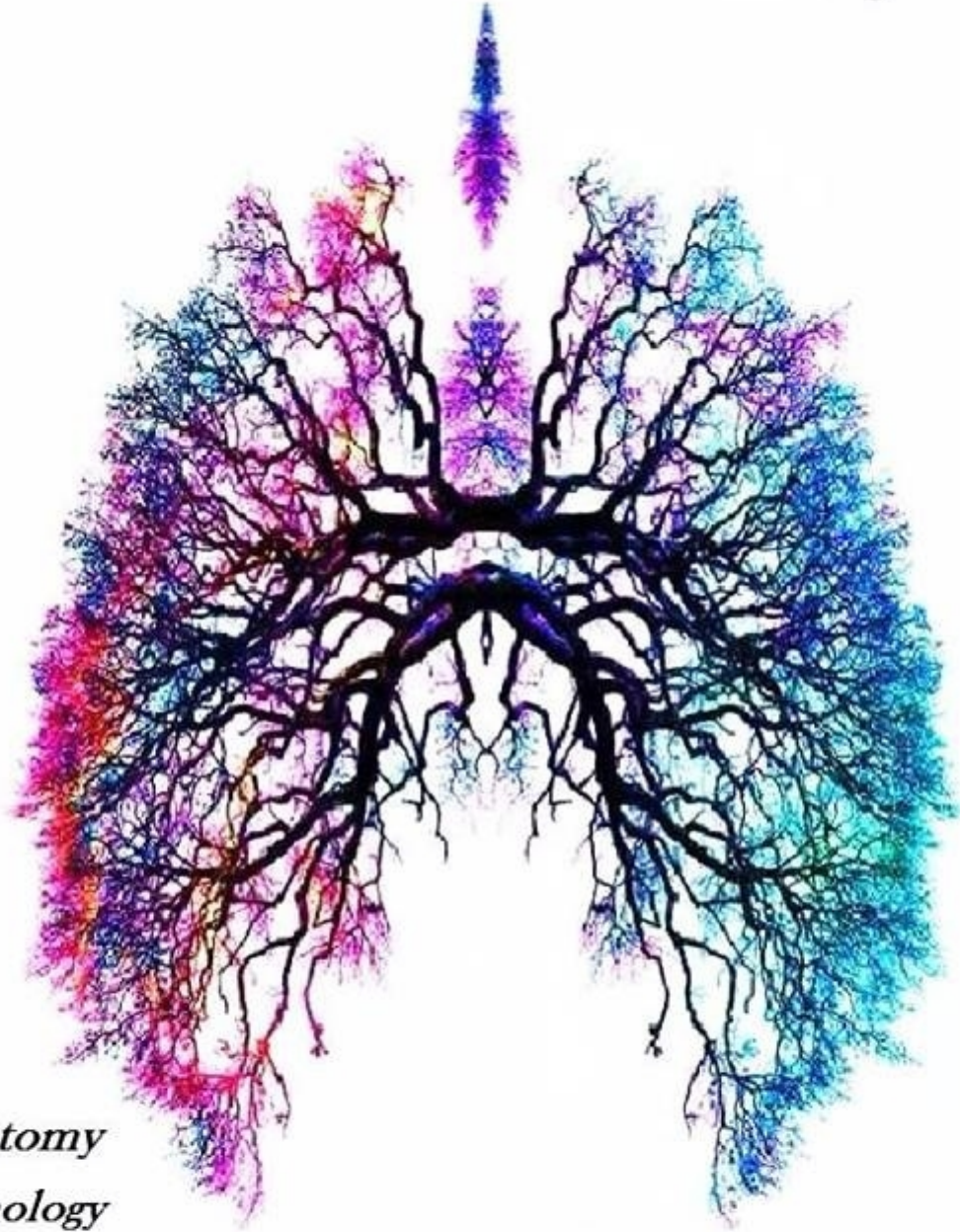


RESPIRATORY SYSTEM

Cover by: Aseel Khatib



- Anatomy*
- Pathology*
- Physiology*
- Pharmacology*
- Microbiology*
- PBL*

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Lecture # 9
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Sheet

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Control of breathing

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 **hyperventilation** (Increased alveolar ventilation; which will increase PO₂ up to 150 mmHg as long as you're breathing normal room air, and decrease PCO₂ to around 0) or **hypoventilation**.

PO₂ and PCO₂ could affect ventilation; when PO₂ reaches levels less than 60 mmHg, alveolar ventilation increases, and as PCO₂ increases, ventilation does as well.

It is very important to understand that **the magnitude of response to decreased PCO₂ is much lower than the response to increased PCO₂**. This is due to the fact that response to decreased PCO₂ is suppression of ventilation which results in decreased PO₂, and by now we know that a PO₂ below 60 mmHg will result in increased alveolar ventilation, antagonizing hypocapnia (low PCO₂). However, increasing ventilation results in higher PO₂ which does NOT suppress ventilation (As the Oxygen-Hemoglobin dissociation curve is sigmoidal). **So a one unit decrease in CO₂ has less effect than a one unit increase in CO₂, due to the antagonizing effect of hypoxia.**

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).

Respiratory muscles

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 (doesn't have the intrinsic ability to generate action potential)

Brain stem control of breathing

1. Medullary respiratory center:

The brain stem is the posterior part of the brain, it's formed by 4 regions, and its last part, the medulla oblongata, is continuous with the spinal cord. The medulla is composed of two collections of neurons that are distinguished by their anatomic location: Dorsal respiratory neurons (**inspiratory** neurons) and Ventral respiratory neurons (**expiratory** + inspiratory neurons).

During **quiet** breathing, the dorsal group is the group of neurons responsible for stimulation of phrenic neurons. On the other hand, the ventral group only plays a role in **forced** inspiration or expiration.

Now take a look at this figure from Costanzo:

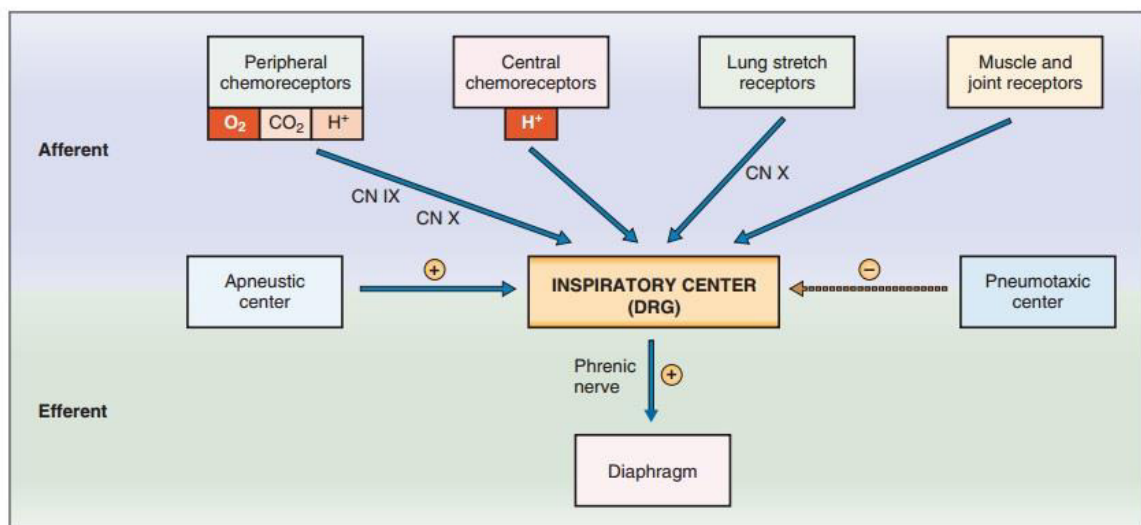


Figure 5-32 Brain stem control of breathing. Afferent (sensory) information reaches the medullary inspiratory center via central and peripheral chemoreceptors and mechanoreceptors. Efferent (motor) information is sent from the inspiratory center to the phrenic nerve, which innervates the diaphragm. CN, Cranial nerve; DRG, dorsal respiratory group.

As illustrated by the figure above, the dorsal respiratory group is under the control of multiple other accessory centers:

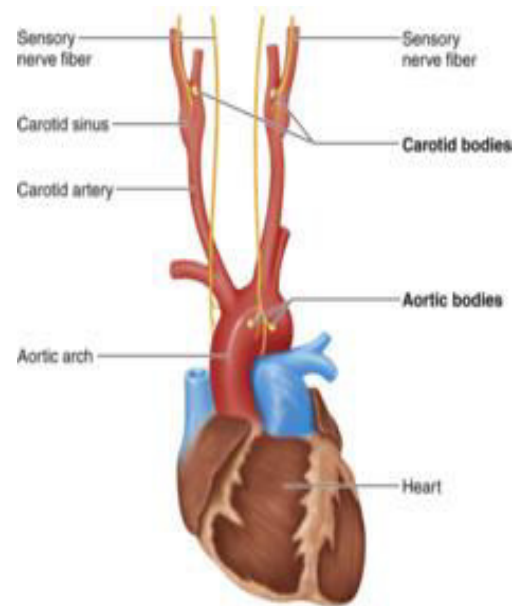
- **Pneumotaxic center:** found in the upper third of the pons (which is located above the medulla), and is the switch off for the dorsal respiratory neurons.
- **Apneustic center:** found in the lower third of the pons, and is the switch on for the dorsal respiratory neurons (read only: Stimulation of these



neurons apparently excites the inspiratory center in the medulla, prolonging the period of action potentials in the phrenic nerve, and thereby prolonging the contraction of the diaphragm.)

2. Chemoreceptors:

- **Peripheral chemoreceptors:** As the name indicates, they're part of the peripheral nervous system and they detect changes in chemical concentrations (of **O₂**, CO₂ and H⁺). These chemoreceptors are located in the carotid and aortic bodies which are found at the carotid and aortic arteries (exact location wasn't mentioned by the doctor but the picture on the right will help clarify things a bit) and relay information regarding ABG values to the dorsal respiratory center through CN IX (carotid bodies) and X (aortic bodies). Don't confuse carotid and aortic bodies with carotid and aortic sinuses which contain baroreceptors that sense the blood pressure.



Structure of carotid and aortic bodies: these bodies are composed of **cells** very similar structurally to neurons (read only: these cells are called Type 1 Glomus cells and are derived from the neural crest.) The cluster of cells is infiltrated with **capillaries** to provide access to the bloodstream, and these cells are innervated by afferent nerve fibres leading back to the dorsal respiratory center in the medulla (through CN IX and X).

<https://www.youtube.com/watch?v=cJXY3Cywrc>

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?! Well actually, interstitial and arterial compositions are almost equal (in order for chemoreceptor cells to sense arterial pO₂ not capillary or venous pO₂.)





Blood 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) O₂ difference is very minimal. In the heart, the A-V difference is around 11mL (which means the heart extracts most of the Oxygen delivered to it, that's why ischemia is very dangerous), in skeletal muscles it's 5ml (this is the extraction ratio; arterial is 20 and venous is 15: $20-15=5$). However, in carotid bodies, the A-V O₂ difference is only 0.5 mL (Arterial: 20, Venous: 19.5).

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).

Minimizing A-V difference could be done by one of two ways:

- 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.

Keep in mind that carotid bodies are sensitive to PO₂ lower than 60 mmHg, but not to PO₂ higher than 100 mmHg. They're also sensitive to increased H⁺ (acidosis) or increased PCO₂ (hypercapnia), but when compared to central chemoreceptor sensitivity, peripheral chemoreceptor sensitivity is only one seventh that of the central, but five times faster. (From Costanzo: The peripheral chemoreceptors also detect increases in PCO₂, but the effect is less important than their response to decreases in PO₂. Detection of changes in PCO₂ by the peripheral chemoreceptors also is less important than detection of changes in PCO₂ by the central chemoreceptors.)

-Note: if we denervate or remove the carotid bodies (which send their impulses through vagus nerve (aortic bodies) and glossopharyngeal nerve (carotid bodies)), and increase CO₂ in the blood, we almost see the same effect in hyperventilation after canceling the peripheral chemoreceptors. Peripheral chemoreceptors do response to H⁺ but only 15% of the central effect but 5 times faster.



- **Central chemoreceptors:** located in the **medulla** and are adjacent to the inspiratory center. Even though H^+ ions can't cross the bbb (charged), central chemoreceptors are sensitive to H^+ concentrations. How? Well CO_2 molecules aren't polar, meaning there are no biological barriers for CO_2 , meaning CO_2 is permeable across the bbb.

Now picture the following scenario:

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.) \rightarrow decreased ventilation \rightarrow decreased PO_2 (100 to 80 mmHg, which means this decrease won't be sensed by any neuron –recall Oxygen haemoglobin dissociation curve) and increases PCO_2 (the maximum PCO_2 you could achieve is 50mmHg) \rightarrow CO_2 crosses the CSF, combines with H_2O forming H_2CO_3 \rightarrow H_2CO_3 dissociates into HCO_3^- and H^+ \rightarrow H^+ stimulates the chemosensitive area (central chemoreceptors) \rightarrow stimulation of dorsal respiratory neurons \rightarrow stimulate the phrenic nerve (stronger stimulation that overcomes the inhibition) \rightarrow diaphragm contraction occurs.

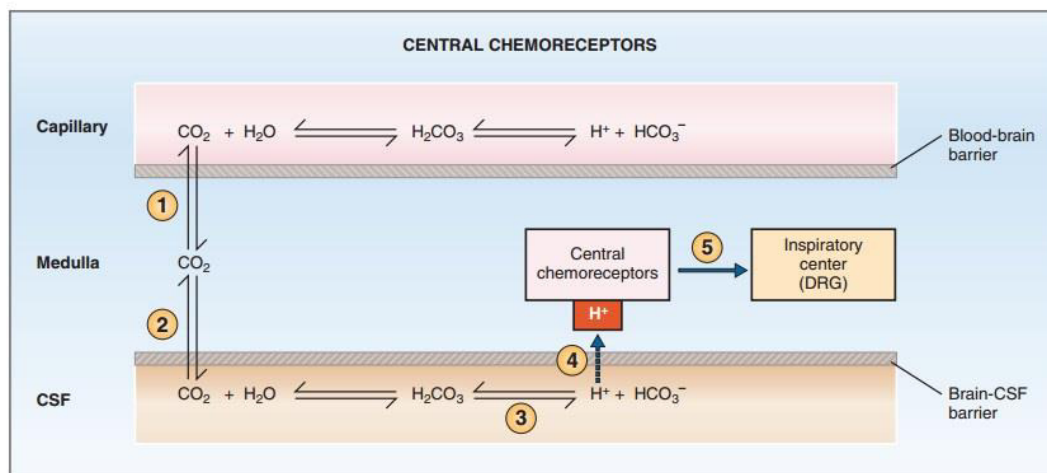


Figure 5-33 Response of central chemoreceptors to pH. The circled numbers correspond to the numbered steps discussed in the text. CSF, Cerebrospinal fluid; DRG, dorsal respiratory group.

The scenario above explains 2 points: 1) It's impossible for anyone to commit suicide by holding their breath and 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.



Responses to exercise

Ventilation increases, but is **NOT driven by ABG values**. PaO₂ remains 100 mmHg (once oxygen consumption increases, ventilation increases as well) and PaCO₂ remains 40 mmHg. The impulses which go to the working muscles also go to the dorsal respiratory neurons to drive ventilation. The moving muscles send feedback to the dorsal respiratory neurons to make them work even more. The moving joints and tendons further command the inspiratory center to increase the inspiration rate (if a person has coma and he moved his leg, hyperventilation occurs and it's driven by the moving joints and muscles.) It's everything that drives ventilation except the ABGs.

From Guyton: The brain, on transmitting motor impulses to the exercising muscles, is believed to transmit at the same time collateral impulses into the brain stem to excite the respiratory center. Actually, when a person begins to exercise, a large share of the total increase in ventilation begins immediately on initiation of the exercise, before any blood chemicals have had time to change. It is likely that most of the increase in respiration results from neurogenic signals transmitted directly into the brain stem respiratory center at the same time that signals go to the body muscles to cause muscle contraction.

Adaptation to high altitudes

If PO₂ decreases below 60 mmHg, peripheral chemoreceptor stimulation occurs (recall that peripheral chemoreceptors are most sensitive to hypoxia), which stimulates the inspiratory center to initiate hyperventilation. So you're hyperventilating to add Oxygen, but you're also losing CO₂, resulting in alkalosis.

Henderson-Hasselbalch equation:

$$\begin{aligned} \text{pH} &= 6.1 + \log [\text{HCO}_3^-] / 0.03 \text{ PCO}_2 \\ &= 6.1 + \log 24 \text{ mmol} / (40 \text{ mmHg} * 0.03) \\ &= 6.1 + \log (24/1.2) \\ &= 7.4 \end{aligned}$$



6.1 is the dissociation constant of carbonic acid. For the CO₂ we multiply by 0.03 (conversion factor) to convert mmHg to millimoles. This equation shows us how when CO₂ increases, pH decreases.

Ascent to high altitudes increases ventilation because of hypoxia (which results from the decreased PO₂ of the inspired air), but it's antagonized by the resulting alkalosis (due to washing out of CO₂). Kidneys, on the other hand, compensate slowly; it takes 3 to 5 days for bicarbonate excretion in the urine by the kidneys to occur (kidneys usually retain HCO₃⁻). So when both CO₂ and HCO₃⁻ are decreased, pH goes back to normal; so after 5 days you'd end up with low CO₂ in the blood but never low pH. Central suppression will be removed, and you're left with peripheral stimulation and therefore your ventilation is increasing to the maximum at that level (4-5 times normal).

When you descend, there's no hypoxia, so there's no peripheral stimulation and your ventilation is going to decrease. Decreased ventilation means accumulation of CO₂ resulting in decreased pH leading to **acidosis**. Acidosis occurs due to CO₂ accumulation while bicarbonate levels are still low (The kidneys need at least a couple of days to go back to normal). Normally, the kidney does not excrete bicarbonate at all. When you descend from a high place, not only will the kidney not excrete bicarbonate, it will produce its own bicarbonate until bicarbonate levels become normal again.

The end

Past paper questions: (The answers are from the website not me)

- 1) Which of the following will return toward normal few weeks following ascending to high altitude (and stay at the top of the mountain)?:
 - **Arterial hydrogen ion concentration**
 - Arterial carbon dioxide tension
 - Arterial bicarbonate ion concentration
 - Arterial hemoglobin concentration
 - Alveolar ventilation



2) Which of the following is most likely cause of a high arterial PCO₂?

- o Increased metabolic activity during exercise
- o Increased alveolar dead space volume
- o **Depressed medullary respiratory centers**
- o Alveolar capillary block
- o Increased alveolar ventilation

3) What happens to arterial blood gases after a period of hyperventilation: >>> **increase Po₂, decrease Pco₂, no change PH₂o**

4) Hyperventilation can result from:

- a- **increase alveolar Pco₂**
- b- increase alveolar Po₂
- c- decrease arterial Pco₂ below 30 mmHg Lejan 2009/2010
- d- direct stimulation of central chemosensitive receptors due to increase PH
- e- a decline of arterial Po₂ from 100 mmHg to 70 mmHg

BRS Physiology questions:

19) Hypoxemia produces hyperventilation by a direct effect on the:

(A) phrenic nerve (B) J receptors (C) lung stretch receptors (D) medullary chemoreceptors (E) carotid and aortic body chemoreceptors

20) Which of the following changes occurs during strenuous exercise?

(A) Ventilation rate and O₂ consumption increase to the same extent (B) Systemic arterial Po₂ decreases to about 70 mm Hg (C) Systemic arterial Pco₂ increases to about 60 mm Hg (D) Systemic venous Pco₂ decreases to about 20 mm Hg (E) Pulmonary blood flow decreases at the expense of systemic blood flow

25. A 38-year-old woman moves with her family from New York City (sea level) to Leadville Colorado (10,200 feet above sea level). Which of the following will occur as a result of residing at high altitude?

(A) Hypoventilation (B) Arterial Po₂ greater than 100 mm Hg (C) Decreased 2,3-diphosphoglycerate (DPG) concentration (D) Shift to the



right of the hemoglobin-O₂ dissociation curve (E) Pulmonary vasodilation (F) Hypertrophy of the left ventricle (G) Respiratory acidosis

Answers and explanations:

19. The answer is E [VIII B 2]. Hypoxemia stimulates breathing by a direct effect on the peripheral chemoreceptors in the carotid and aortic bodies. Central (medullary) chemoreceptors are stimulated by CO₂ (or H⁺). The J receptors and lung stretch receptors are not chemoreceptors. The phrenic nerve innervates the diaphragm, and its activity is determined by the output of the brain stem breathing center.

20. The answer is A [IX A]. During exercise, the ventilation rate increases to match the increased O₂ consumption and CO₂ production. This matching is accomplished without a change in mean arterial Po₂ or Pco₂. Venous Pco₂ increases because extra CO₂ is being produced by the exercising muscle. Because this CO₂ will be blown off by the hyperventilating lungs, it does not increase the arterial Pco₂. Pulmonary blood flow (cardiac output) increases manifold during strenuous exercise.

25. The answer is D. At high altitudes, the Po₂ of alveolar air is decreased because barometric pressure is decreased. As a result, arterial Po₂ is decreased (<100 mm Hg), and hypoxemia occurs and causes hyperventilation by an effect on peripheral chemoreceptors. Hyperventilation leads to respiratory alkalosis. 2,3-Diphosphoglycerate (DPG) levels increase adaptively; 2,3-DPG binds to hemoglobin and causes the hemoglobin-O₂ dissociation curve to shift to the right to improve unloading of O₂ in the tissues. The pulmonary vasculature vasoconstricts in response to alveolar hypoxia, resulting in increased pulmonary arterial pressure and hypertrophy of the right ventricle (not the left ventricle).