How does absorption take place?

Absorption is mediated by: simple diffusion, facilitated diffusion, active transport, pinocytosis and osmosis (water follow the concentration gradient made by the motion of ions and nutrients). **How about the limiting factor of absorption?** Well...by limiting factors we meant the requirement in order to have absorption. In this case, we need to have **adequate digestion (enzymes, pH, etc.)**, site of absorption, transit time, co-factors and **transporters**.

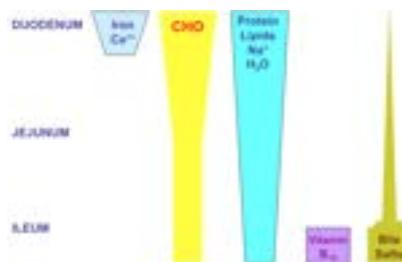


Figure 4.79: Absorption efficiency along the SI.

We've said before you need to reabsorb 9L of fluid but **where?** well...7L will be reabsorbed in the SI while the 2L will be reabsorbed in the colon. However, the maximum capacity of absorption they can do is twice that: 15L/day for SI and 4-5L/day for colon.

Absorption of Different Nutrients

The followings are illustrations of absorption of carbohydrates, protein and fat.

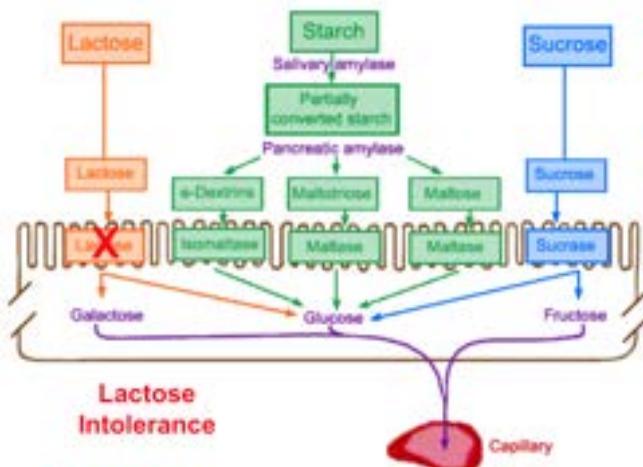


Figure 4.80: Absorption and digestion of carbohydrates (no need to know the SI enzymes).

Remark 4.15. ***lactose intolerance*** is characterized by missing the enzymes lactase therefore ingestion of lactose can lead to diarrhea, distension and bloating.

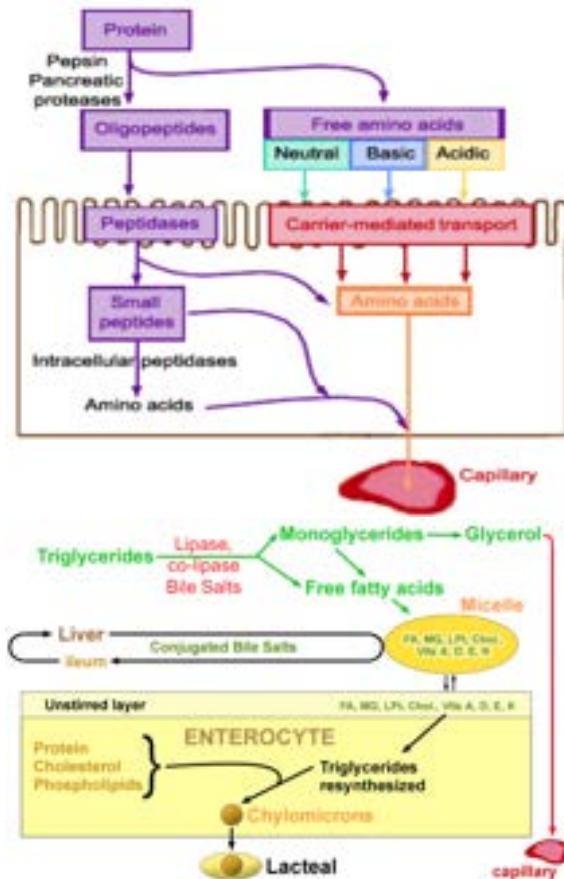


Figure 4.81: Absorption and digestion of proteins and fat

Just to say, the efficiency of absorption by the GIT is very high where there's absorption of 99% of carbohydrates, 95% of fat and 92% of proteins. This high efficiency is due to effective coordination of neural, hormonal, motor and secretory activities of organs. In general, in response to a meal, a wave of secretory activity proceeds and accompanies the meal. There are

also a wave of motor activity that receives and accommodate the meal.

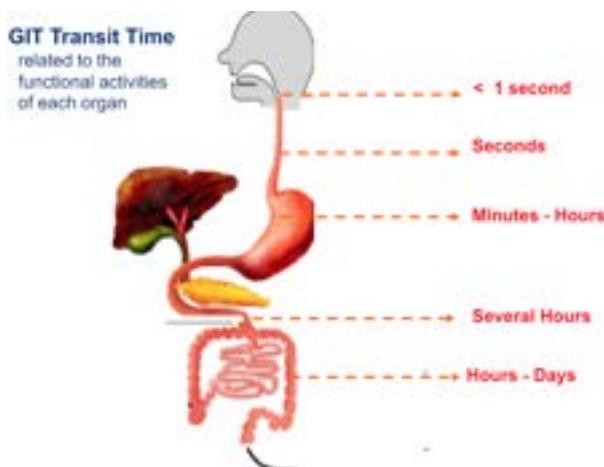


Figure 4.82: GIT transit time.

The transit time also partially help with such efficiency and is determined by the functional activities of each organ.

Lastly, due to the amount of enzymatic activities and function of the GIT, it needs lots of protective mechanisms and this includes: mucin, inactive proteases, trypsin inhibitor, GMC, sphincters, negative feedback of gastrin, neutralization, MMC and etc.

Definition 5.1. The **renal system** is a system of organs used to filter fluid and excrete toxin and metabolic waste products

5.1 Anatomy of the Kidneys and Urine Formation

Before look at the anatomy of the kidney, we need to look at its functions. First off, it's obvious that the kidneys are for making urine which means it has a direct effect on the regulation of water, inorganic ion, and acid-base balance. It helps with removing metabolic waste products from the blood and excreting them in the urine. Not only removing metabolites, it can also remove toxins and foreign chemicals via urine (this is why sometimes the coloration and smell of urine might be different). Last but not least, kidneys help with producing important hormones such as **erythropoietin (EPO)** that help with red blood cell production, **renin** for blood pressure regulation and Na^+ balance, and **1,25-dehydroxyvitamin D** that influences Ca^{2+} balance.

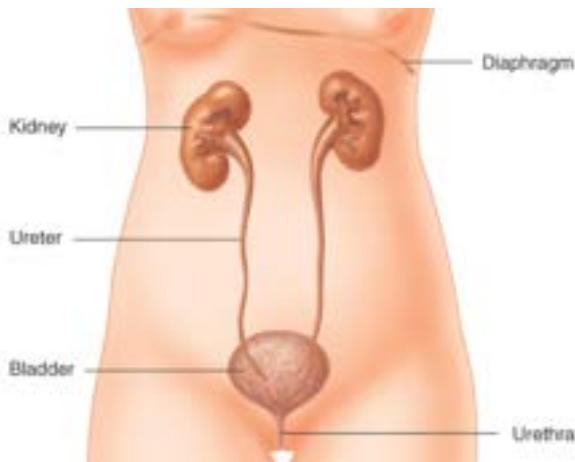


Figure 5.1: Anatomy of the Kidney

5.1.1 Gross Anatomy of the Kidneys

Kidneys are paired organs with each weigh 150g and an adult kidney has the size of an average fist. They're located behind the **peritoneum** on either side of the vertebral column against the posterior abdominal wall. A simple way to think of its location is near your back below the diaphragm/chest. Both kidneys are connected to the **bladder** via 2 long tubes called **ureter**.

If we bisect the kidney longitudinally, we can see regions with different coloration. The outer side of it is called **renal cortex** while the inner side is called **renal medulla** which are these inverse pyramid structures. Inside the kidney there's also a space called the **renal pelvis** where urine made from the cortex and medulla is released into. The renal pelvis is connected to the ureter and transfer urine into the bladder.

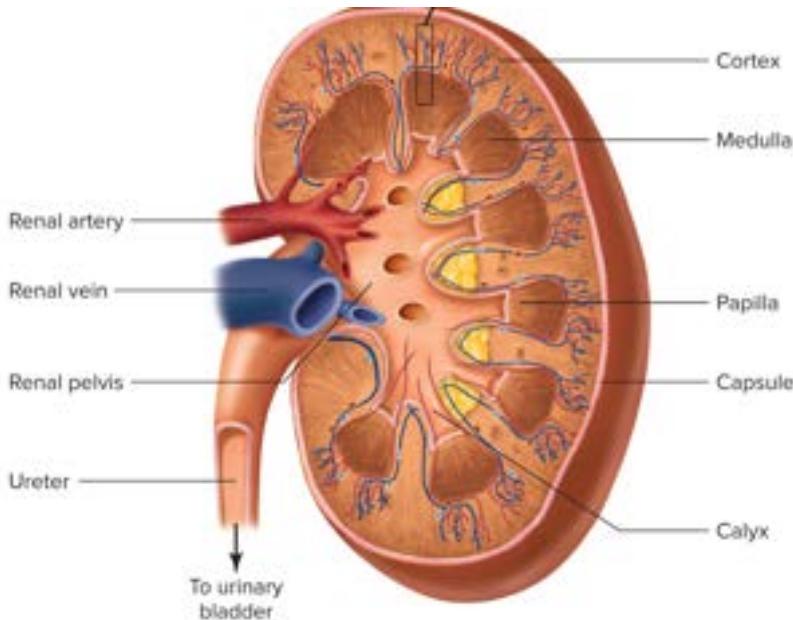


Figure 5.2: Kidney anatomy

The kidneys have 2 major vascular systems coming in and out of it: **renal artery** and **veins** respectively. The renal artery is a direct branching from the descending aorta while the renal veins branch directly back to the inferior vena cava. Within the kidney, the arteries and veins branch parallel

with each other (only different in flow direction). From the renal artery, it branches to any arteries that goes in between the medulla called the **interlobar artery**. As the arteries reach the junction between medulla and cortex, the all merge together forming an arch called **arcuate artery**. From the arcuate artery, it branches further perpendicularly to the cortex and it is called **interlobular artery**. The interlobular artery eventually give rise to **afferent arterioles** which gives blood supply to **nephrons** which are functional units of urine formation.

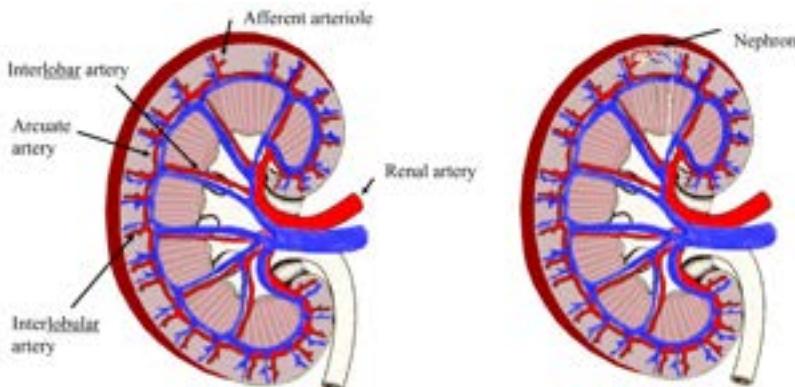


Figure 5.3: Kidney blood circulation (nephrons are not to scale).

5.1.2 Anatomy of Nephrons and Its Components

Each kidney contains roughly 1 million subunits called **nephrons**. Each nephrons are made up of 2 components/structures: **tubules** and **renal corpuscles**. The renal corpuscle is made up of 2 other components: **Glomerulus** (capillary loops) and **Bowman's capsule**.

Remark 5.1. *We tend use glomerulus interchangeably with renal corpuscle (including the bowman capsule as well).*

One thing you will notice (see Figure 5.4) is that the renal corpuscle is always in the cortex and it will receive blood supply by afferent arterioles. Once the afferent arteriole leaves, it is called **efferent arteriole**. Following the renal corpuscle is a hollow tube surrounded by monolayer of epithelial cells that enter the medulla then go back into the cortex then back to the medulla and finally reach the renal pelvis.

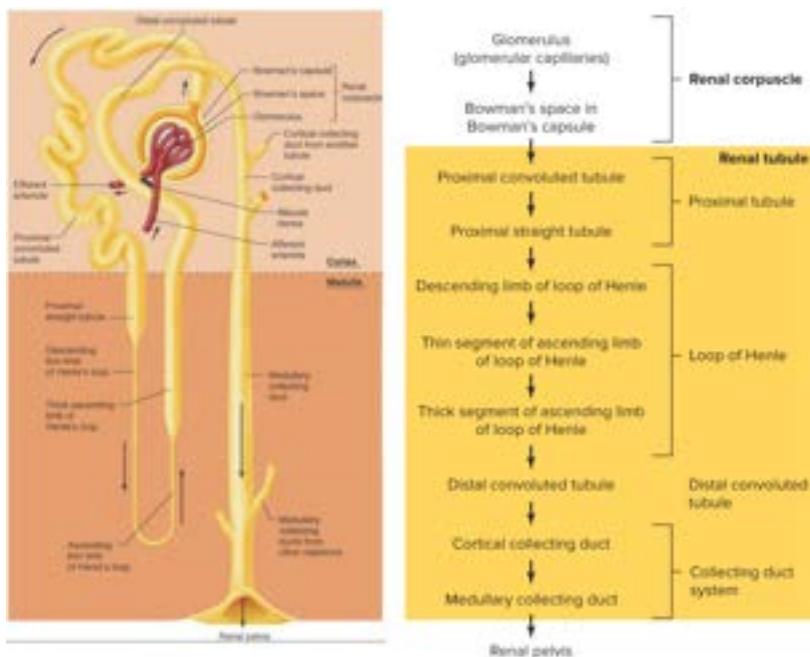


Figure 5.4: Anatomy of nephrons and their components.

Now, we can look at the table (see Figure 5.4, right), the first portion of the renal tubule is the **proximal tubule** which starts from the glomerulus in to cortex reaching to the medulla. From here, the tube becomes narrower and it is now called **loop of Henle**. The loop of Henle first descends into the medulla then ascends back out and starts thickening; it passes through the cortex and touches the original glomerulus (every nephrons are like this). After this, it is called the **distal convoluted tubule** or just **distal tubule**, which will loop back around in the cortex, here other tubes from other nephrons merge to it. Then this merged tube will move into the medulla and it is now called **collecting duct** and pour into the renal pelvis.

To summarize from the table, we begin from the renal corpuscle then proximal tubules, loop of Henle, distal tubules and finally collecting ducts.

Renal Corpuscle

The best way to understand the structure of renal corpuscle is to think of the glomerulus as a ball of looping capillaries and Bowman's capsule as a ball made from a monolayer of epithelial cells. Now the renal corpuscle is simply this looping capillaries ball punch into the monolayer ball. Now, the glomerulus does not change shape but the Bowman's capsule will now hug around the glomerulus forming a half moon crescent.

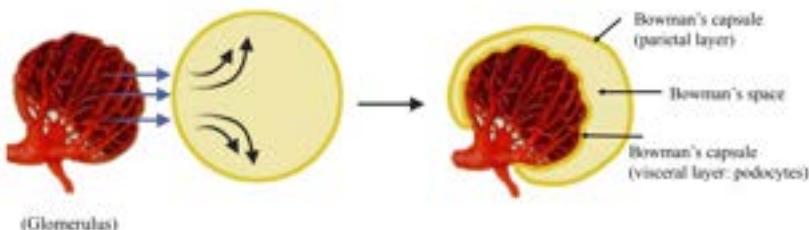


Figure 5.5: Simple illustration of renal corpuscle.

1 side of the Bowman's capsule does not touch the glomerulus and is called the **parietal layer** (unimportant). The other side touches glomerulus and is called **visceral layer** made of cells called **podocytes**.

We can zoom into the renal corpuscle more and see the glomerulus in detail. You can see the afferent arteriole coming in forming a looping capillary that is the glomerulus then leave by the efferent arteriole. We can see also attaching to the afferent arteriole is the distal tubule.

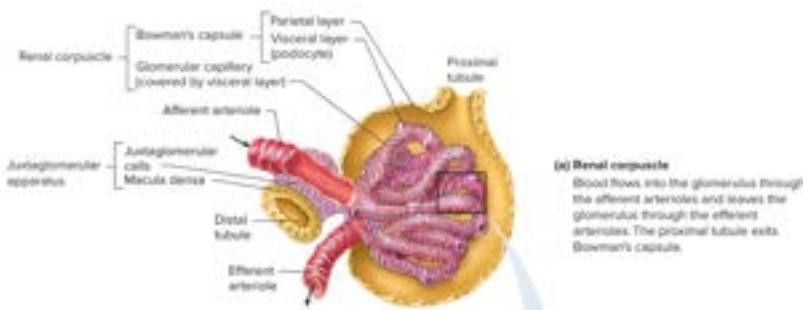


Figure 5.6: Zoom in illustration of renal corpuscle.

The distal tubule is made from thick cells called **macula densa**. The connection between afferent arteriole and the distal tubule is mediated by the **juxtaglomerular cells** or **renin secreting cells** and together with macula densa, they make up the **juxtaglomerular apparatus**.

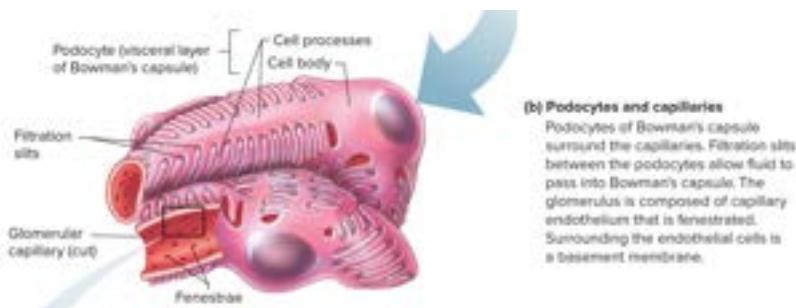


Figure 5.7: Zoom in illustration of the glomerulus.

Now we're going to zoom even further in the glomerulus and look at its wall. The glomerulus is the entangled capillary which is surrounded by the visceral layer of the Bowman's capsule called podocytes. The podocytes have these foot-like processes that can inter-digitate very tightly around the capillary wall and this is important to keep a filtration barrier in the glomerulus.



Figure 5.8: Cross section illustration and EM of the capillary.

We can now look at the cross section with illustration and electron micrograph. Here, we can see the bottom is the capillary while the top is the podocyte and each of the pot-like structure are the foot processes. These foot processes are interconnected by a **filtration slit**. On the other hand, the capillary has openings called **fenestration** allow small molecules like water to flow from it to the **basement membrane** then through the filtra-

tion slit and the foot processes. Together this is called the **glomerular filtration** which is the first step to urine formation.

In summary, the glomerulus (plural: glomeruli) is entangled capillary loops surrounded by Bowman's capsule. The capillary wall consists of endothelial cells, glomerula basement membrane and podocytes. The main job of glomerulus is to filter blood and make urine.

We can also summarize the consecutive segments of nephron as the following table. First the proximal tubule starts in the cortex and continues into the medulla. Then, it's the loop of Henle start in the medulla and loop around and goes back into the cortex. The distal tubule then starts in the cortex and loop around to be the beginning of the collecting duct which goes into the medulla.

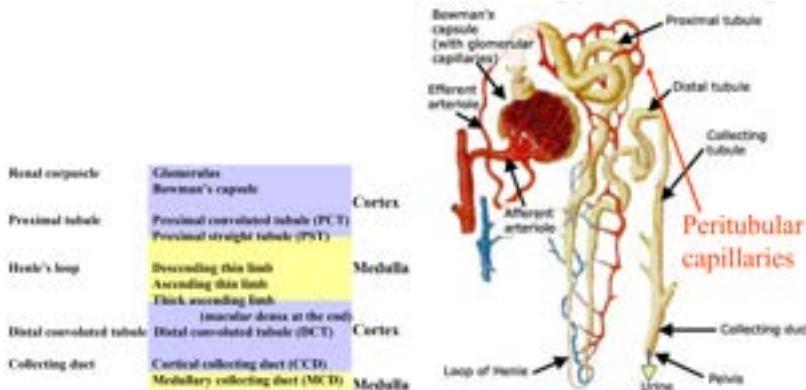


Figure 5.9: Consecutive segments of nephron and its vascular supply.

Another thing we didn't mention was the blood supply to the nephron. Now as the blood leave the glomerulus, it branches out and supply blood to the tubules not only in the cortex but deep in the medulla. The capillaries branching from the efferent arteriole to supply blood to the nephron are called **peritubular capillaries** after which the blood comes back to venous system.

5.1.3 Basic Formation of Urine

There are 3 main processes in forming urine: **glomerular filtration, tubular secretion and absorption**. Glomerular filtration is the first step where blood is filtered into the Bowman's space. In tubular secretion, molecules move from the peritubular capillaries into the tubular lumen while tubular reabsorption is the opposite.

First, glomerular filtration brings fluid in blood into the Bowman's space. What we found is the glomerular filtrate (fluid post-filtration) has the same composition as plasma however it is **cell and proteins-free** i.e. red blood cells, white blood cells, plasma proteins will be filtered from the fluid. If these components exist in urine, you might have some nephrological conditions. Next is both tubular secretion and reabsorption. As the glomerular filtrate moves through the tubules, its composition will be altered by the movement of substances. So like we've said before, reabsorption when substance moves from the tubules into the peritubular capillaries while secretion is from the peritubular capillaries back to the tubules.

Remark 5.2. *Secretion and excretion are different. Excretion is the final elimination in the urine while secretion is the movement of substance.*

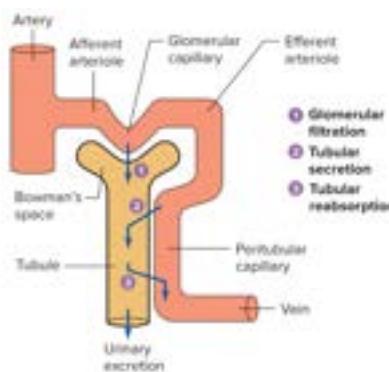


Figure 5.10: Simplified illustration of urine formation.

We can look at the formation of urine via the following simplified illustration. Here, we see the afferent arteriole comes in and back out of the renal corpuscle via efferent arteriole which then becomes the peritubular capillary. In 1, it is glomerular filtration then 2 it's the movement into the

tubules from capillaries which is secretion; and finally 3, it's the opposing movement which is reabsorption.

This links directly to the following equation which describe the amount of a substance excreted out by urine at the end (taken all of the formation steps into consideration).

$$\text{Amount excreted} = \frac{\text{Amount filtered}}{} + \frac{\text{Amount secreted}}{} - \frac{\text{Amount reabsorbed}}{}$$

Note: these amount changes from 1 substance to the next

Example 5.1.1. In **Para-amino-hippurate**, substance is filtered through the glomerulus but the bulk still remain in the peritubular. Then that same bulk will be secreted back into the tubules and excreted out as urine. This is not an endogenous substance (must be injected in) but it's useful to determine the renal plasma flow.

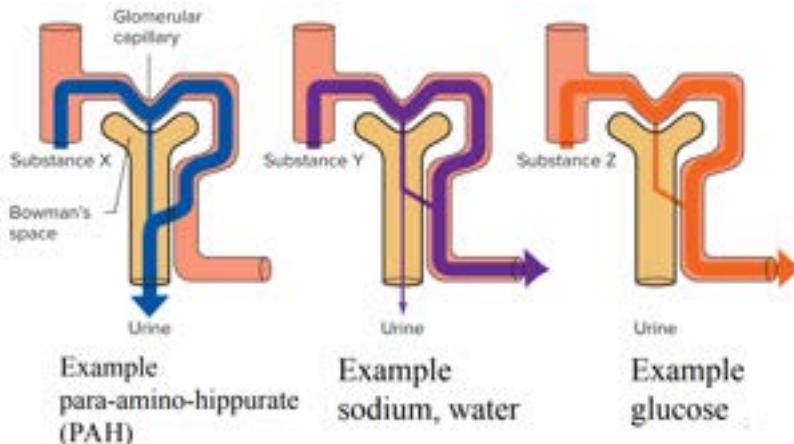


Figure 5.11: Different example of urine formation schematic.

In the second example, the substance has some filtration and the bulk still remain in the peritubular capillaries. This time, some of the substance in the filtrate is reabsorbed but there's no secretion. In fact, majority of substance will flow this scheme like water and Na^+ (reabsorption rate of 99% and filtration rate of 1%).

In the last example, the substance has some filtration and bulk like

other. However, the filtrate will all get reabsorbed back into the peritubular capillaries. Substances that follow these scheme include: glucose and amino acids. These substances need to be kept in the body, otherwise there's a conditions e.g. glucose will get excreted in urine when blood glucose level is high which is indicative of **diabetes mellitus**.

To end this lecture, the rate of filtration, reabsorption and secretion is controlled physiological. This means when the body content of a substance goes above normal, homeostatic mechanism can regulate its elimination e.g. If a normal person drinks a lot of water, reabsorption of water is decreased and excess water will be excreted in the urine.

5.2 Urine Formation

In this lecture, we will look at how urine is formed which we've briefly looked over in the previous lecture. There are 3 steps to form urine: filtration, secretion and reabsorption.

5.2.1 Glomerular Filtration

First step to urine formation is the filtering in the Bowman's capsule. Here, plasma from the glomerular capillaries will be change into filtrate which has almost the same constituents that is water and low-molecular weight substances. Components of plasma that will not be filtered through are: cells like red blood cells, proteins (albumins, globulins, etc.) and protein-bound substances (Ca^{2+} , fatty acids, etc.). If these substances are present in urine, it is indicative of a pathological condition e.g. red blood cells in urine is indicative of **hematuria**, proteins in urine will be for **proteinuria**, etc.

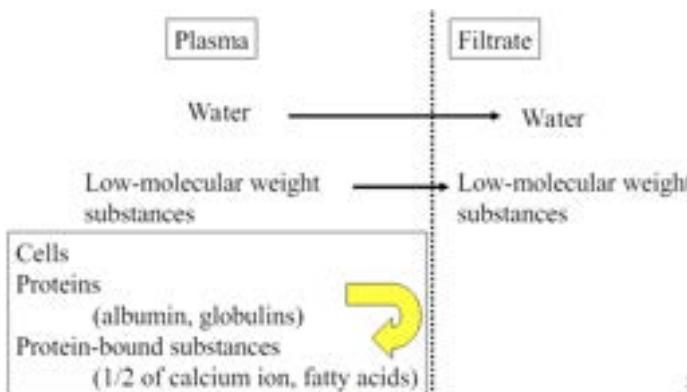


Figure 5.12: Glomerular filtration.

What are the main drive forces for filtration? Well...there are 3 main forces that contribute into glomerular filtration. First you have the pressure that favour filtration that is the capillary blood pressure of around 60mmHg. We also have 2 forces that oppose filtration: fluid's pressure by the Bowman's capsule and plasma protein osmotic (oncotic) pressure, which are 15 and 29mmHg respectively. If we add all of these forces up, we get a net glomerular filtration pressure of 16mmHg.

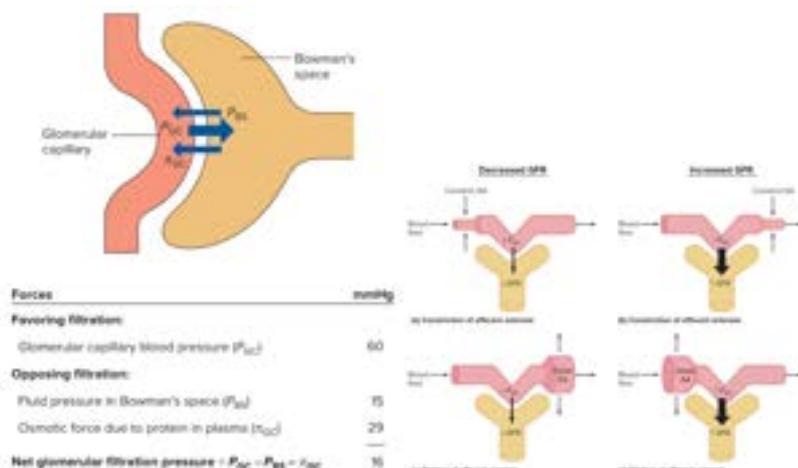


Figure 5.13: Forces contribute to glomerular filtration and regulatory factors of GFR.

Definition 5.2. **Glomerular filtration rate (GFR)** is the volume of fluid from the glomeruli into the Bowman's capsule per unit of time.

GFR are regulated by many factors such as: **net filtration pressure, membrane permeability and filtration surface area**. When these factors are altered or impaired in a pathological conditions, it can lead to a change in GFR. In normal person of 70kg, their GFR is roughly 180L/day (125mL/min). Given that the total plasma volume of this person is 3.5L, then **plasma is filtered roughly 51 times a day at the glomeruli!**

We can look at some regulatory factors of GFR (see Figure 5.14, right). First, if we want to decrease GFR, we need to decrease the net glomerular filtration pressure which can be done by constricting the afferent arteriole lead to the decrease of blood pressure of the glomerular capillary and subsequently the net glomerular filtration. Another way to do this is to dilate the efferent arteriole which also decrease GFR. If we want to increase GFR, we can do the opposite of what we've done for the other 2.

Definition 5.3. **Filtered load** is the total amount of any freely filtered substance and is given as the following equation

$$\text{filtered load} = \text{GFR} \times \text{Substance's plasma concentration} \quad (5.1)$$

Example 5.2.1. The average person GFR is around 180L/day and glucose concentration in plasma is around 1g/L. Therefore, by the above equation, the filtered load of glucose is around 180g/day.

Another thing we can get from filtered load is knowing whether the substance will be secreted or reabsorbed. If filtered load > the amount excreted in urine then such substance was reabsorbed; otherwise, if filtered load < the amount excreted in urine thus such substance was secreted.

Remark 5.3. *GFR is unique from 1 individual to the next while filtered load is unique from 1 substance to the next.*

Example 5.2.2. GFR in 1 person can be 180 while another person can be 190L/day. Meanwhile, filtered load of Na^+ is different from that of K^+ in a person.

5.2.2 Tubular Reabsorption

Reabsorption is the motion of substance moving from the tubular lumen into the peritubular capillary. There are 2 types of reabsorption: **paracellular** and **transcellular**. We can look at the following illustration and see the tubular lumen surrounded by epithelial cuboidal cells that are connected to each other by tight junctions.

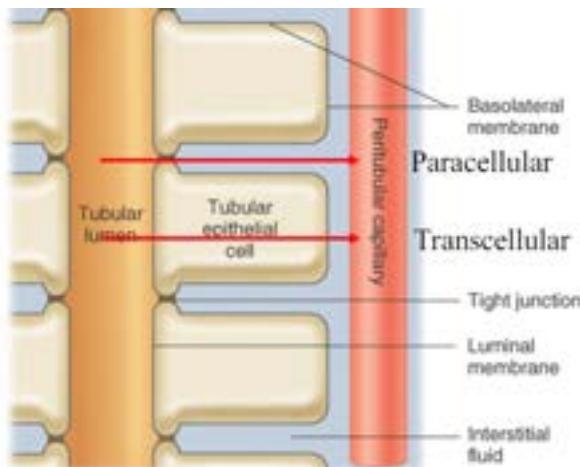


Figure 5.14: 2 types of reabsorption.

These epithelial cells can be divided into 2 membrane portions: the side facing the tubular lumen is called the **luminal membrane** while the side facing the peritubular capillary is called the **basolateral membrane**. Paracellular reabsorption is when the substance move between the epithelial cells, while transcellular reabsorption is when the substance move from the tubular lumen across the epithelial cells into the peritubular capillary.

We will now go back to some numbers just to give out an idea how much of each substance is reabsorbed into the peritubular capillary. We can see water getting filtered out at around 180L/day but only 1.8 is excreted in urine per day; this also means that the reabsorption ratio is 99%. If we look at for Na^+ , we see a similar reabsorption ratio of 99.5%. Glucose, on the other hand, has the highest reabsorption rate of all of them of 100% while urea is 44% which makes sense since urea is a metabolic waste and should not be kept in the body. K^+ is interesting with a net reabsorption rate of 86.1%, this is because it is both secreted and reabsorbed.

TABLE 14-2 Average Values for Several Components that Undergo Filtration and Reabsorption			
SUBSTANCE	AMOUNT FILTERED PER DAY	AMOUNT EXCRETED PER DAY	PERCENT REABSORBED
Water, L	180	1.8	99
Sodium, g	630	3.2	99.5
Glucose, g	180	0	100
Urea, g	54	30	44
Potassium, mEq	720	100	NET 86.1

Summary of Reabsorption

Filtered load are large and is generally larger than the amount of substance in the body. Reabsorption of waste products are relatively incomplete (e.g. urea) while that of useful plasma component are relatively complete (e.g. water, Na^+ , etc.). Lastly, reabsorption of certain plasma components are not regulated while others are e.g. glucose and amino acid has no regulation in tubular reabsorption, but water and Na^+ are highly regulated which mean reabsorption rate is depending on physiological needs.

Reabsorption Transportation

Reabsorption follows 2 mechanisms: **diffusion** and **mediated transport**. Reabsorption by diffusion follows the paracellular route i.e. move across the tight junction of tubular epithelial cells.

Example 5.2.3. Urea reabsorption in the proximal tubules is made by diffusion. Urea is freely filtered in the glomerulus. At the proximal tubules, water is reabsorbed which make urea concentration in the tubular lumen increases. Because of the higher concentration of urea in the lumen than in the interstitial space, it will diffuse through the interstitial fluid and finally in the peritubular capillaries.

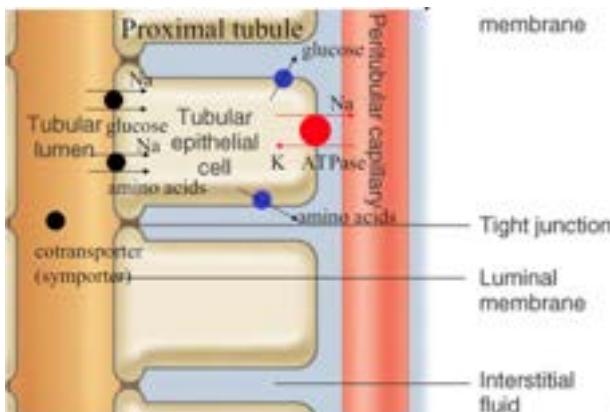


Figure 5.15: Mediated transport mechanism.

The other mechanism is **mediated transport** which follows the transcellular route i.e. move across the tubular epithelial cells. It typically requires a transport protein in the plasma membrane of tubular epithelial cells and is usually coupled with a reabsorption of Na^+ . We can first look at the Na^+/K^+ ATPase on the basolateral membrane of the tubular epithelial cells that can transport Na^+ in the interstitial space while K^+ into luminal side using ATP. We also have 2 **co-transporters (symporters)** that brings Na^+ and another substance (glucose, amino acids, etc.) on the same direction into the tubular epithelial. These symporters are not energy driven but is driven by the low $[Na^+]$ in the cell. Back on the basolateral side, we also have 2 other transporter that release amino acids and glucose back into the interstitial space. All of the substances released in the interstitial

space will be brought back into the peritubular capillary which complete reabsorption.

General Information on Solute Transport

Solute transportation can be classified according to its energy usage: **passive and active**. Passive transport is a type of transport that doesn't require energy and is further sub-classified into: **diffusion, facilitated diffusion (use a protein transport) and solvent drag**. Facilitated diffusion can be done by either a channel, uniport or coupled transporter (antiport or sym-port). Meanwhile, active transport is a type that require energy and a protein transport to bring solute against its electrochemical gradient. Active transport and facilitated diffusion can be both grouped together as **mediated transport** which is a type of transport that require a protein channel.

Transport Maximum

1 last concept that's related to reabsorption is **transport maximum**. To simplify, transport maximum is the limit when membrane transport protein become saturated and tubules can no longer reabsorb substances.

Example 5.2.4. In people with uncontrolled **diabetes mellitus**, the plasma concentration of glucose can become very high and the filtered load of glucose exceeds the capacity of the tubules to reabsorb glucose (T_m is exceeded). As a result, glucose appears in the urine that is indicative of **glucosuria**.

5.2.3 Tubular Secretion

There are not a lot of things that are secreted (from the peritubular capillaries into the tubular lumen) and the only ones are: K^+ and H^+ . They're mediated by diffusion or transcellular mediated transport and is coupled to the reabsorption of Na^+ .

Tubular secretion is divided according to the segment of the tubule. First, we need to know that in order to filter substance through, you need to get a large GFR which also means you have a large filtered load. With this large filtered load, we need to get some reabsorption of substances. This happens in the proximal tubules where reabsorption of most filtered water and solutes but it is also a major site of secretion for many solutes beside K^+ . As we move toward the Henle's loop, it performs reabsorption

with large quantities of major ions but not a lot of water. Finally, we're at the distal convoluted tubule and collecting duct where the volume of water and solutes are relatively reduced before. Here, it also determines the final amounts excreted in the urine by adjusting the rate of reabsorption and also secretion (in some cases). What's more important is that **most homeostatic controls are exerted here.**

5.2.4 Clearance

Definition 5.4. **Clearance** (of a substance) is the volume of plasma from which that substance (S) is completely removed ("cleared") by the kidneys per unit time and is given as the following equation

$$\text{Clearance of S} (C_S) = \frac{\text{Mass of S excreted per unit time}}{\text{Plasma Concentration of S} (P_S)} \quad (5.2)$$

where the mass of S excreted per unit time which is also defined as the urine concentration (U_S) times the urine volume per unit time (V). We can thus rewrite the equation as follows

$$C_S = \frac{U_S V}{P_S} \quad (5.3)$$

Why do we use clearance? Well...it can be used to estimate the GFR.

Inulin Clearance

Inulin is a polysaccharide that can be administered intravenously and is freely filtered at the glomerulus but is not reabsorbed, secreted nor metabolized by the tubule. If you calculate the clearance of inulin, it will be equal to GFR. Essentially, inulin injection is the most accurate marker to measure GFR (important nephrological number to see if the kidney is functioning correctly).

$$C_{IN} = GFR \quad (5.4)$$

We can look at the calculation of inulin clearance. Let's say you know that patient secrete a urine volume of 2.4L/day and the plasma concentration of injected inulin is 4mg/L. After injection, we can collect the urine of the patient which we measure to have inulin concentration of 300mg/L. Now, we can determine the amount of inulin excreted in the urine as $2.4 \times 300 = 720\text{mg/day}$. We can now determine the originating volume of plasma from which the 720mg of inulin comes from that is $720 \div 4 = 180\text{L/day}$. This

will be our clearance but knowing that clearance of inulin is equal to the GFR, this is the patient GFR.

Nevertheless, this is inconvenient since this substance is exogenous and 1 injection require patient to stay at the facility for hours along with multiple blood sampling. So, we can another way to measure GFR.

Creatinine Clearance

Creatinine is a waste product produced by muscle. It's freely filtered at the glomerulus but is not reabsorbed nor metabolized by the tubule. There are some secretion but is small. This substance is an endogenous substance which allow us to measure GFR easier.

$$C_{\text{cr}} = \frac{U_{\text{cr}} V}{P_{\text{cr}}} \quad (5.5)$$

First, patient will collect their own urine over a 24 hours period (1 day). Supposed that patient has urine volume of 2L/day, $U_{\text{cr}} = 9.6 \text{ mmol/L}$ and $P_{\text{cr}} = 0.3 \text{ mmol/L}$ hence

$$C_{\text{cr}} = \frac{9.6 \times 2}{0.3} = 64 \text{ L/day}$$

If the normal GFR is 180L/day, we can see that the person lost approximately 2/3 of the GFR. Unfortunately, this patient has a disease called **glomerulonephritis** (inflammation of the glomerulus).

Clearance vs GFR

GFR is unique for each person while clearance can be calculated for different substances. If clearance of a substance is $>$ GFR, the substance is secreted at the tubule; while, clearance of a substance is $<$ GFR, the substance is reabsorbed at the tubule.

We can use this understanding and look back at one of the illustration of secretion and reabsorption of different substance. First you have this substance X that was first filtered through the glomerulus and then vigorously secreted from the peritubular capillary later on. There's only 1 substance that fit such scenario and it is the para-amino-hippurate which can be used as a marker for plasma flow. The other 2 scenarios is when clearance of the substance less than GFR which lead to reabsorption and most substance falls into this category.

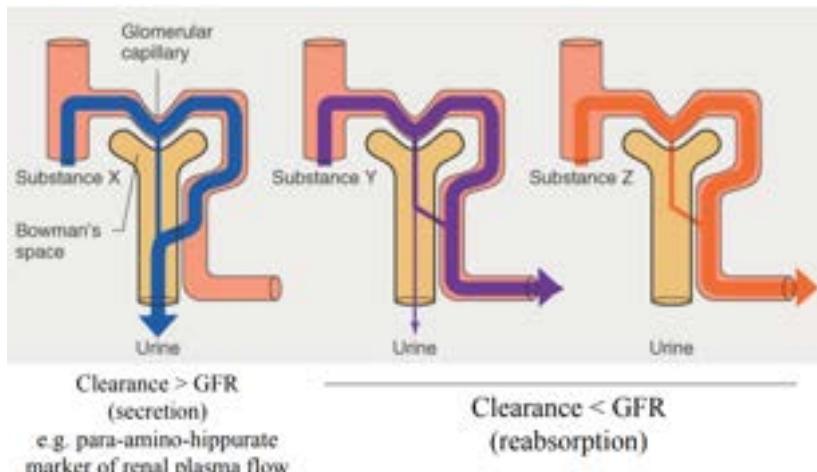


Figure 5.16: Clearance of different substance with respect to the GFR

End of Lecture —

5.3 Regulation of Sodium Balance

In this lecture we will look at how the urinary system performs sodium (Na^+) balance. As we know, Na^+ is very important for the body thus its regulation is vital in the body. Before that, we will look at both water and Na^+ together because their regulations are intertwined and are important. The total body balance of water and Na^+ must be maintained for you to have normal blood pressure and sustain life.

The following numbers are representative of an average person's water input and output. On average, a person's Water intake via liquid is around 1.2L, 1.0L from food and also 350mL via metabolic processes in the body. This means we consume on average a total of 2.55L of water. To have a balance, you also have to output this water which is through: insensible loss of 900mL, sweat of 50mL, feces of 100mL and most output is through urine of 1500mL. This also totals into 2.55L hence input and output balance.

Remark 5.4. You can see the excretion of water by urine is almost the same as the liquid intake.

Intake	
In liquids	1200 ml
In food	1000 ml
-Metabolically-produced	350 ml
Total	2550 ml
Output	
Inensible loss (skin and lungs)	500 ml
Sweat	50 ml
In feces	100 ml
Urine	1500 ml
Total	2550 ml

Figure 5.17: Average water input and output of a person.

A small trick healthcare professional tends to use is that balance out the metabolically produced water and insensible loss of water to get a rough estimate amount of water to give to a patient. e.g. From the above example, we would give the patient $900 - 350 = 550 \approx 500\text{mL}$ of water.

Now, according to world standard, majority if not all of intake of Na^+ is from food of 10.50g in the form of NaCl (9-9.5g in Canadian standard). Its output is through sweat of only 0.25g, feces of 0.25mg and most is in urine of 10.00g. Your body regulate its own output of Na^+ via urine but cannot regulate sweat and feces (environment-dependent) e.g. diseases that cause diarrhea would lead to feces have higher Na^+ output; higher temperature can lead to higher Na^+ secretion and sweat.

Intake	
	10.50 g
Output	
Sweat	0.25 g
Feces	0.25 g
Urine	10.00 g
Total	10.50 g

Figure 5.18: Average Na^+ input and output of a person.

In general, healthy people are in water and Na^+ balance. The dynamic range of water output can vary from 0.4L to 25L/day. The reason that it can go so high can be caused by **compulsive drinking** or simply vigorous exercising. On the other hand, dynamic range of NaCl output can vary from 0.05g to 25g/day which can be due to salty food consumption.

5.3.1 Sodium and Water Processing

Now, we will look at the general principle of renal processes of Na^+ and water. Both Na^+ and water are filtered but 99% are reabsorbed and is never secreted. 2/3 of these reabsorption occurs in the proximal tubules however major hormonal controlled reabsorption occurs much later in the distal convoluted tubules.

Na^+ reabsorption is an active process that occurs in all tubular segments beside the descending limb of the Henle's loop. On the other hand, water reabsorption is by diffusion and is dependt on Na^+ reabsorption. Now we will leave water and focus only Na^+ regulation.

5.3.2 Sodium reabsorption

Like we've said above Na^+ reabsorption is active. Here, we're looking at the the **cortical collecting duct (CCD)** where Na^+ reabsorption is hormonally controlled. Na^+ reabsorption will be triggered by activation of Na^+/K^+ -ATPase on the basolateral membrane of the cuboidal epithelial cells.

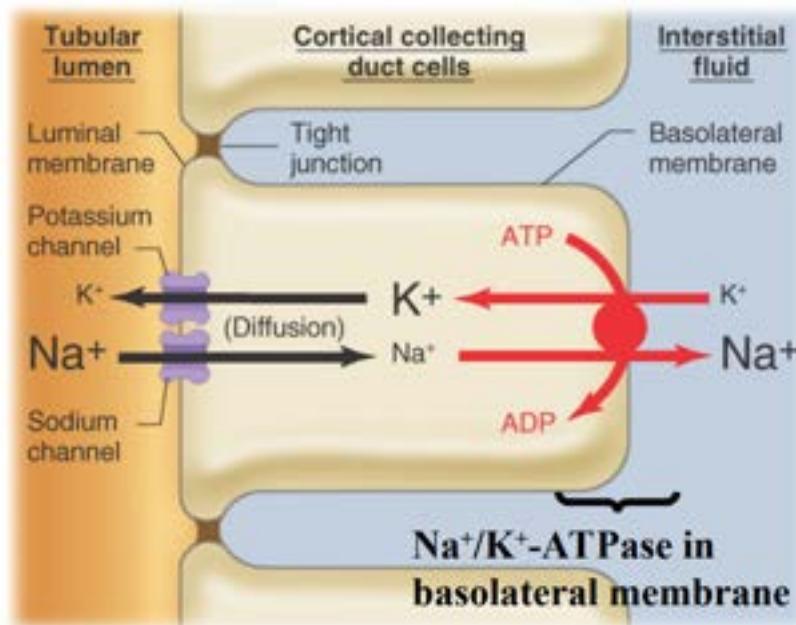


Figure 5.19: Active Na^+ reabsorption.

Na^+/K^+ -ATPase will pump out Na^+ into the interstitial space (ISF) while take in K^+ using ATP. In the cell, $[\text{Na}^+]$ is low so **how can sodium get out?** Well... Na^+ enter the tubular epithelial cells from the tubular lumen using a Na^+ channel that doesn't require ATP but only concentration gradient. There's also K^+ channel near it to let K^+ out along its concentration gradient into the tubular lumen i.e. K^+ secretion in the CCD. Basically, the overall picture is that when Na^+ disappear from the tubular lumen it will reappear in the ISF and reaborbed by the peritubular capillary.

To summarize this, we have active Na^+/K^+ -ATPase pumps transport Na^+ out of the cells and keep the intracellular concentration of Na^+ low

on the basolateral membrane. Meanwhile, Na^+ moves downhill from the tubular lumen into the tubular epithelial cells on the apical membrane. Interestingly, the transport of Na^+ into the tubular epithelial cells is dependent on the location of the tubules e.g. in the proximal tubule we have Na^+/H^+ antiporter and $Na^+/glucose$ cotransporter, in the CCD it's the Na^+ channel.

5.3.3 Renal Regulation of Sodium

Regulation of Na^+ is very simple. When Na^+ goes up, urine Na^+ excretion will increase v.v. however there's a delay unlike the faster balance of water.

To do such regulation, the kidney need to know if you have too much or little of Na^+ in the body. So **how does it detect the total body Na^+ ?** Well...it needs to know the distribution of Na^+ which is a major extracellular solute. Our body are mostly made of water (60% of body weight) which are distributed into intercellular fluid (ICF, 40% BW) and extracellular fluid (ECF, 20% BW). The ECF is divided into 2 other compartments: interstitial fluid (ISF, 3/4 ECF) and plasma (1/4 ECF). Na^+ is only in the ECF and the only way to detect this ECF volume is through plasma which is the vasculature. The vasculature has lots of baroreceptors to detect its blood pressure but in this case it's to detect the filling of the vessels which is a marker for Na^+ amount e.g. **if it's overfilled the body think it has high Na^+ v.v.**

Remark 5.5. *Plasma concentration of Na^+ of is not a marker for total body Na^+ . It only reflects the relative relationship of total body Na^+ and water.*

So **how does the kidney reacts to sodium excretion?** Well... Na^+ excretion is determined by the amount filtered and the amount reabsorbed. This is regulated by regulating GFR (minor) or Na^+ reabsorption (major).

Regulation via GFR

The following is the diagram of regulation via controlling GFR. Supposed that a person is losing lots of Na^+ and water due to diarrhea. This lead to decrease of plasma volume and thus venous pressure. The venous pressure is detected by baroreceptors and stimulate the **renal sympathetic nerve (renal SN)** activity. Venous pressure also changes venous return and atrial pressure which also lead to renal SN activation. Atrial pressure decreases will lead to ventricular end-diastolic volume decreases and subsequently a decrease in SV, CO and then atrial blood pressure. Atrial blood pressure

can signal back to the renal SN but also directly constricting afferent arteriole. Together, All of this decrease net glomerular filtration pressure, lead to decrease of GFR and thus decrease the total Na^+ and water excreted.

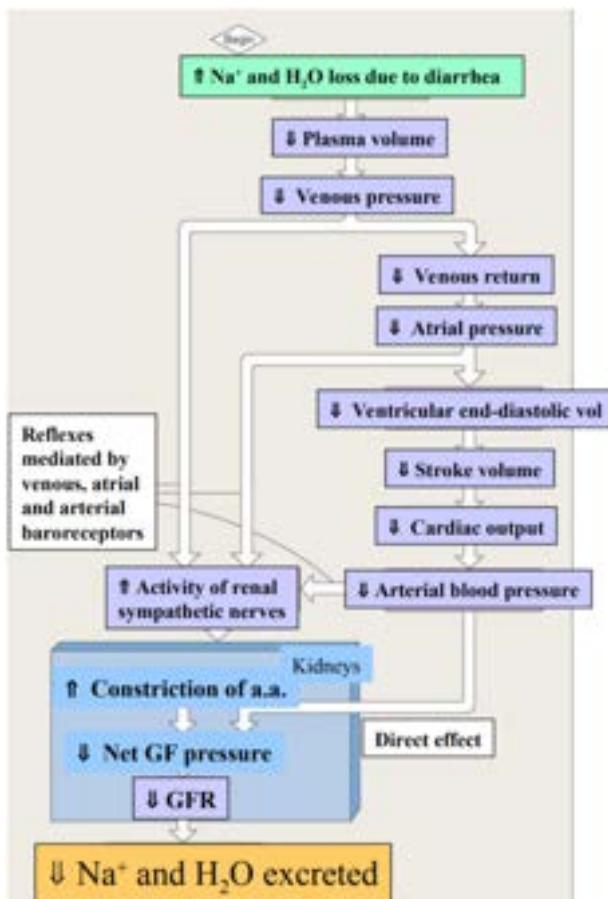


Figure 5.20: Na^+ excretion regulation via GFR diagram.

Remark 5.6. The signalling between different pressures and the renal SN is mediated by various atrial and venous baroreceptors.

Regulation via Reabsorption

The key hormone in reabsorption control is **aldosterone** made by the adrenal cortex, zona glomerulosa. Aldosterone stimulates Na^+ reabsorption in the DCT and CCD. If aldosterone is not present, 2% of filtered load is excreted which is around 35g of Na^+ i.e. excretion is too high. When aldosterone is high, almost 0% is excreted.

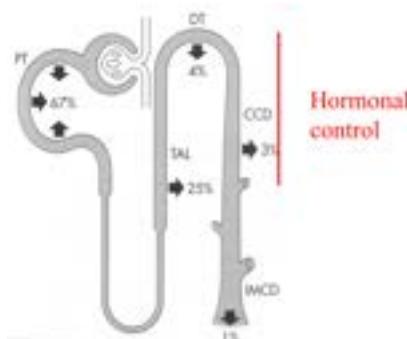


Figure 5.21: Na^+ excretion regulation by reabsorption.

To visualize this, we have 67% is reabsorbed in the proximal tubules (PT), 25% in the tubular ascending limb (TAL), 4% in the distal tubules (DT), 3% in the CCD and finally only 1% is left for excretion.

So how does aldosterone regulate? Well...aldosterone can be upregulated and activate the Na^+/K^+ ATPase as well as Na^+ and K^+ channels. Essentially, it increases reabsorption Na^+ as well as K^+ and H^+ secretion. This becomes relevant with a disease called **primary hyperaldosteronism**. This disease is characterized by an increase in blood pressure due to high Na^+ reabsorption but low K^+ and H^+ secretion (**metabolic alkalosis**). This is what aldosterone do but now there's must be a reverse link from Na^+ to aldosterone regulation.

The link of Na^+ to aldosterone regulation is through the **renin-aldosterone system (RAS)**. Here, we have aldosterone made in the adrenal cortex and its secretion is stimulated by many factors but predominantly **angiotensin II** which is the catalyzed form of **angiotensin I** made by **angiotensin converting enzymes (ACE)**. However, the rate limiting step to aldosterone secretion is before that which is the conversion of **angiotensinogen** to an-

giotensin I by **renin**. Renin is secreted by the kidney in response of vasular filling.

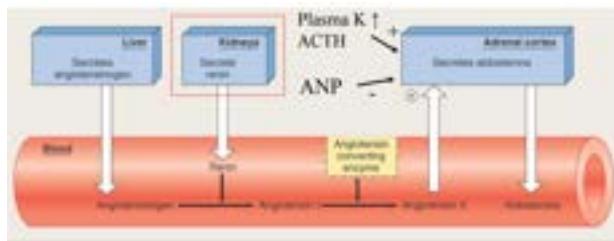


Figure 5.22: Secretion of aldosterone is limited by the secretion of renin by the kidney.

Where does renin comes from? Well...it's from the juxtaglomerular apparatus. Looking at the juxtaglomerular apparatus, we see the tubule (ending of the TAL and beginning of the distal convoluted tubule) connected via mesangial cells to the afferent and efferent arterioles at the Bowman's capsule. Focusing on the afferent arteriole, we can see green cells which are **juxtaglomerular cells** that does renin secretion.

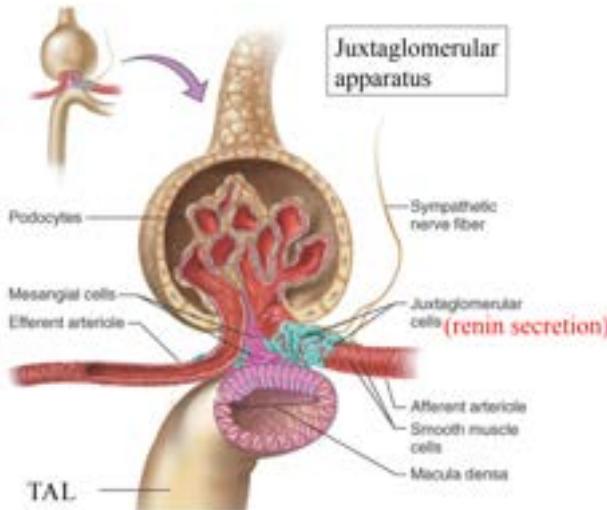


Figure 5.23: Juxtaglomerular apparatus and renin secretion.

The activation of this cells is made by 3 components: first, you have

sympathetic nerve fiber activating it but also cause afferent arteriole constriction. Second, you have column-like cells in the TAL called **macula densa** that can send signals within the tubular lumen to the juxtaglomerular cells. Third stimulus comes from vascular tension i.e. if blood pressure goes down, cells activation goes down hence lower renin secretion.

So to summarize this, you have a decrease of plasma volume then through the first diagram (Figure 5.20), renal SN is activated, arterial pressure and GFR decreased which means less NaCl is delivered to the macula densa. All of these 3 pathways lead to renin secretion which lead to increase plasma angiotensin II. An increase in angiotensin II increase aldosterone production and secretion to the plasma which increases Na^+ and water absorption and subsequently decreases their excretion.

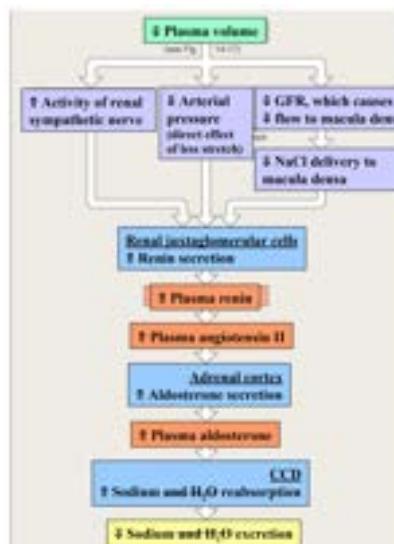


Figure 5.24: Renin secretion regulation and Na^+ reabsorption.

Remark 5.7. *Aldosterone does not stimulate water reabsorption in the CCD directly.*

Lastly, there are other pathway to regulate Na^+ excretion. First, it is through **Atrial natriuretic peptide (ANP)** which is a peptide hormone secreted by cells in the cardiac atria. ANP inhibits reabsorption of Na^+ in

the kidney and increase GFR (opposite of aldosterone). Its secretion is stimulated by a high total body Na^+ .

Second is high blood pressure which can lead an increase of Na^+ excretion in the kidney. Nevertheless, we must note that this can only occur at dangerously high blood pressure e.g. 220 systolic.

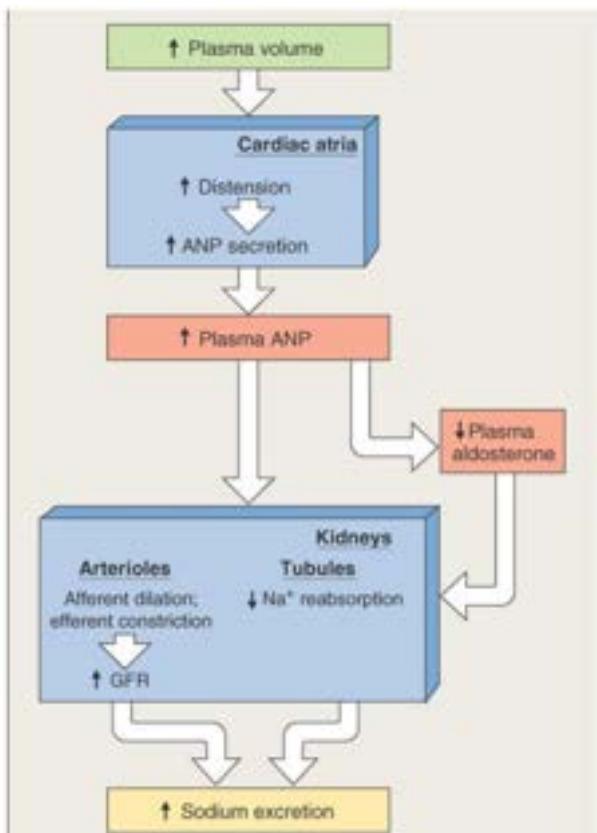


Figure 5.25: Effects of ANP on Na^+ secretion.

5.4 Regulation of Water Balance

Today's subject is water balance by the renal system but before that, we need to establish some terminology.

- **Osmolarity:** total solute concentration of a solution; measure of water concentration in that the higher the solution osmolarity, the lower the water concentration.
- **Hypoosmotic:** having total solute concentration less than that of normal extracellular fluid (300 mOsm).
- **Isoosmotic:** having total solute concentration equal to that of normal extracellular fluid.
- **Hyperosmotic:** having total solute concentration greater than that of normal extracellular fluid.

5.4.1 Water Reabsorption

We've looked at the the balance between input and output of water previous lecture where urine output has the most effect and is the only output that's controllable by the body. Water regulation is similar to Na^+ . It's freely filtered but 99% is reabsorbed in the proximal tubule (2/3 the total reabsorption). The major hormonal control of water reabsorption is in the collecting duct (CD).

The most important about water reabsorption is that it's a passive process at all time but is dependent on Na^+ reabsorption. Look at the PT, initially, we have the initiation of Na^+ / K^+ ATPase on the basolateral membrane. This makes the Na^+ concentration in the epithelial cells to decrease which makes Na^+ in the tubule lumen to be reabsorbed. When Na^+ left and goes into the interstitial fluid, the tubular lumen's osmolarity decreases while the interstitial osmolarity increases. This different in osmolarity causes net diffusion of water from the lumen into the interstitial fluid follow either the transcellular or paracellular pathway. From the interstitium, water, Na^+ and others can move into the peritubular capillary via bulk flow.

The body needs to maintain a good water balance i.e. input matches output. When water intake is small, its output as urine will be low (e.g. 0.4L) which means that the kidney reabsorbs more water. On the other hand,

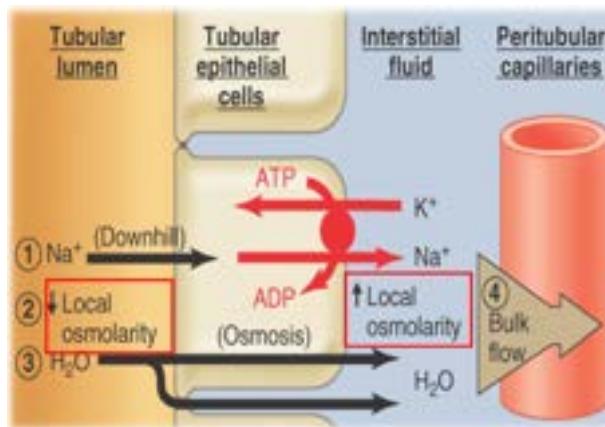


Figure 5.26: Water reabsorption dependent on Na^+ reabsorption.

when water intake is high, its output as urine will be high (e.g. 25L) which means that the kidney reabsorbs less water. This regulation of reabsorption takes place in the CD and is dependent on 2 components: **osmolarity of the interstitium and CD's water permeability (by vasopressin)**.

5.4.2 Countercurrent Multiplier System

The **countercurrent multiplier system** is a system that allows the build up of solutes in the interstitium and concentrate water. The kidney has the ability to concentrate urine up to 1400mOsm/L (more than 4x that of blood osmolarity). Majority of these concentration takes place when the tubular fluid passes through the medullary collecting duct and is **dependent on the hyperosmolarity of the interstitial fluid**. Not only that, In the presence of vasopressin, water diffuses out of the ducts into the interstitial fluid in the medulla to be carried away.

How does the medullary interstitial fluid become hyperosmotic ?

Well...it's because of the function of the Henle's loop. Before looking at the mechanism, let's see briefly on the anatomy of the Henle's loop. First, starting the proximal tubule, it will descend deep into the medulla via the descending limb. Then, it will loop back up via the [thick] ascending limb and then goes to the distal convoluted tubules.

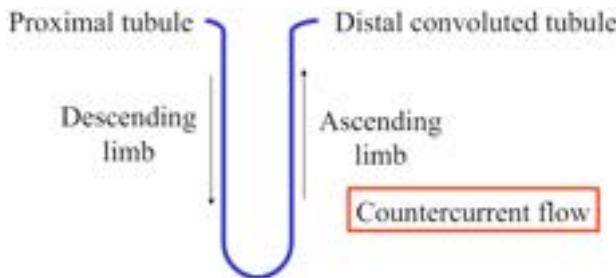


Figure 5.27: Anatomy of the Henle's loop

Remark 5.8. Descending and ascending limb, though part of the Henle's loop, do not have different properties regarding water and Na^+ permeability.

We can now look at the countercurrent multiplier system.

Mechanism of Action (Countercurrent multiplier system): Starting in the ascending limb where NaCl reabsorption is very active but impermeable to water the luminal fluid becomes hypoosmotic while interstitial fluid become hyperosmotic due to the movement of NaCl . Then, at the descending limb, where water is permeable while NaCl reabsorption is low, water will move into the interstitial fluid due to its hyperosmolarity. Because water left the luminal fluid, it's now hyperosmotic which will become hypoosmotic in the ascending limb. In general, isoosmotic luminal fluid from the proximal enter the descending limb becomes hyperosmotic then hypoosmotic as it leaves the ascending limb.

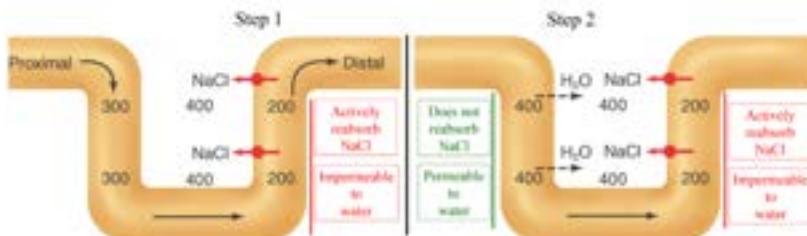


Figure 5.28: 2 major steps in countercurrent multiplier system.

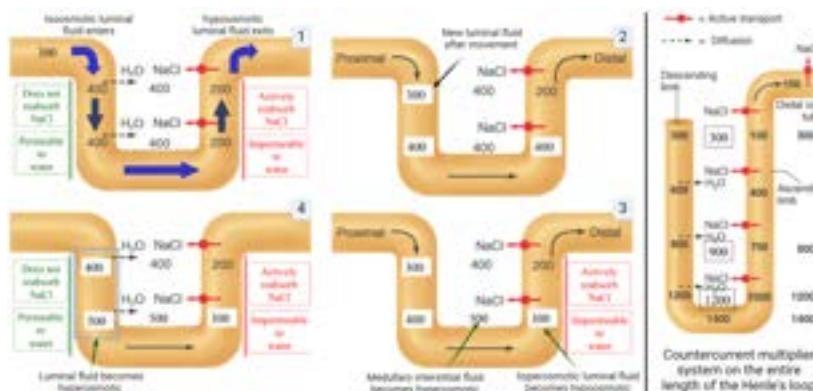


Figure 5.29: Countercurrent multiplier system detailed illustration.

Remark 5.9. *The maximum osmolarity that the kidney can concentrate is dependent on the length of the Henle's loop (proportionate to its body).*

Example 5.4.1. Mouse that lives in the desert requires its body to have the highest water reabsorption. This is also why we can see that their loop is much longer (proportionate to the body) and its maximum medullary osmolarity reaches up to 3000mOsm/L.

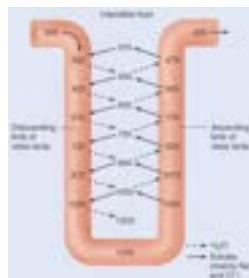


Figure 5.30: Vasa recta illustration.

Before moving onto vasopressin, we need to talk about a hairpin-shaped vascular system that runs parallel with the loop of Henle and is a branch of peritubular system called **vasa recta**. It can provide nutrients and oxygen to tubular epithelial cells but also receive all of the released material from the tubules. The numbers in the illustration of vasa recta might be intimi-

dating but all you need to realize is that it minimizes the washout of solute from the medulla.

Remark 5.10. Though we've only mentioned NaCl as one of the solute for hyperosmolarity of the medulla, there's also urea that does the contribution.

5.4.3 Water Permeability of the Tubules

Water reabsorption depends on the water permeability of the tubules. This permeability depends on where along the tubular segment you are e.g. proximal tubules has high water permeability. The water permeability property of a tubule largely depends on the presence of water channels (termed **aquaporins**) in the plasma membrane (also depends on the tightness of tight junction but not so important). Water permeability, mediated by aquaporins, in the cortical and medial collective duct (CCD and MCD respectively) is under a hormonal control of **vasopressin**.

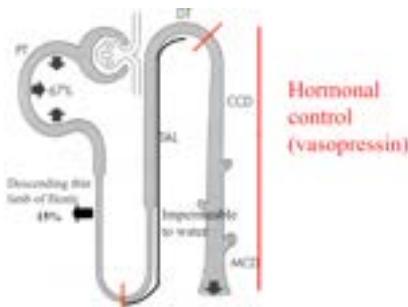


Figure 5.31: Water reabsorption along tubular segment. First water is permeable in the proximal tubule till the descending limb. Then it becomes impermeable in the ascending limb and part of the distal tubule. Finally in the CCD and MCD, it's permeable but under vasopressin control

Vasopressin is a peptide, anti-diuretic hormone (ADH). It's made by a group of hypothalamic neurons then carried down and released from the posterior pituitary gland. These vasopressin can bind and couple to GPCRs V1 located in smooth muscle and V2 in the kidney. Upon coupling and activation, it will stimulate the insertion of aquaporins in the luminal membrane of the collecting duct cells thus increases water permeability.

Essentially, when vasopressin is present, collecting ducts become water permeable leading to water reabsorption. On the contrary, when vasopressin is not present, collecting duct is water impermeable leading to **water diuresis**. In fact, **diabetes insipidus** is caused by malfunction of the vasopressin system (something wrong with vasopressin secretion or its receptors).

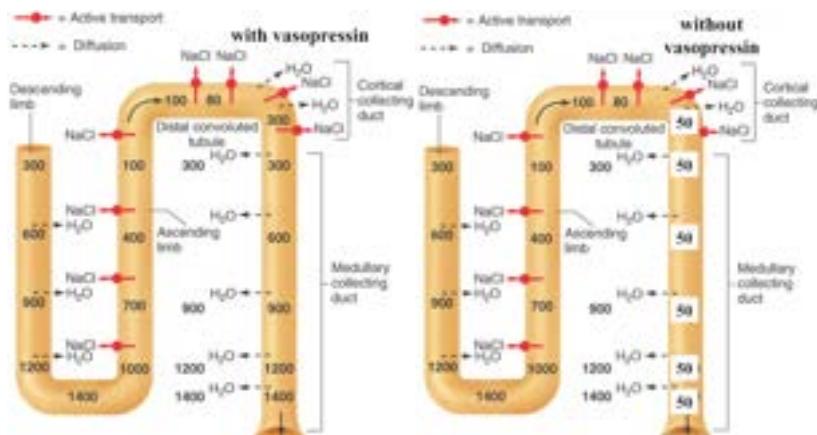


Figure 5.32: Differences in luminal fluid osmolarity with and without vasopressin.

If we look at the tubules with vasopressin, after luminal leave the loop of Henle and is now hypoosmotic, it will become further hypoosmotic due to the action of distal tubule. Nevertheless, when it reaches CCD and MCD under the influence of vasopressin, we can see a massive removal of water into the interstitial fluid thereby increases the luminal fluid all the way to 1400mOsm/L. Wait...**how come then the interstitial fluid not become diluted?** Well...it's because of the vasa recta uptake of this released water. On the other hand, when vasopressin is not present, hypoosmotic luminal leaving the distal tubule will have no modification and stay hypoosmotic (roughly 50mOsm/L).

5.4.4 Regulation of Vasopressin

Water excretion is mainly regulated by the rate of water reabsorption from the tubules. Vasopressin regulates this rate. Hence, **vasopressin is a major regulator of water excretion**. This also mean regulate vasopressin secretion also regulate water reabsorption rate, and there are 2 mechanisms: osmoreceptor (more important) and baroreceptor (less sensitive) control.

Starting with the osmoreceptors, supposed that we consumed excess amount of water. First, the total body fluid osmolarity will decrease which lead to the activation of hypothalamic osmoreceptors. This activation decreases vasopressin secretion from the posterior pituitary gland thereby de-

crease plasma vasopressin concentration. This ultimately decrease tubular water permeability and reabsorption therefore increases water secretion (increase urine volume). This system is sensitive and can be triggered by a change of only 1-2% of plasma osmolarity.

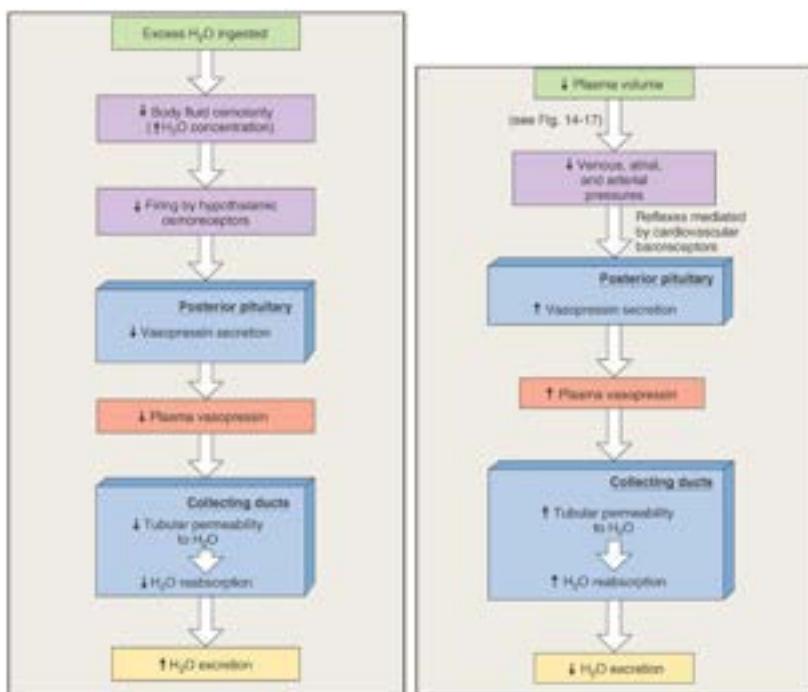


Figure 5.33: Vasopressin secretion control by osmoreceptors and baroreceptors.

With baroreceptors, it's less sensitive; let's say that there's a decrease in plasma volume, maybe due to diarrhea or hemorrhage. So a decrease in plasma volume will decrease venous, arterial and atrial pressure which decreases baroreceptors activity. The decrease in its activity can be sensed by the posterior pituitary gland which increase vasopressin secretion and thus increase tubular water permeability and reabsorption therefore decreases water secretion (decreases urine volume).

Why do we feel thirsty?

Well...Because it doesn't really matter how hard vasopressin is working if the body is not intaking water. **Thirst** is a very important mechanism to maintain water balance and can be stimulated by many stimuli, one of the most important is plasma osmolarity e.g. when you eat very salty food, plasma osmolarity goes up which can be sensed by the osmoreceptors and lead to the thirsty sensation. Another stimuli that's important is through dry mouth and throat. On the other hand, we have a mechanism called metering of water intake by GI tract that can stop thirst e.g. when you drink water, even before water reabsorbed, your thirst is already over.

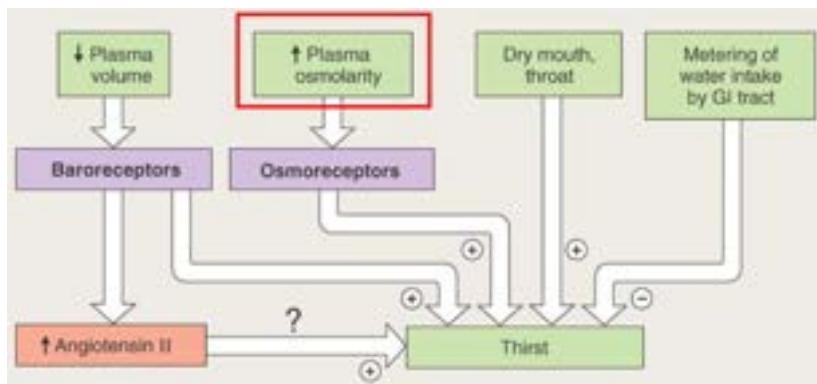


Figure 5.34: Stimuli that trigger thirst.

Remark 5.11. As people age, these sensing mechanism for thirst becomes weaker which is why many elderly may fall ill or die because of a heat wave.

What about sweating?

Well...sweating is a combination of loss of water (primary) and Na^+ . When you have severe sweating, you will have have 2 scenarios: increase plasma osmolarity but also decrease plasma volume. First, when plasma osmolarity increases, vasopressin secretion will be stimulated lead to decrease water excretion and increase its reabsorption. When plasma volume decreases due to decrease in Na^+ , it trigger a decrease of GFR and plasma aldosterone which also lead to decrease Na^+ excretion and increase its reabsorption.

We can see that the normal value of Na^+ plasma concentration is around 140mEq/L but if a person sweat a lot, their Na^+ concentration can go up to 150mEq/L. **Does that mean they have more sodium in the body?** Well...no because they sweating lead to bigger loss of water than Na^+ . For this reason, Na^+ plasma concentration is not a good marker for the total Na^+ in the body.

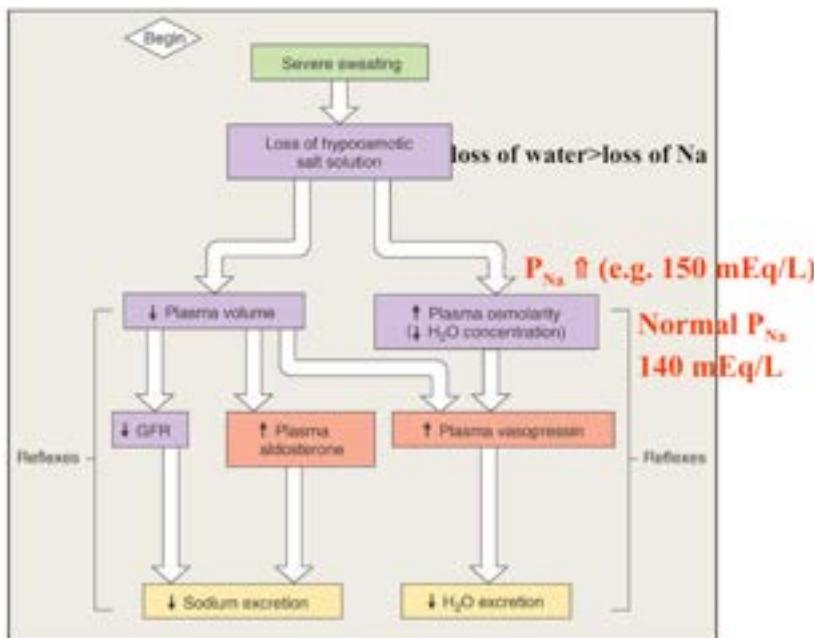


Figure 5.35: Severe sweat illustration.

End of Lecture —

5.5 Regulation of Potassium

In today's lecture, we will look at the regulation of potassium then we end with some regulation on hydrogen ion.

Potassium (K^+) is the most abundant intracellular ion (98% in the ICF and only 2% in the ECF). Even at a small amount, K^+ concentration in the extracellular fluid is extremely important for the function of excitable tissues (nerve and muscle). This is because the resting membrane potentials of these tissues are directly related to the relative intracellular and extracellular K concentrations. With that, it's necessary to control this small amount of K^+ otherwise there might be major issues with muscles and nerves.

Definition 5.5. **Hyperkalemia** is defined as a high concentration of K^+ in the ECF ($> 5\text{mEq/L}$) while **hypokalemia** is a low concentration of K^+ in the ECF ($< 3.5\text{mEq/L}$).

In either case, they cause abnormal rhythms of the heart as well as abnormal skeletal muscle contraction.

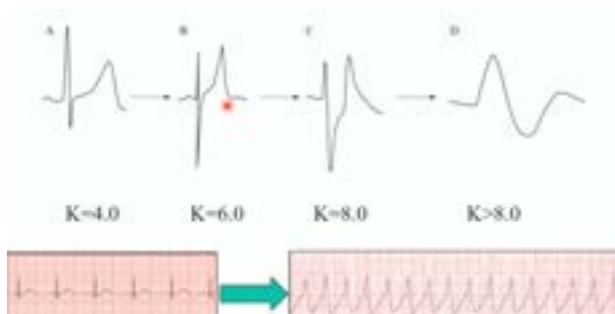


Figure 5.36: Hyperkalemia lead to VTAC and then cardiac arrest

Looking at the ECG of a patient with normal K^+ concentration, we can see the typical P, QRS and T wave. As they become hyperkalemic at $[K^+]=6.0$, we can first see the elevation of the T-wave. At $[K^+]=8.0$, their QRS complex becomes very wide. When $[K^+]$ gets extremely high, you will get an ECG that's sinusoidal-like and is indicative of **ventricular tachycardia (VTAC)** and can lead to **cardiac arrest**. Hypokalemia is also dangerous but not as drastic.

5.5.1 Potassium Secretion

Majority of K^+ we get is through dietary intake e.g. food that are rich in potassium include: banana, papaya, starfruits, pineapple and watermelon. Most of K^+ output is through urine excretion (90%) while the rest is through feces and sweat. This is also the reason why the control of K^+ level is mediated by the renal system.

Like Na^+ and water, K^+ is freely filtered at glomerulus. Normally, the tubules reabsorb most of this filtered K^+ so that very little of it appears in the urine. Even then K^+ can be secreted at the CCD which means that changes in K^+ excretion is due to K^+ secretion in the CCD and some in the DCT (these are the 2 segments under aldosterone controlled for Na^+ reabsorption). The net reabsorption of K^+ is a wide range of 15 – 99% which corresponds to the K^+ intake i.e. high K^+ intake lead to lower reabsorption and v.v., but under normal condition the reabsorption on average is 86%

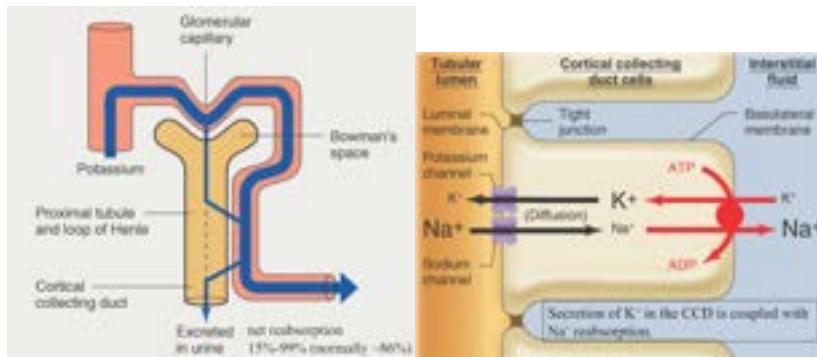


Figure 5.37: Secretion of K^+

Looking at the CCD, we begin, like always, with the Na^+/K^+ ATPase which will bring Na^+ into the ISF while K^+ to the epithelial cell interior. Here, as K^+ build up, it will be drained into the tubular lumen via K^+ channels.

Remark 5.12. K^+ secretion is always coupled with Na^+ reabsorption in the CCD.

This secretion process is regulated by dietary intake of K^+ but also more importantly, aldosterone.

5.5.2 Aldosterone Effects on Potassium

Supposed that a person increased their intake of K^+ . First, plasma K^+ level rises which trigger the adrenal cortex to secret lots of aldosterone. Aldosterone, secreted to the plasma, will travel to the CCD which and increase K^+ secretion. There's a second pathway where an increase in K^+ can directly increase K^+ secretion in the CCD. In both case, it will drive up K^+ secretion.

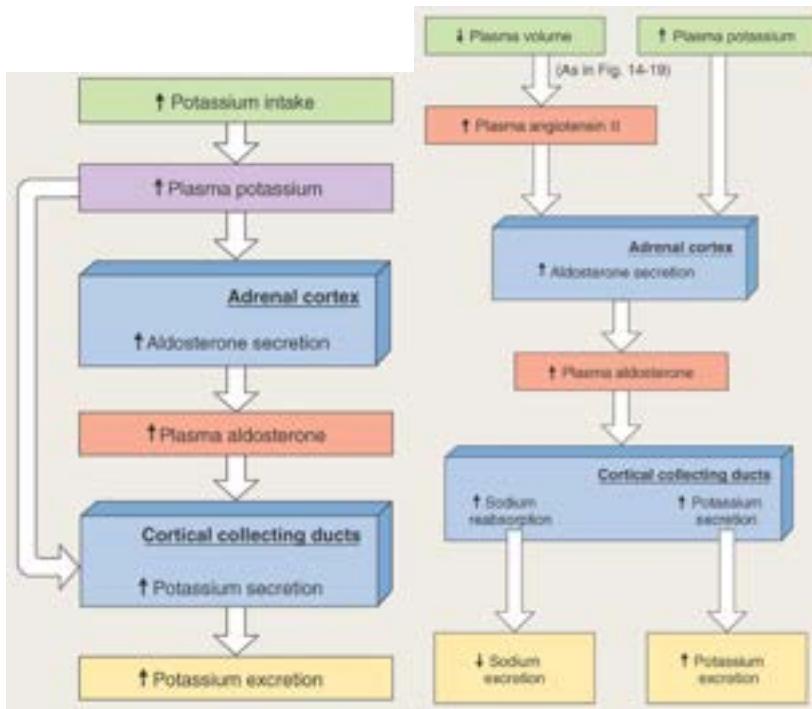


Figure 5.38: Regulation of K^+ by aldosterone and other causes

Interesting if we increases plasma volume, we would increase plasma angiotensin II which increase aldosterone and hence lead to increase K^+ secretion. Now, the figure shown is quite misleading (not wrong) because in a way, it's suggesting that if you have volume depletion, you'd lose a lot of K^+ which lead to hypokalemia. The truth is, when you have decrease plasma volume, it's because of a decrease of Na^+ in plasma. When there's a decrease in plasma Na^+ , not a lot of Na^+ will be delivered to the; CCD

but because you need Na^+ to couple with K^+ secretion, you won't have hypokalemia even when lots of aldosterone is forcing K^+ secretion.

The condition can lead to patients developing hypokalemia is called **hyperaldosteronism** which is characterized by a hyper-release of aldosterone. The most common cause of this is adenoma of the adrenal gland that produces aldosterone autonomously. What this condition will do is increase fluid volume, hypertension, hypokalemia and renin is completely suppressed. We can often observe in these patient **metabolic alkalosis**

5.6 Regulation of Hydrogen Ion I

Metabolic reactions are highly sensitive to the hydrogen ion (H^+) concentration of the environment. Therefore, H^+ concentration of the ECF is tightly regulated of around pH 7.4 and $[H^+] \sim 40\text{nmol/L}$.



In order to understand regulation of H^+ , we need to look at an important mass reaction that occurs a lot in our body and that's the conversion of CO_2 and water to H^+ and bicarbonate. To begin with, CO_2 can combine with H_2O via an enzyme called **carbonic anhydrase** to form **carbonic acid** (H_2CO_3). This carbonic acid and rapidly be broken down into **bicarbonate** HCO_3^- and H^+ . Interestingly, regulation of H^+ is actually dependent on the regulation of HCO_3^- e.g. When HCO_3^- is lost from the body, the above equation will favour the creation of new product which lead to increase production of more HCO_3^- and H^+ . On the other hand, when the body gain HCO_3^- , above equation will favour creation of reactants which lead to increase metabolism of H^+ and HCO_3^- back to CO_2 and H_2O . So essentially, HCO_3^- concentration always inversely impacts the H^+ concentration.

There are many sources of H^+ gain but also loss which is demonstrated in the table below. Here we have H^+ generated from CO_2 , production of **non-volatile acids** (does not turn into gas easily) from proteins and other materials metabolism, loss of HCO_3^- in urine and in diarrhea and other organic molecules.

TABLE 14-7 Sources of Hydrogen Ion Gain or Loss

Gain
1. Generation of hydrogen ions from CO_2
2. Production of nonvolatile acids from the metabolism of protein and other organic molecules
3. Gain of hydrogen ions due to loss of bicarbonate in diarrhea or other nongastric GI fluids
4. Gain of hydrogen ions due to loss of bicarbonate in the urine
Loss
1. Utilization of hydrogen ions in the metabolism of various organic anions
2. Loss of hydrogen ions in vomitus
3. Loss of hydrogen ions in the urine
4. Hyperventilation (loss of CO_2)

5.6.1 Buffering

When it comes to non-volatile acids in the body, we have many like: **phosphoric, sulfuric and lactic acids**. These are constantly made and consumed by our body and they also contribute H^+ to our body at a net production rate of 40 – 80mmol/day. This may not look very much but considering the range that your body need to keep H^+ at is only 40nmol, 40 – 80mmol is enormous.



Evidently, it's not good to have this much acid in your body so we need a *buffering* mechanism to remove that H^+ load. Anything can be a buffer as long as it binds reversibly to H^+ . When there's excess H^+ released, these extra- and intracellular buffers will come and neutralize them to keep the normal ECF pH of 7.4 only. Even a minute change in pH from 7.4-7.1 can lead to severe consequences to the body.

These extra- and intracellular buffers that we've mentioned are HCO_3^- ; phosphates and proteins respectively. It's important to realize that **buffering does not remove H^+ but only store it temporarily**. (see equation above as demonstration).

$$\text{pH} = -\log [\text{H}^+] \quad (5.8)$$

Above is the equation that tie pH and $[H^+]$ together.

The way to deal with the acid load and remove them completely is through the respiratory system (by controlling CO_2) and renal system (by controlling HCO_3^-). Both system will work together to minimize changes in H^+ (pH) but we'll only focus on the renal system for obvious reason.

5.6.2 Renal Mechanism of Hydrogen Ion Control

The renal mechanism of H^+ control is very simple and it's through controlling HCO_3^- . When you have low $[H^+]$ (or high pH which is **alkalosis**), the kidneys will excrete more HCO_3^- ; and we've previously said, this will lead to increase production of HCO_3^- and H^+ . Meanwhile, when you have high $[H^+]$ (or low pH which is **acidosis**), they kidneys will produce new HCO_3^- and add to the plasma; this will drive up the usage of H^+ and HCO_3^- making CO_2 and H_2O . This concept is related to the *Henderson-Hasselback equation* which allow us to determine plasma pH using HCO_3^- and CO_2 concentration and it's given as the following

$$pH = 6.1 + \log_{10} \frac{[HCO_3^-]}{[CO_2]} \quad (5.9)$$

or

$$pH = -\log_{10} K_a + \log_{10} \frac{[HCO_3^-]}{0.03[CO_2]} \quad (5.10)$$

where [x] is the concentration (mmol/L) of the substance x (with the second equation $[CO_2]$ is measured in mmHg), K_a is the dissociation constant for CO_2/HCO_3^- system and 0.03 is the solubility of CO_2 at $37^\circ C$.

In the kidney, the amount of HCO_3^- excreted is equal to the amount filtered, add with amount secreted and finally subtracted with the amount reabsorbed. We won't care much about the amount secreted because it doesn't happen as often. Let's start in the proximal tubular epithelial cells. So there's water and CO_2 everywhere in its lumen and also an abundant of HCO_3^- . These carbonic acids will generate HCO_3^- and H^+ vigorously. There's also some HCO_3^- in the tubular lumen because it's freely filtered and reaches the proximal tubules. Along the wall of this tubule is called **brush border** and is rich the carbonic anhydrase that can perform the reverse reaction to produce H^+ and HCO_3^- . So **what's responsible to bring out the H^+ ?** Well...it's mediated by either Na^+/H^+ antiporter or H^+/K^+ -ATPase. As

for the HCO_3^- in the epithelial cell, it will be transported to the interstitium through a channel down its concentration gradient and eventually carried away by peritubular capillaries.

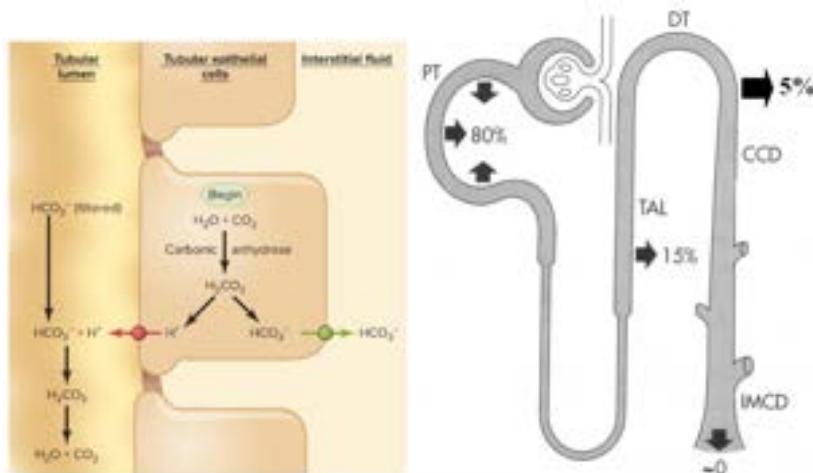


Figure 5.39: H^+ control in the kidney and HCO_3^- reabsorption at different tubular segment.

So what happens here is that as 1 HCO_3^- arrives to the proximal tubules post-filtration, 1 HCO_3^- will reappear in blood. Normally, the kidneys reabsorb all filtered HCO_3^- i.e. by the time luminal fluid leaves the proximal tubule, there's no HCO_3^- left. These reabsorptions happen most of the time except in the cases of alkalosis where HCO_3^- is excreted out. Like other ions such as Na^+ , proximal tubules do majority of the reabsorption (80%), 15% is from the ascending limb, and 5% left is in the CCD.

What we see here is no new HCO_3^- is being generated but we need to generate more to buffer the 40 – 80 mmol of new non-volatile acids each day so **how can we compensate?** Well...the kidney has 2 ways to make new HCO_3^- to the plasma: secrete and excrete H^+ on non- HCO_3^- buffers (e.g. phosphate) and glutamine metabolism with NH_4^+ excretion. In both processes, they're viewed by the body as H^+ excretion by the kidney and together they will contribute new HCO_3^- to compensate generation of non-volatile acids in the body.

Synthesis of New Bicarbonate to Plasma

In the first mechanism, it happens when all of the HCO_3^- has been reabsorbed and no longer available in the lumen. When this happened, the same mechanism as before occurred, that is, catalyze water and CO_2 to make carbonic acid that rapidly dissociate into H^+ and HCO_3^- . This new HCO_3^- can leave into the interstitial space. Wait...so what's the difference? Well...the difference is when H^+ leaves into the tubular lumen where it will bind to **hydrogen phosphate HPO_4^{2-}** to form dihydrogen phosphate (precursor to phosphoric acid) to be excreted instead.

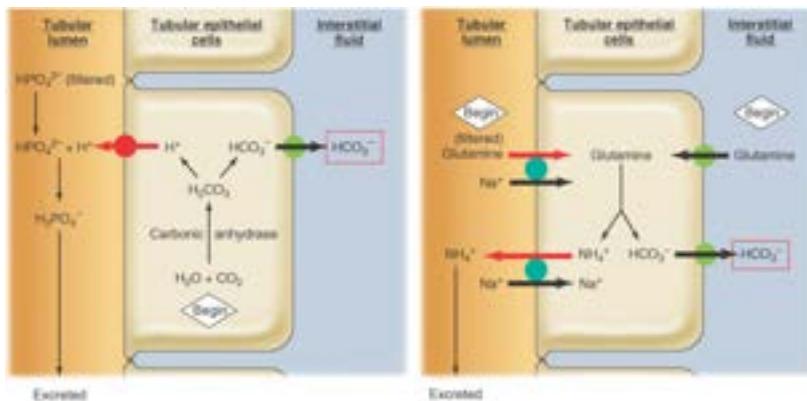


Figure 5.40: 2 mechanisms to synthesize new HCO_3^- .

In the second mechanism, you have freely filtered amino acid that will be 100% reabsorbed and 1 of these amino acid is **glutamine**. When glutamine is brought to the tubular epithelial cells (mainly proximal tubules) from either the tubular lumen or interstitial space, it will be broken down into ammonia (NH_3) and HCO_3^- . The newly made HCO_3^- can leave to the interstitium and that's the end. Another way to think of this is when NH_3 is made, it can bind to 1 H^+ to form NH_4^+ which leaves to the tubular lumen and excreted out i.e. elimination of H^+ . This process is called **H^+ excretion bound to NH_2** .

5.7 Regulation of Hydrogen Ion II

In this lecture, we will finish about the regulation of H^+ and then finish off with diuretic and kidney diseases.

Definition 5.6. When there's low H^+ concentration, pH is high which is **alkalosis**. **Acidosis** is the exact opposite where pH is low (high $[H^+]$).

Alkalosis and acidosis can be caused by respiratory and metabolic problems. In both respiratory alkalosis and acidosis, it's a result from altered respiration while both metabolic alkalosis/acidosis is due to other cause that lead to an increase/decrease of the body's pH respectively.

5.7.1 Renal Response to Alkalosis and Acidosis

When there's too much H^+ due to alkalosis, sufficient H^+ will be secreted to reabsorb all the filtered HCO_3^- . Still more H^+ are secreted and this contributes new HCO_3^- to the plasma as these H^+ are excreted bound to non- HCO_3^- buffer such as HPO_4^{2-} . You can also have tubular glutamine metabolism and ammonium excretion are enhanced which make more HCO_3^- to the plasma. The outcome is that there will be a net of more HCO_3^- added to the plasma to compensate acidosis. We can in fact see **urine becomes acidic (pH 4.4)**.

in response to alkalosis, the opposite will occur. First, Rate of H^+ secretion is inadequate to reabsorb all the filtered HCO_3^- , so the significant amounts of HCO_3^- are excreted in the urine. There is little or no H^+ secretion on non- HCO_3^- urinary buffers. Tubular glutamine metabolism and ammonium excretion are decreased, so that little to no new HCO_3^- is contributed to the plasma from this source.

As a result, the net plasma HCO_3^- deceases which compensate for alkalosis. Like before, we can observe **urine becomes basic/alkaline (pH> 7.4)**.

PRIMARY DISORDER	H^+	HCO_3^-	CO_2	CAUSE OF HCO_3^- CHANGE	CAUSE OF CO_2 CHANGE
Respiratory acidosis	↑	↑	↓	Renal compensation	Primary abnormality
Respiratory alkalosis	↓	↓	↑	Primary abnormality	Reflex ventilatory compensation
Metabolic acidosis	↑	↓	↑	Primary abnormality	
Metabolic alkalosis	↓	↑	↓		

The above is the summary table of acidosis and alkalosis along with movement of substances. In either case of respiratory alkalosis and acidosis, the primary abnormality is due to changes of CO_2 and you can compensate this by the kidney. When it's metabolic (both), it's primary cause is

change in HCO_3^- and our body compensate by having the ventilation reflex.

Let's see how the above table is filled up. With acidosis, $[\text{H}^+]$ is always high; while in alkalosis, $[\text{H}^+]$ is always low. Now for respiratory, we can use the mass reaction equation and see that when we increase CO_2 , $[\text{H}^+]$ increases which is indicative for respiratory acidosis. Now, use the Henderson-Hasselbach (HH) equation, we can see that to minimize ΔpH , by increasing $[\text{CO}_2]$ we also need to increase $[\text{HCO}_3^-]$. Respiratory alkalosis is the opposite where you have a decrease in CO_2 leading to decrease of $[\text{H}^+]$ and with the HH equation, $[\text{HCO}_3^-]$ decreases.

	H^+	HCO_3^-	P_{CO_2}
Resp acidosis	↑	↑	↑
Resp alkalosis	↓	↓	↓
Met acidosis	↑	↓	↓
Met alkalosis	↓	↑	↑



$$\text{pH} = 6.1 + \log_{10} \frac{[\text{HCO}_3^-]}{[\text{CO}_2]}$$

For metabolic, we need to look at HCO_3^- instead of CO_2 . In metabolic acidosis, you have your HCO_3^- decreases which lead to reaction moving to the right generating more H^+ . To compensate this, CO_2 in the reactant side need to go in the same direction as HCO_3^- i.e. also decreases. In metabolic alkalosis, the opposite effect occur where an increase in HCO_3^- will cause body to compensate by increases CO_2 .

5.7.2 Clinical Example

The most common respiratory acidosis is **respiratory failure** [with CO_2 retention]; while for respiratory alkalosis is **hyperventilation** (e.g. climb to higher altitude). Interestingly, **we can also observe alkalosis in pregnant women**. Somehow, during pregnancy, the respiratory center is stimulated and produce a mild case of respiratory alkalosis.

Most frequent metabolic acidosis is caused by **diarrhea** (loss of HCO_3^-) and **renal failure** (accumulation of inorganic acids). On the other hand,

metabolic alkalosis is less common but the most frequent is **vomiting** and **[primary] hyperaldosteronism**.

5.8 Diuretic and Kidney Diseases

Definition 5.7. **Diuretic** is a class of drug to increase urine volume i.e. it causes diuresis.

Diuretics are the most commonly used drugs to deal with kidney disease. Its function through inhibition of reabsorption of Na^+ along with Cl^- and HCO_3^- which result in increase excretion of these ions. Because water is coupled with them, its excretion is increased too.

There are 2 classes: **Loop (most common)** and **K^+ -sparring**. Loop diuretics acts on the TAL of the loop of Henle. It inhibits the $Na^+-K^+-2Cl^-$ cotransporter and they're the most commonly used diuretics e.g. **Furosemide** is a type of loop diuretics commonly used. Just to recapitulate, it acts at the TAL where Na^+ reabsorption is at 25% but then **why don't we just do reabsorption in the PT?** Well...we do have drugs that do that; however, it's more effective to target the distal part. This is because that specific drug is not as powerful and if you have no absorption at PT, it's going to compensate at distal.

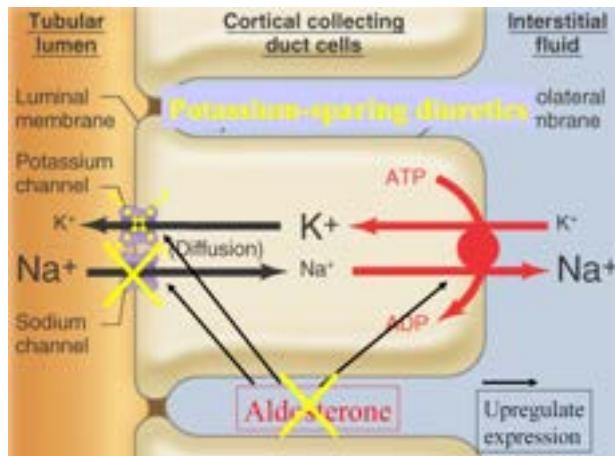


Figure 5.41: K^+ -sparring diuretics in CCD.

K^+ -sparring diuretics is a chemical class and not just 1 drug. It inhibits Na^+ reabsorption in the CCD and also K^+ secretion here. Unlike other diuretics that lead to hypokalemia (such as furosemide), $[K^+]$ in the plasma does not decrease. Looking at the CCD tubular epithelial cells, we can see all of the channel we've talked about before. If you block aldosterone with chemicals like **spironolactone**, you will block Na^+ reabsorption and K^+ secretion. Another way to do this is blocking the Na^+ channel alone through a chemical called **ameloride** and because Na^+ channel is coupled with K^+ channel, K^+ secretion is also inhibited.

5.8.1 Clinical Use of Diuretics

Diuretics is used when there's renal retention of salt and water that can lead to **edema**.

Example 5.8.1. When there's **congestive heart failure (CAF)**, patient previously experienced cardiac failure that lead to low CO which lead to accumulation of salt and water in the leg. Furthermore, in certain cases, you can have accumulation of fluid in the lung which can lead to shortness of breath.

Example 5.8.2. When patient experiences **hypertension**, it might be caused renal retention of salt and water. In this scenario, we don't use powerful drug such as furosemide but a different one called **thiazide** that acts on the DCT.

5.8.2 Kidney Failure

Definition 5.8. **Kiney failture** is a condition where your kidney lost its ability to filter waste product.

Some of the common symptoms from kidney failture are:

- **Proteinuria**, Proteins found in urine.
- **Waste product in blood** like urea, creatinine, phosphate, etc.
- **High blood $[K^+]$** .
- **Metabolic acidosis**.
- **Anemia** (decrease EPO secretion).

- **Decrease in 1,25-dihydroxyvitamin D secretion** (lead to **hypocalcemia**).

We call it renal failure when more than 90% of nephrons stop working (50% loss is fine which is why kidney donation is a thing), patient cannot sustain life so there must be intervention by a renal replacement therapy (RRT). There are mainly 3 types: **hemodialysis**, **peritoneal dialysis** and **kidney transplantation**.

5.8.3 Treatment of Kidney failure

Under **hemodialysis** treatment, patient first have surgeries to have their veins widened. After, they'll be hooked up onto a machine called the **dialyzer** through their widened vein and that's where cleaning of blood is going to happen. This circulate 3-4h per day and 3-4 times per week.

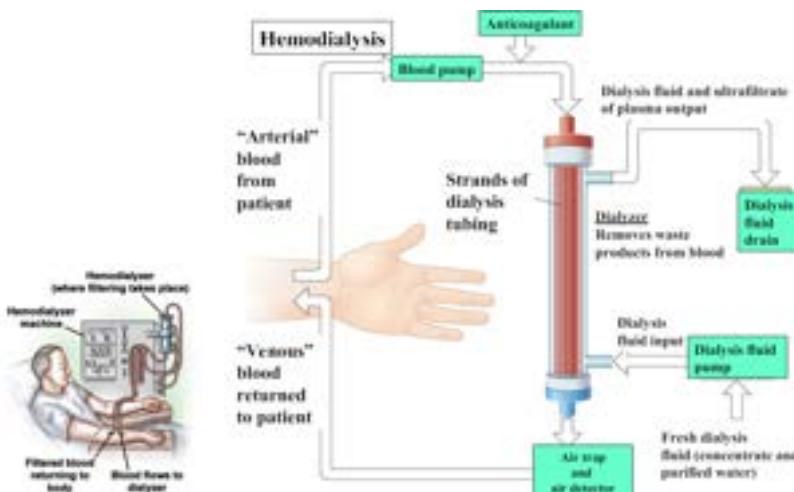


Figure 5.42: Hemodialysis simple mechanism illustration.

Looking at hemodialysis more closely, you have blood gets pump to the dialyzer at a rate of 350-400mL/min. To prevent coagulation, we add in anticoagulant such as **heparins**. This blood then goes through the dialyzer which is these hollow fibers. These membranes are semipermeable so you can pump in clea liquid called the **diaslyte** and exchange with the waste product. This will then return back to the patient.

Peritoneal dialysis is less known but is also important. In this dialysis, we use the peritoneal as the dialysis membrane. We basically infuse the dialisate directly to the peritoneal space; then, water and solute will exchange across the peritoneal space. In order to have this fluid injection, the patient will have a peritoneal catheter embedded in the abdomen. First, the dialisate is added in (around 2L) then the patient can disconnect from the injection and move around freely for a few hours. After, the fluid will need to be drained for fresh dialisate to come in.

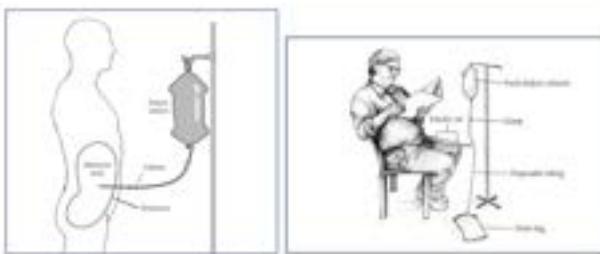


Figure 5.43: peritoneal dialysis illustration.

Nowadays, we have a cycler mediate this exchange automatically overnight. The advantage of peritoneal dialysis treatment is that you can perform it at home.

Both of these dialysis methods are life maintenance treatment but the best RRT currently is **kidney transplantation**. The kidney can come from either a deceased person (called **cadaveric transplant**) or from a living related/unrelated donor. The reason that we can do unrelated transplantation is because anti-rejection treatment has improved so much since the first transplantation. **Then why aren't we doing more kidney transplantation?** Well...because as of today, there's an organ shortage problem hence transplantation is hard to come by. Nevertheless, in the end, the transplanted kidney will function normally while the **donor can still go through daily life with 1 kidney.**

End of Lecture —

Note to Author: Good luck on your final exam on April 17th, 2024!!!



This course look at the physiology of cardiovascular, respiratory, digestive, endocrine and renal systems.

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