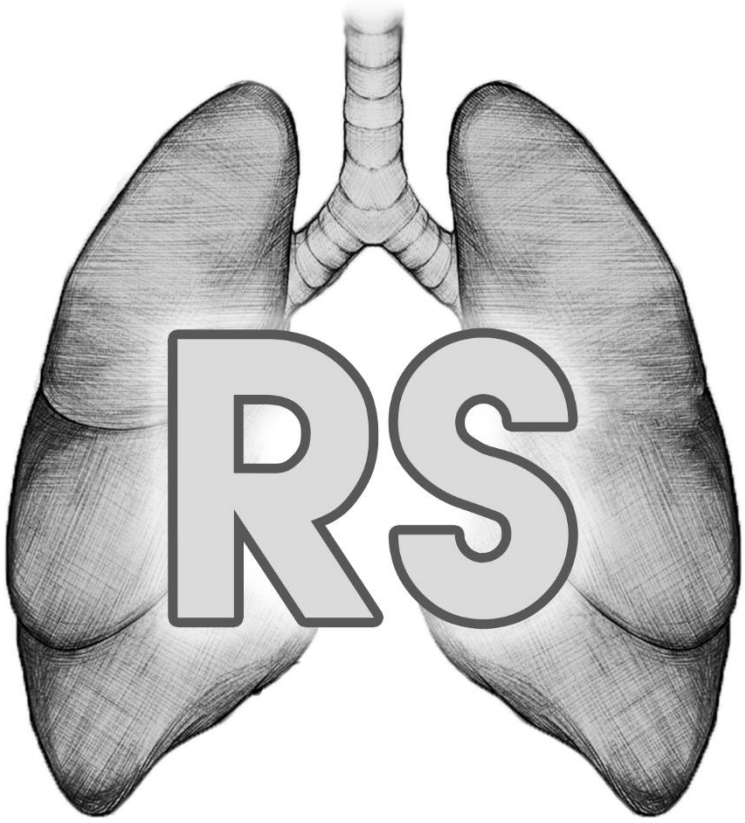

PHYSIOLOGY

☑ Sheet ○ Slide ○ Handout

Number

9

Subject

Control of Breathing

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Date: 00/00/2016

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بسم الله الرحمن الرحيم

Before we start …

●This sheet was written according to the recording of section 2

●The order of ideas in this sheet is a little bit different from that in the recording.

●I used multiple sources in this sheet (Section 2+3 records, Guyton, Costanzo) to make it comprehensive as much as I can.

●I've added some figures and curves to clarify some pointes, if you got confused with any figure, you can skip it. **Required figures are marked with star ☆**

●Enjoy

I. Introduction

●In very early lectures in this system, we said that the main purpose of having Cardiopulmonary system is to have normal arterial blood gases profile, i.e PO2= 100mmHg, PCO2=40 and pH=7.4.

- What's special about biosystems is that they are designed to resist sudden changes in their essential components through controlling (or buffering) systems, this is called ***homeostasis***.
- Studying and understanding regulation mechanisms is very important, as it's the main purpose of studying physiology for us as doctors.
- As you study any regulation mechanism in medical school, try to think about the best way to reach homeostasis, try to ask why do we have this structure or this system, and what are the possible situations that may alter this system? Your answers for these questions, probably, will describe our normal regulatory mechanism!

● So The purpose of the respiratory control system is the maintenance of homeostasis of Oxygen, CO2 and H+. In other words, it guarantees normal ABGs (Arterial Blood Gas values); **PaO2: 100 mmHg, PaCO2: 40 mmHg, pH: 7.4**

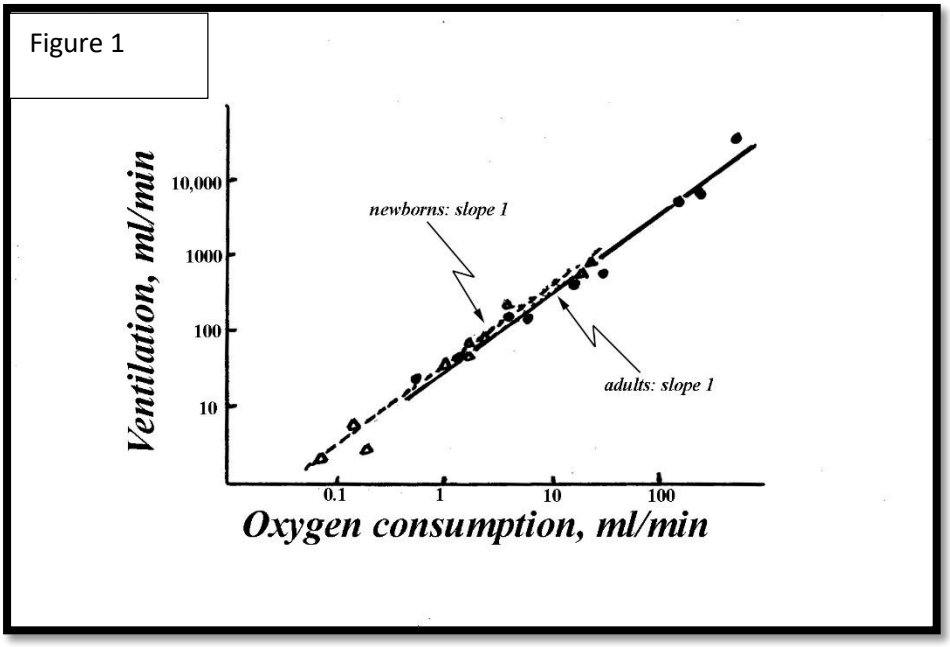
- These three elements will feedback to the respiratory center, which will stimulate or inhibit respiratory muscles.
- The tools the respiratory center will use to maintain normal ABGs are either ***increased ventilation or decreased ventilation***
- ***increased ventilation*** will try to increase PO2 up to 150 mmHg and decrease PCO2 to around 0, as long as you're breathing normal room air
- While ***decreased ventilation*** will try to shift PO2 and PCO2 to their values in venous blood (increase CO2 and decrease O2).

II. Blood gases homeostasis

A) Oxygen

•let's talk about each gas individually; arterial PO2 (and alveolar PO2 as well) depends on two variables; ***alveolar ventilation*** and ***oxygen consumption*** (see figure 1).

Figure 1



- The slope of this curve represents arterial PO2. Notice that, under normal regulatory mechanisms, PO2 levels are kept constant, despite the big variation in these components.

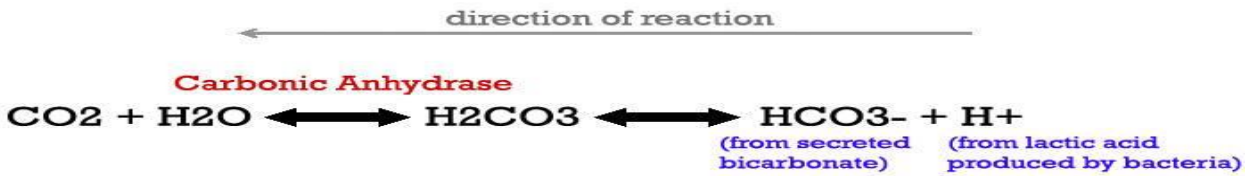
- Arterial PO2 is directly proportional to ***alveolar ventilation*** but <u>inversely</u> proportional to ***oxygen consumption***.
- Now if you wanted to increase arterial PO2, you have two choices, either you ***increase the rate of ventilation***, or ***decrease your oxygen consumption*** ***(***or both – Dr. Faisal style 😂).
- Similarly, if you wanted to decrease arterial PO2, you have two choices, either you ***decrease the rate of ventilation***, or ***increase your oxygen consumption***.
- But normally, arterial PO2 is kept around normal values because of our regulatory mechanisms; during exercise, for example, alveolar ventilation and oxygen consumption are increased in a proportional way, and thus not affecting arterial PO2 (the slope).

●Before talking about regulatory mechanisms in details, can you think about some mechanisms to regulate our arterial oxygen concentration?!

- As you know, most of oxygen is carried on hemoglobin, hemoglobin saturation curve is sigmoidal, so hemoglobin, by it self, is able to prevent increased oxygen concentrations in the plasma, and even decreased oxygen concentration as long as its PO2 is above 60mmHg.
- We can also put some chemoreceptors to sense any change in oxygen levels in the plasma.
- And finally, we have to find a way to tell the lungs " I'm doing extra efforts, So give me more oxygen please 😜"

B) Carbon dioxide and hydrogen

●As you know from biochemistry, blood CO2 and hydrogen concentrations are associated with each other, and strictly regulated through Carbon dioxide-Bicarbonate buffer system, through this equation:



●So CO2, and Hydrogen levels (or pH) are in equilibrium, If CO2 are raised, hydrogen concentration will go up and pH will drop. If hydrogen concentration increased, CO2 will go up and pH will fall.

- This buffer system is very important to maintain blood pH normal, as blood pH = -log[H], and its calculated through this equation:

Henderson Hasselbalch equation

$$pH = 6.1 + \log \frac{[HCO_3^-]}{0.03 \times paCO2}$$

#Note_1: 6.1 is the dissociation constant of carbonic acid.
#Note_2: For the CO2 we multiply by 0.03 (conversion factor), as each 0.03 mMol exerts partial pressure of 1 mmHg.

- This equation shows us how when CO2 increases, pH decreases.
- Despite this strict regulation, this buffer system my fail to maintain normal blood pH in some cases. In chronic situations, there's no problem as some other long term buffering systems will work. But In acute cases, it may cause big problems.
- Normal blood pH is 7.4, if it fall below 7.35 this will leas to acidosis. If it go above 7.45, it causes alkalosis.

●like oxygen, blood PCO2 is the product of two variables; CO2 production, and Ventilation.

- PCO2 is directly proportional to CO2 production, but inversely proportional to ventilation.
- So we can say that PCO2= CO2 production/alveolar ventilation × K (constant).

●As we will see later in this sheet, CO2 is the main regulator of respiration, so we define hyperventilation and hypoventilation according to alveolar CO2 levels.

- ***Hyperventilation*** occurs when CO2 production is less than CO2 wash out → decrease alveolar PCO2 → less CO2 → less H+ → higher pH.
- ***Hypoventilation*** occurs when CO2 production is more than CO2 wash out → increase alveolar PCO2 → higher CO2 → higher H+ → less pH.
- You have to be careful that hyper- and hypo- ventilation differ from increased or decreased ventilation.

Note: during exercise both hyperventilation and increased CO_2 production occur, which prevents the pH from changing

●But why it's important to maintain blood CO2 levels and pH at the normal ranges? (another way to ask this question is, *what are the effects of hypo- and hyper- Ventilation on a normal person?*)

- In cases of hypoventilation, CO2 retention will increase, so the rate of CO2 wash out will be less than CO2 production → higher CO2 → higher H+ → less pH → **Acidosis** → Acidosis is very dangerous, as it suppresses CNS enzymes (by denaturation), leading to coma and probably death.
- While hyperventilation will increase CO2 wash out much more than CO2 production → less CO2 → less H+ → higher pH → **Alkalosis** → Alkalosis is also very dangerous as it makes these enzymes *(CNS Enzymes)* hyperactive and might cause tetanization in the respiratory muscles and death, read this clinical correlate to appreciate this :👇

Clinical correlate : Carbopedal spasm

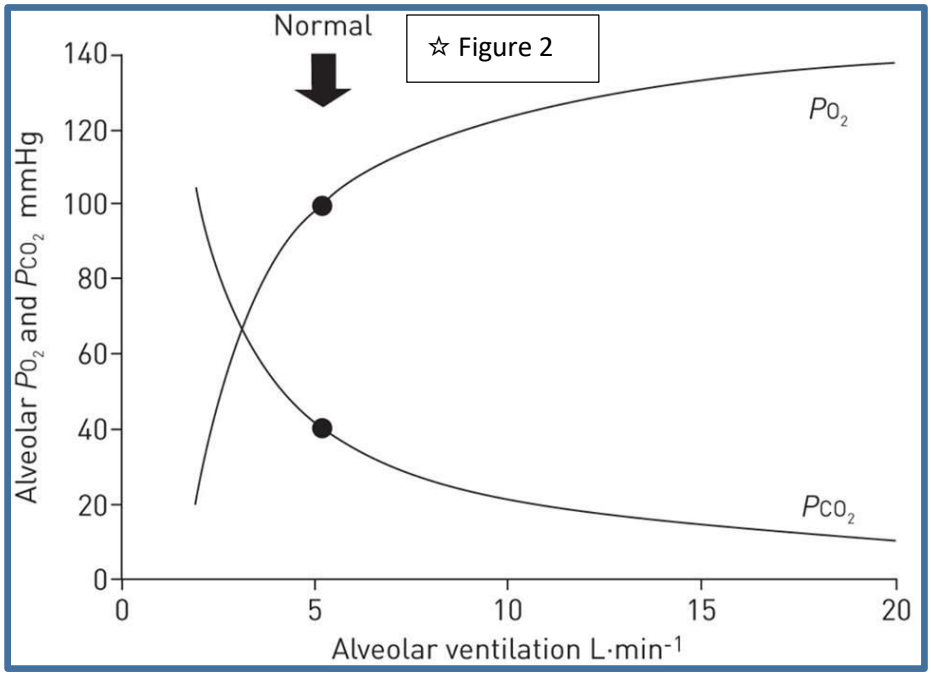
●Many females suffer from spasms/tetanization in their extremities after crying a lot in a Funeral or as a part of post-exam syndrome for example :p *"emotionally"*. The real cause of this is that crying a lot lead to hyperventilation, which will cause this spasms. But how does this occur?

- Calcium concentration in the blood is around 8-9 mg/dl, 50% of this calcium is free, and the other 50% is bound to proteins.
- Free calcium is the functional one, this is what's important to stay in homeostasis.
- Crying will cause hyperventilation → less CO_2 → less H^+ → higher pH → **Alkalosis** → decrease the amount of free calcium → hypocalcemia!
- Now hypocalcemia won't affect skeletal muscles contraction a lot, as it uses its own calcium that's stored in Sarcoplasmic reticulum. But its effects on CNS are more dangerous, as it stimulates the motor neurons to send more impulses, which will lead to muscular spasm. *(called **Carpopedal** spasm)
- To mange this situation, you have to calm your patient down, then give her a bag and ask her to breathe on it many times. This will reduce CO_2 loss, leading to CO_2 retention and increasing CO_2 levels, decreasing her pH.

●Before talking about regulatory mechanisms in details, can you think about some mechanisms to regulate our arterial carbon dioxide and protons concentration?!

- It's obvious that pH buffering systems, such as kidneys and even chemical buffers, play an important role in carbon dioxide homeostasis.
- Another way to control blood CO_2 levels is by controlling ventilation by having certain receptors that sense CO_2 and H levels in the blood.
- Because CO_2 doesn't have carrier molecules that regulate its concentrations in the plasma (like hemoglobin), CO_2 levels in the blood is directed to strict regulation through ventilation, actually, the whole respiratory process is driven mainly by blood CO_2 levels rather than O_2 levels.

●So to sum up, under normal conditions, alveolar ventilation is around 4.2 L/min, which maintains gases homeostasis (PO_2=100mmHg / PCO_2=40 mmHg)



☆ Figure 2

III. Control of breathing

●Respiratory muscles are skeletal, voluntary muscles that **lack automaticity.**

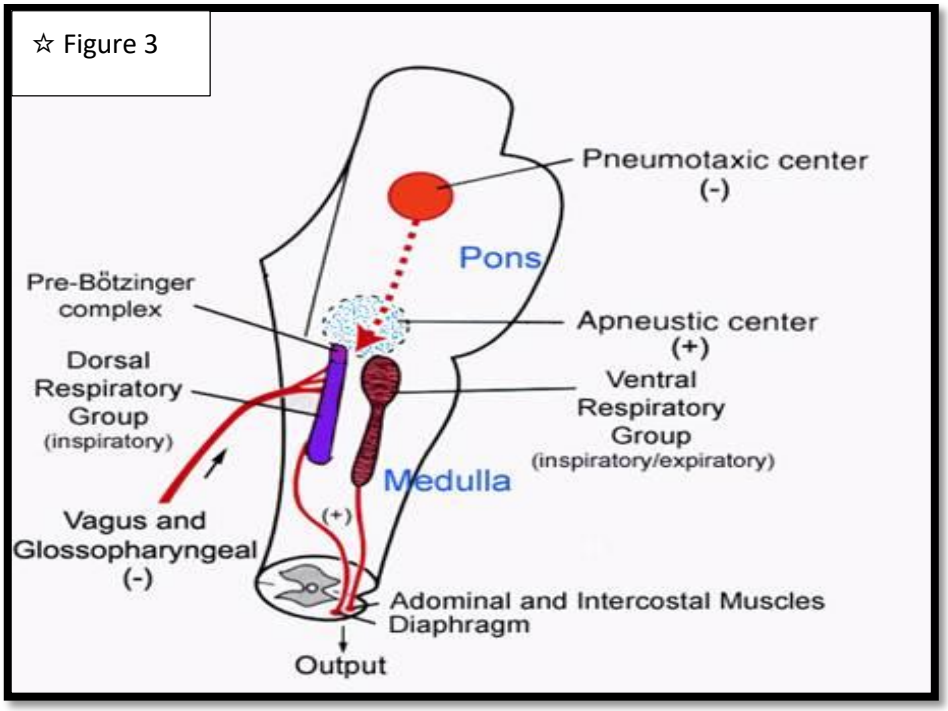
- Unlike modified cardiomyocytes, respiratory muscles can't generate their own action potential; they must receive an external stimulus which is from a motor neuron.
- The diaphragm is innervated by the phrenic nerve which is formed from the cervical nerves C3, C4 and C5.
- The inspiratory center sends its motor output to the diaphragm via the phrenic nerve, so phrenic neurons need input from higher centers.
- So phrenic nerve **doesn't have the intrinsic ability to generate action potential**.

●We said that phrenic nerve requires higher stimulation in order to send impulses to the diaphragm, these impulses come from the CNS.

- When studying the CNS, we will classify it into three parts; ***the brain*** (the order), ***the spinal cord*** (the action) and the ***brain stem*** (the bridge that connects order to action). *To be continued…*

- The brain stem contains many Centers of neurons that regulate our biological activates (like cardiac centers, vascular centers and respiratory centers).
- In neurology, when we say ***Center/group*** it means a population of neurons that work together to do certain functions.
- The brain stem is classified into 4 regions anatomically, in respiratory system we are concerned with two parts; ***medulla oblongata*** and the ***pons***.

☆ Figure 3



• The medulla is composed of two collections of neurons that are distinguished by their anatomic location (see figure 3):

- ***Dorsal respiratory neurons*** (inspiratory neurons) and ***Ventral respiratory neurons*** (expiratory + inspiratory neurons).
- The dorsal respiratory group is under the control of multiple other **Accessory** centers, the most important ones are: ***Pneumotaxic center*** (found in the upper third of the pons) and ***Apneustic center*** (found in the lower third of the pons).

●Now let's talk about the functions of these centers, starting with the dorsal center:

- During quiet breathing, the ***dorsal group*** is neurons responsible for stimulation of phrenic neurons, it sends impulses for 2 seconds, then stop firing for 3 seconds.
- As a result, the duration of inspiration is 2 seconds, and the duration of expiration is 3 seconds, resulting in a respiratory cycle of 5 seconds. Respiratory rate= 60/5=12 breaths/minute (respiratory cycles).
- ***Pneumotaxic center*** is the ***switch off*** for the dorsal respiratory neurons.
- ***Apneustic center*** is the ***switch on*** *for* the dorsal respiratory neurons.
- If we cut (canceled) the communication between Pneumotaxic and dorsal Center, Apneustic center will be the only driver of dorsal Center, causing sustained inspiration with occasional expiration, a situation called ***apneusis*** *"prolonged inspiration"***.**

*External intercostal muscles also involved in inspiration,

They are innervated by neurons located through the thoracic spinal cord through T1-T12

While the diaphragm is innervated by the cervical part.

*The Ventral respiratory neurons: inspiratory + expiratory neurons , they are inactive during quiet breathing, but during active breathing (exercise) they become active along with the dorsal "both"

Now these neurons have another collection of neurons located in the medulla called the central chemoreceptor cells "chemo-sensitive neurons"

They are sensitive to H^+

● On the other hand, the ***ventral group*** only plays a role in forced ***inspiration*** or ***expiration.*** Actually, it's the center that's connected with the chemoreceptors to regulate our breathing.

- So to understand the function of the ventral group, we have to study the chemoreceptors first .. هذا ما سنراه في الحلقة القادمة👇

IV. Chemoreceptors

●We have two populations of these chemoreceptors; the first population is located in the CNS, the other one is located peripherally.

A) *Central chemoreceptors*

● ***Central chemoreceptor***s are located in the medulla and are adjacent to the inspiratory center.

- These receptors are very sensitive to H^+ and CO2.
- Even though H+ ions can't cross the BBB (charged), central chemoreceptors are sensitive to H+ concentrations, Because CO2 molecules are non-polar, so it can cross any membrane as its not exist.
- SO high CO2 in the blood → high CO2 in CSF → High H+ in CSF → Stimulation of central chemoreceptors.

●In our sarcastic literature, we have a story of a stupid man who died because he forgot to breathe "صباغ:مرة محشش مات، لبيش ؟؟.... نسي يتنفس😂 , (صفار:ها ها ها بايخة. -_-)"

is that possible ??

- If We ask someone to hold his breath, The cerebral cortex, which is known to control voluntary respiration, will send impulses through the corticospinal tract, directly inhibiting phrenic neurons.
- This will decreased ventilation → decreased PO_2 (100 to 80 mmHg, which means this decrease won't be sensed by any neuron –recall Oxygen hemoglobin dissociation curve) and increases PCO_2 (the maximum PCO_2 you could achieve is 50mmHg).

CO_2 **by itself** has suppressive effect on dorsal neurons if elevated to 100

It was used as anesthetic in 1930s

To be continued…

- CO_2 crosses the CSF easily, combines with H2O forming H_2CO_3 → H_2CO_3 dissociates into HCO_3- and H+ → H+ stimulates the chemosensitive area (central chemoreceptors) → stimulation of dorsal respiratory neurons → stimulate the phrenic nerve (stronger stimulation that overcomes the inhibition) → diaphragm contraction occurs.
- The scenario above explains 2 points:
  1. It is impossible for anyone to commit suicide by holding their breath or ينسى يتنفس
  2. CO_2 is the main controller of the respiratory center through H^+, which means that if someone had acidosis without increased CO_2 levels, it takes a long time for the H^+ ions to enter the CSF.

B) Peripheral chemoreceptors

●The brain is located in the cranial cavity, separated from its external environment by BBB, how can it know what goes around in the body?

- It puts its own "cameras" all over the body, these cameras are called receptors.

●Now think about it, where is the best place to put receptors that regulate respiration?

- It's in the major (Central) arteries, to give the brain the complete picture about blood gases situation, which reflects repository function.

● ***Peripheral chemoreceptors*** are part of the peripheral nervous system and they detect changes in chemical concentrations (of O_2, CO_2 and H^+).

*Carotid Bodies are more important than Aortic bodies

- These chemoreceptors are located in the carotid and aortic bodies which are found at the carotid and aortic arteries and relay information regarding ABG values to the dorsal respiratory center through CN IX (carotid bodies) and X (aortic bodies).
- These chemoreceptors are most sensitive for oxygen, and start firing at PO_2 less than 60mmHg. (Remember oxygen-hemoglobin dissociation curve)
- Don't confuse carotid and aortic bodies with carotid and aortic sinuses which contain baroreceptors that sense the blood pressure.

● These bodies are composed of cells very similar structurally to neurons

- The cluster of cells is infiltrated with capillaries to provide access to the bloodstream, and these cells are innervated by afferent nerve fibers leading back to the dorsal respiratory center in the medulla (through CN IX and X).
- Carotid and aortic bodies have their own blood supply and venous drainage.

●The chemoreceptor cells aren't in direct contact with the arterial blood, they're only in contact with the interstitium so how will this cell be able to sense ABGs and relay them to the brain?!

- Remember that the interstitium, usually, has gases profile similar to venous blood, which has no benefit for these receptors.
- To solve this problem, we have two choices :

1) If those cells are metabolically inactive, they won't consume Oxygen, so whatever Oxygen is delivered to these is going to be the same after blood passes by them. However, carotid body cells are the most active cells in our body, so this method won't work with Carotid bodies, which takes us to the second point.

2) **High amounts of Oxygen available due to very high blood flow.**

- So flow is very high so that a very little amount of oxygen is extracted, which means the partial pressure of oxygen does not drop significantly as blood is passing through the carotid body.
- As blood passes through the carotid body, its composition remains arterial; the arteriovenous (A-V) O_2 difference is very minimal.

Blood Flow to Different Organs

Tissue	Blood flow (ml/g/min)	A-V difference Vol%
Heart	0.8	11
Brain	0.5	6.2
Sk muscles	0.03	6
Liver	0.6	3.4
Kidney	4.2	1.4
Carotid bodies	20	0.5

- Blood flow to these bodies is huge and enormous. In fact, they have the highest blood flow per gram of tissue in our bodies (20 mL of blood/gram tissue weight), and their weight is actually 25-30 milligram yet they have their own artery. After that come the kidneys (4 mL/ gram tissue weight). Skeletal muscles have a blood flow of 0.003 mL/gram tissue weight).

● Keep in mind that carotid bodies are sensitive to PO_2 lower than 60 mmHg, but not to PO2 higher than 60mmHg.

- They're also sensitive to increased H^+ (acidosis) or increased PCO_2 (hypercapnia), but when compared to central chemoreceptor sensitivity, **peripheral chemoreceptor sensitivity is only one seventh that of the central, but five times faster.**
- **I**f we denervate or remove the carotid bodies (which send their impulses through vagus nerve (aortic bodies) and glossopharngyeal nerve (carotid bodies), and increase CO_2 in the blood, we almost see the same effect in hyperventilation after canceling the peripheral chemoreceptors.

Le Fin.

"Difficult roads often lead to beautiful destinations"

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