صدقة جارية عن المغفور له بإذن الله **عمر عطية** من دفعة 2023 – كلية الطب، الجامعة الأردنية.

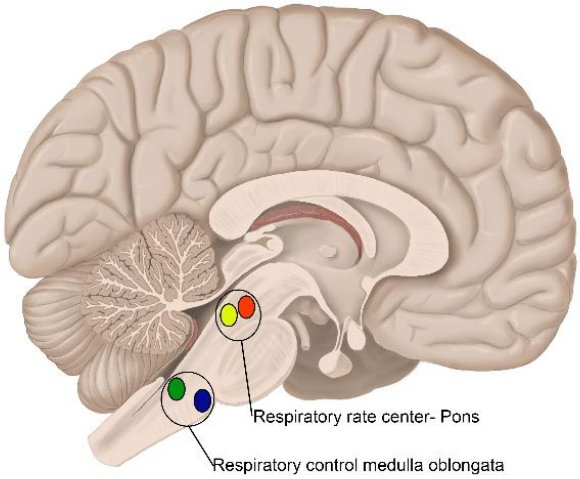
اللهم ارحمه واغفر له وأكرم نزله ووسع مدخله، لا تنسوه من دعائكم، إنا لله وإنا إليه راجعون.

#فريق_دوبامين_العلمي

Respiratory System Physiology

Comprehensive File 11 – V1

Dr. Yanal Shafagoj



Written By:

Mohammad Mahasneh

Reviewed By:

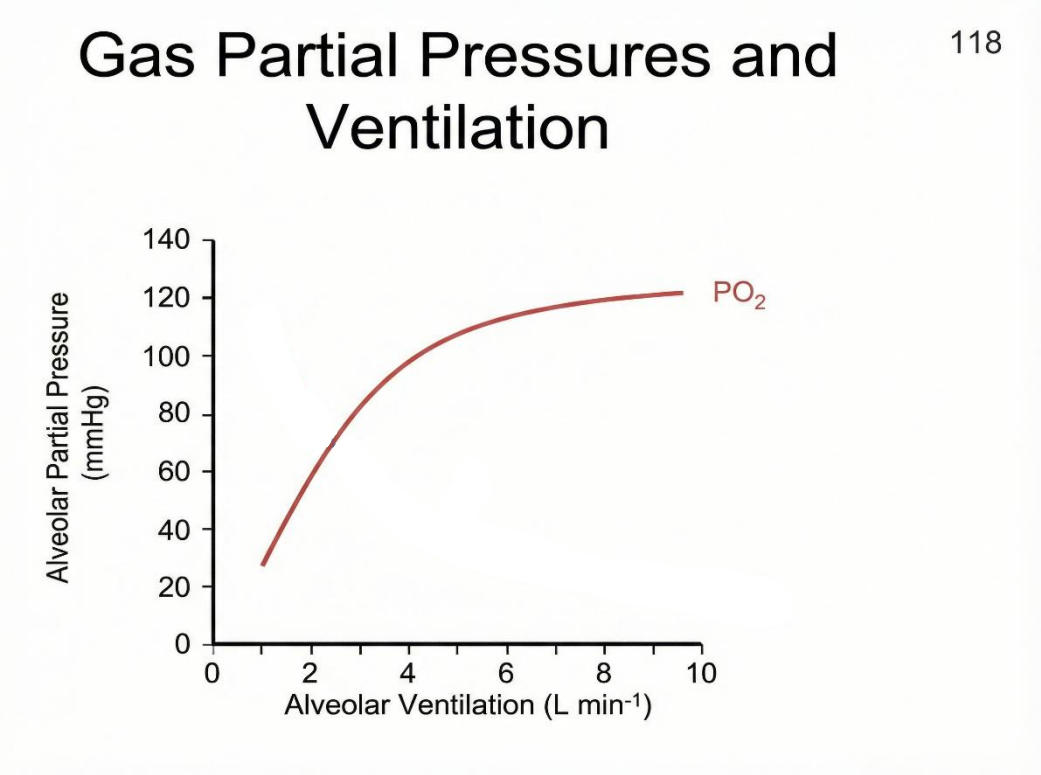
Almothana Khalil

Control of Breathing

The controller system aims to achieve homeostasis, maintaining $O_2 \approx 100$ mmHg, $CO_2 \approx 40$ mmHg, and proper H^+ regulation (normal ABGs).
This is achieved only by increasing or decreasing ventilation, along with the presence of a feedback system, which is mediated by various receptors, and stimuli include:

- Increases and decreases in PCO_2.
- Increases and decreases in H^+ concentration.
- A decrease in PO_2 only (not an increase).

Effect of Alveolar Ventilation on P_AO_2 and P_ACO_2



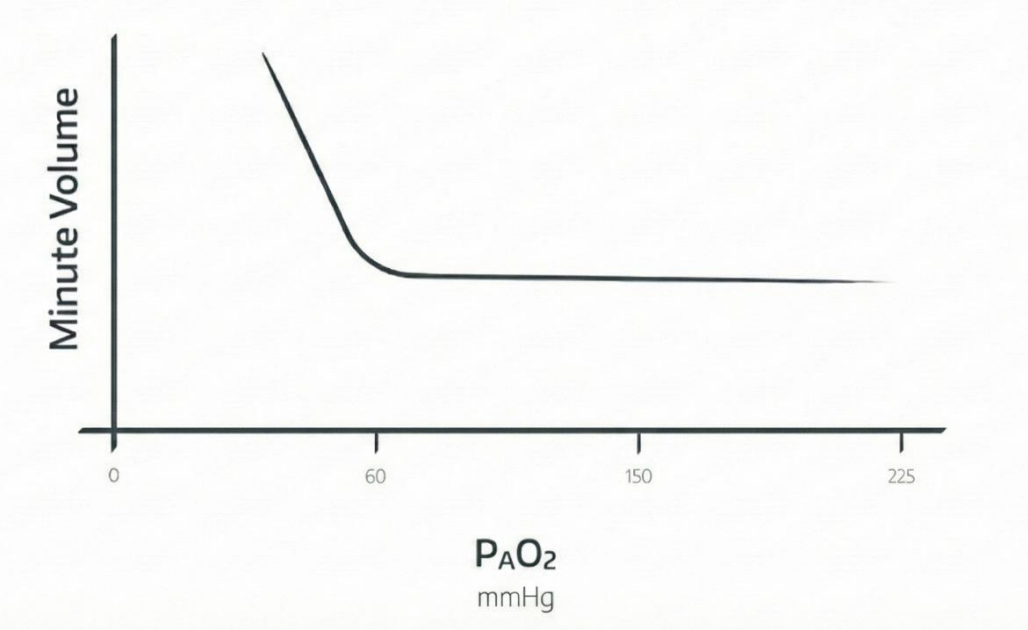
When $\dot{V}_A$ (alveolar ventilation) is within the normal range, $P_AO_2 \approx 100$ mmHg.
With increased $\dot{V}_A$ (hyperventilation), the maximum P_AO_2 that can be reached is ≈ 150 mmHg, as the lungs attempt to make alveolar air composition closer to inspired air.
In hypoventilation, alveolar gas composition shifts toward mixed venous blood values.

P_AO_2 is directly proportional to the ratio ($\dot{V}_A$ / $\dot{V}O_2$), meaning that alveolar oxygen tension increases when alveolar ventilation rises relative to oxygen consumption. Thus, increasing $\dot{V}_A$ leads to an increase in P_AO_2. $\dot{V}O_2$ can reach ≈ 5000 mL/min in athletes during maximal exercise ($VO_{2,\ max}$).

When alveolar ventilation ($\dot{V}_A$) is plotted against PCO_2, an increase in $\dot{V}_A$ leads to a decrease in PCO_2.

P_ACO_2 is equal to (($\dot{V}CO_2$ / $\dot{V}_A$) × 0.862), meaning that for a constant CO_2 production, increasing ventilation lowers arterial CO_2 levels.

P_AO_2–$\dot{V}A$ Relationship



In this curve, alveolar ventilation is the dependent variable and is represented on the y-axis, while P_AO_2 is the independent variable on the x-axis.

When P_AO_2 is ≥ 100 mmHg, alveolar ventilation ($\dot{V}_A \approx 4.2$ L/min) does not change.

In the decreasing part of the curve, no change ($\dot{V}_A \approx 4.2$ L/min) happens until P_AO_2 falls below ~60 mmHg, where $\dot{V}_A$ increases sharply.

P_ACO_2–$\dot{V}A$ Relationship

In the P_aCO_2–$\dot{V}_A$ relationship, P_ACO_2 decreases as alveolar ventilation increases. However, when ventilation is plotted against P_ACO_2, an increase in P_ACO_2 causes a linear increase in ventilation.

If one lung region is hyperventilated, such as the apex, and another is hypoventilated, such as the base, CO_2 acts as a self-compensatory gas, because mixing blood with different CO_2 levels tends to correct these differences due to the linear CO_2 dissociation curve, unlike oxygen, which has a sigmoidal dissociation curve. Bidirectional changes in CO_2 strongly stimulate the respiratory center, whereas oxygen has a weaker effect except at low levels (< 60 mmHg).

The linear dissociation curve of carbon dioxide also explains why it is not affected by venous admixture as oxygen.

Closing Volume of the Lungs

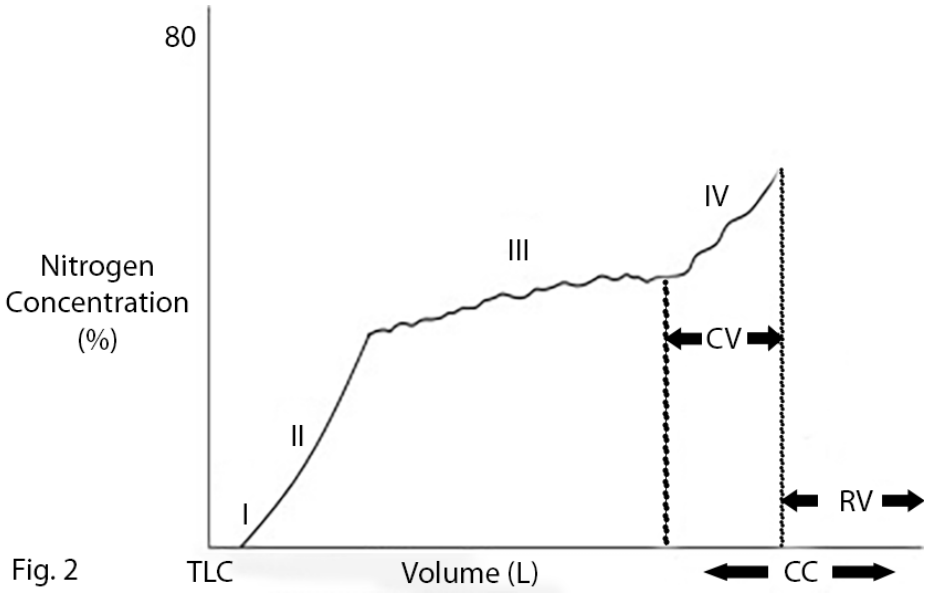


Fig. 2

In a standing individual, the intrapleural pressure around the apex is approximately −8 mmHg, while near the base it is around −2 mmHg. As a result, apical alveoli are more inflated at rest, yet the airways remain patent. When asking where the first portion of the inhaled tidal volume goes, the answer is the apex, because despite being already inflated, airway resistance there is lower, allowing air to enter first, although the volume delivered is small compared to that delivered to the base.

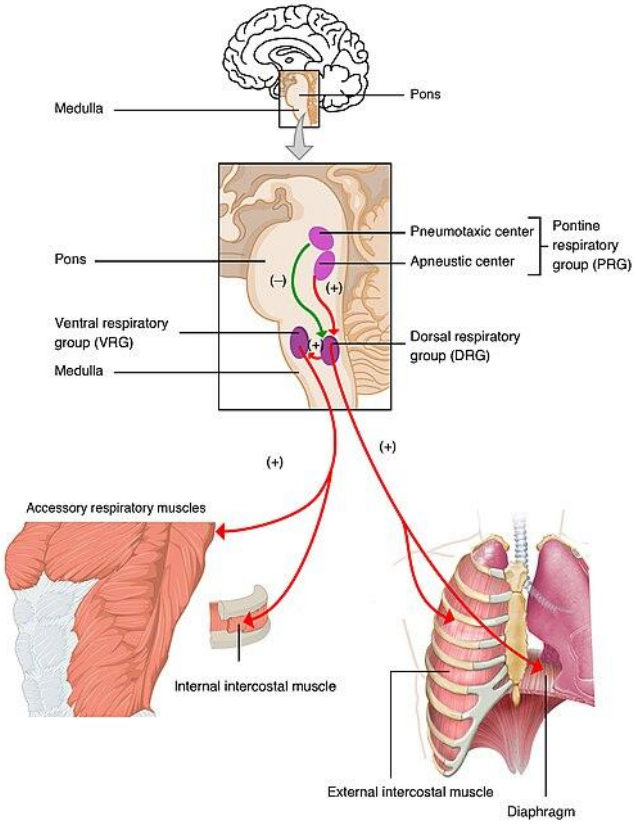
As discussed previously, when using Fowler's method after inhalation of 100% oxygen, plotting expired air volume against nitrogen concentration produces an initial rise followed by a plateau, where air from both apical and basal parts is uniformly exhaled.

During inspiration, most of the tidal volume is directed to the lung bases, leading to greater dilution of nitrogen in the basal alveoli. PO_2 in apical alveoli is about 130 mmHg and their PN_2 is higher than in basal alveoli, where PO_2 is around 90 mmHg.

In case of COPD, airway obstruction tends to affect the basal airways first, since they are surrounded by a less negative intrapleural pressure (≈ −2 mmHg) compared to the apex, this leads to the alteration of the normal plateau seen in Fowler's method, because early closure of basal airways causes nitrogen-rich air from late-emptying lung (apical) units to appear within the plateau, leading to a rise in N_2 concentration at a point where the curve would normally remain flat.

The volume expired after closure of the basal airways is called the closing volume (CV). Under normal conditions, it occurs near the residual volume, but with aging, the closing volume shifts closer to the functional residual capacity (FRC), making it a sensitive indicator of increased airway resistance.

The Respiratory Centers



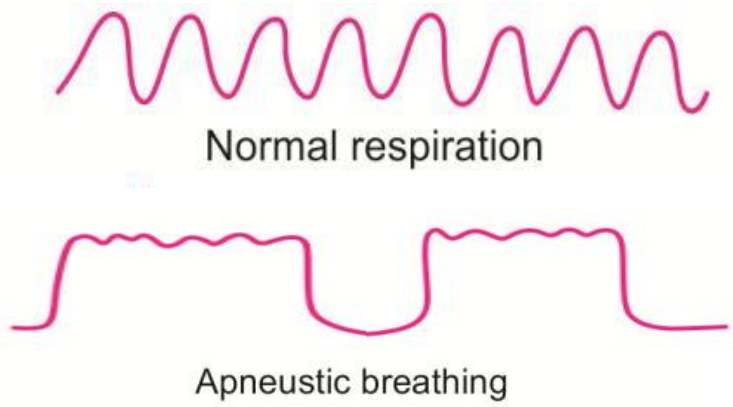
The brainstem consists of three regions: the midbrain, pons, and medulla oblongata, which is continuous with the spinal cord. The primary respiratory center is located in the medulla oblongata, while an accessory respiratory center is present in the pons.

The respiratory center in the medulla oblongata consists of groups of neurons divided into the dorsal respiratory group (DRG), which contains inspiratory neurons, and the ventral respiratory group (VRG), which contains both inspiratory and expiratory neurons. At rest, the DRG neurons discharge rhythmically, synapsing with and stimulating phrenic neurons arising from the C3–C5 segments of the spinal cord, which provide motor innervation to the diaphragm. The DRG neurons fire for approximately 2 seconds, then stop for about 3 seconds, producing one respiratory cycle every 5 seconds, corresponding to a respiratory rate of about 12 breaths per minute.

During quiet breathing, the inspiratory neurons are the only active neurons, whereas the ventral respiratory neurons become active during exercise, when additional respiratory muscles are required for breathing.

The Accessory Respiratory Centers

The accessory respiratory centers are in the pons. The pneumotaxic center is located in the upper third of the pons, and it suppresses the activity of the dorsal respiratory group (DRG), thereby terminating inspiration. The lower third of the pons contains the apneustic center, which stimulates the DRG. If an injury interrupts the pneumotaxic center input to the DRG, prolonged inspiration with occasional expiration occurs.



Take a break and click here to listen to a story from Dr. Yanal

CO_2 and H^+ effects on the respiratory centers

The dorsal respiratory group (DRG) requires feedback from different centers. Near the DRG in the medulla oblongata, there is a chemosensitive area that is sensitive to increased H^+ levels, as occurs in acidosis. Stimulation of this chemosensitive area activates the DRG, leading to an increase in ventilation.

When a person intentionally holds their breath, the cerebral cortex sends inhibitory signals to the phrenic nuclei via the corticospinal tract, bypassing the dorsal respiratory group (DRG). This leads to a rise in P_aCO_2 from about 40 to 50 mmHg. As CO_2 crosses the CNS barriers, it combines with H_2O and is converted into HCO_3^- and H^+ by carbonic anhydrase, increasing H^+ concentration. The rise in H^+ stimulates the chemosensitive area, which activates the DRG, causing it to stimulate the phrenic nuclei and override cortical inhibition. Making prolonged voluntary breath-holding impossible.

When CO_2 increases excessively, it can directly depress the dorsal respiratory group (DRG), rather than stimulating it indirectly through the chemosensitive area. At very high CO_2 levels, this central depressant effect overrides the normal stimulatory response.

Oxygen Effects on the Respiratory Center

In case of severe hypoxemia, decreased oxygen concentrations will directly inhibit DRG as the neurons will become depleted of ATP, not as a feedback mechanism.

The carotid bodies have a very high blood flow of about 20 mL/min per gram of tissue and transmit information about P_aO_2 to the brain. When P_aO_2 falls below about 60 mmHg, they stimulate the nucleus tractus solitarius (NTS), which then stimulates the dorsal respiratory group (DRG), leading to an increase in ventilation. Thus, carotid bodies are primarily sensitive to hypoxemia. They also participate in CO_2 and H^+ regulation, where their response is faster (5X) than that of central chemoreceptors, but less effective, contributing only about one-seventh of the total ventilatory stimulus. Aortic bodies are also present, but with less important contribution than carotid bodies.

The carotid bodies carry their stimuli through the glossopharyngeal nerve (CN IX), while the aortic bodies transmit their signals via the vagus nerve (CN X). If both peripheral pathways are cut, CO_2 regulation is still maintained, with approximately 90% provided by central chemoreceptors, indicating that the peripheral carotid and aortic bodies together contribute about 10% to CO_2 regulation.

Hyper- and Hypoventilation

Hyperventilation occurs only when P_aO_2 falls below 60 mmHg and refers to a state in which CO_2 production is less than alveolar ventilation, whereas hypoventilation occurs when CO_2 production exceeds alveolar ventilation. Increased ventilation during exercise is not considered hyperventilation, as it represents a different physiological situation.

During exercise, arterial blood gases (ABGs) remain within normal limits. This is because P_AO_2 is directly proportional to the ratio $\dot{V}A/\dot{V}O_2$, and during exercise both alveolar ventilation and oxygen consumption increase proportionally, so P_aO_2 remains normal, and the same applies to P_aCO_2. Since ABGs do not change significantly, the increase in ventilation through higher respiratory rate and tidal volume is driven instead by receptors in the muscles and joints, which stimulate ventilation during exercise.

At high altitude, a decrease in $P_{inspired}O_2$ can cause P_AO_2 to fall below 60 mmHg even at rest. This leads to increased ventilation and greater CO_2 elimination. In this situation, two opposing stimuli are present: hypoxia, which provides a peripheral ventilatory stimulus arising from the carotid bodies, and hypocapnia, which centrally suppresses ventilation.

Recall that $pH = 6.1 + \log (HCO_3^- / CO_2)$. To keep the pH unchanged when CO_2 decreases, HCO_3^- must also decrease, which occurs through excretion in the urine. This contrasts with normal conditions, in which HCO_3^- is not excreted, but instead is added to the venous side of the renal capillaries by kidney cells.

The protein concentration in blood is high, around 6-8 g/dL, providing significant buffering capacity, whereas the cerebrospinal fluid (CSF) contains much less protein, about 45 mg/dL, and therefore has fewer buffers. As a result, changes in blood CO_2 concentration are strongly reflected as changes in CSF H^+ concentration. Accordingly, bicarbonate concentration differs between the two, with plasma HCO_3^- around 28 mEq/L and a lower bicarbonate level in CSF (around 24 mEq/L).

Changes from VERSION 0 to VERSION 1:

1. **Page 4;** apical alveoli have ~~lower~~ higher PN_2

2. **Page 4;** *the closing volume explanation was partially rephrased for clarity*

3. **Page 6; second paragraph (refining for context clarity in feedback loops):**
   - This leads to a rise in P_ACO_2 from about 40 to 50 mmHg.
   - This leads to a rise in P_aCO_2 from about 40 to 50 mmHg.

4. **Page 7; first paragraph (refining for scientific accuracy):**
   - In case of hypoxemia, decreased oxygen concentrations will directly inhibit DRG as the neurons will become depleted of ATP.
   - In case of severe hypoxemia, decreased oxygen concentrations will directly inhibit DRG as the neurons will become depleted of ATP, not as a feedback mechanism.