**Pulmonary Physiology**

Gas Exchange

Thursday, February 5, 2015 • 8:30 – 9:40 a.m.

Richard M. Schwartzstein, M.D.

 ASSIGNMENT: This session will be done as a “flipped classroom” rather than as a traditional lecture. You must read these notes and attempt to answer the thought questions *before* coming to class.

**Supplementary reading**


I. Introduction — To survive, we need to get oxygen from the atmosphere into the blood (to support aerobic metabolism) and we must eliminate carbon dioxide (the product of carbohydrate metabolism). The principles underlying the process can be thought of collectively as “gas exchange,” which is dependent on getting gas into and out of alveoli that are receiving blood, i.e., those alveoli that are both ventilated (getting gas) and perfused (getting blood).

Optimal gas exchange depends upon matching ventilation and perfusion within the lung; many disease states associated with low oxygen levels or high carbon dioxide levels can be explained by “mismatching” of ventilation and perfusion.

A. Goals: at the end of this session, you should be able…

- To define the concepts of dead space and shunt.
- To delineate the implications of changes in breathing pattern on gas exchange.
- To describe the implications for gas exchange of the differences between the ways in which oxygen and carbon dioxide bind with hemoglobin.
- To describe the physiological implications for gas exchange of the anatomy of the pulmonary circulation.
- To define and be able to distinguish among the physiologic causes of hypoxemia.
- To define and be able to distinguish among the physiologic causes of hypercapnia.

B. Why should you care?

- A wide range of disease states, both respiratory and non-respiratory, are complicated by alterations in oxygen and carbon dioxide levels
- To address acid-base problems, and to understand the ability of the body to compensate for metabolic disorders, you must have a firm foundation in the principles of gas exchange.

A note about symbols: when dealing with gas exchange, “P” refers to partial pressure of a gas. A small “a,” as in PaO₂, refers to the partial pressure of the gas, in this case oxygen, in the arterial blood. A capital “A,” as in PAO₂, refers to the partial pressure of the gas in the alveolus. “V” refers to volume (as we have been discussing in the mechanics lectures) and V with a dot over it ( V̇ ) refers to a change in volume per unit time (this usually means “flow” but in the case of oxygen consumption,  V̇O₂, or carbon dioxide production,  V̇CO₂, it refers to the volume of gas [e.g., number of ml of gas] being consumed [oxygen] or produced [carbon dioxide] by the body per unit time – in these cases, it represents a “rate” and is analogous to flow).

II. Alveolar ventilation and carbon dioxide elimination

A. Components of ventilation: alveolar ventilation and dead space ventilation. Alveolar ventilation ( V̇ₐ) represents the gas that enters and exits perfused alveoli, i.e., units of the lung that are receiving blood and in which gas exchange may take place. Dead space ventilation ( V̇₃) represents the gas
that enters parts of the lung in which gas exchange does not take place, e.g., central airways or non-perfused alveoli. Together, alveolar ventilation and dead space ventilation equal total ventilation, to which we usually refer as minute ventilation (the number of liters per minute of gas that someone is breathing), and is denoted as expired ventilation or $\dot{V}_{E}$ (note: the dot over the V indicates volume/unit time, i.e., flow)

$$\dot{V}_{E} = \dot{V}_{A} + \dot{V}_{D}$$

1. Components of dead space: **anatomic dead space** (gas that enters central airways; approximately 150 cc or 1 ml/pound of body weight) and **alveolar dead space** (gas that enters alveoli that are not perfused; amount varies according to the pathology of the lung; in normal individuals approximately 20-50 cc).

2. In the normal individual, the dead space to tidal volume ratio ($V_D/VT$) is approximately 0.3, i.e., for a typical 500 ml breath, approximately 170 ml is ventilating dead space and does not participate in gas exchange.

3. Relationship between alveolar ventilation, carbon dioxide production ($\dot{V}_{CO2}$), and partial pressure of carbon dioxide in arterial blood ($PaCO_2$):

$$\dot{V}_{A} = \frac{K \cdot \dot{V}_{CO2}}{PaCO_2}$$

For a given level of carbon dioxide production, an increase in alveolar ventilation will result in a decrease in $PaCO_2$. If carbon dioxide production increases, as might occur during exercise or an infection when metabolic activity is elevated, alveolar ventilation must increase or the patient will become **hypercapnic** (i.e., will have an elevated $PaCO_2$). This relationship can be used to determine changes in ventilator settings for patients in respiratory failure in whom the $PaCO_2$ is not at the level you desire.

The relationship described by the equation above is a form of “clearance” equation for carbon dioxide. It is analogous to “creatinine clearance” in renal physiology, which we will discuss in detail in the renal section of IHP. With respect to carbon dioxide, the lungs may be viewed as an excretory organ.

The body has a tremendous ability to compensate, with respect to $CO_2$ elimination, for poorly ventilated areas of lung by hyperventilating well-ventilated areas of lung (NOTE – this hyperventilation is not as effective in compensating for hypoxemia, i.e., for getting oxygen into the blood, as we will discuss in a minute).
FIGURE 1

FIGURE 1. Relationship between alveolar ventilation and alveolar PCO₂. The body is able to greatly reduce alveolar PCO₂ by increasing ventilation. In addition, be aware of the shift in the curve that occurs when carbon dioxide production in increased, e.g., with exercise. With carbon dioxide production increased, higher alveolar ventilation is needed to maintain the same PaCO₂. Note: A maximally ventilated alveolus will have an alveolar PCO₂ of approximately 10-12 mm Hg. Note 2 – there is a typo in the graph: PaCO₂ above 40 is labeled as “hyperventilation” and should be “hypoventilation”.

QUESTION 1: In what way might one view chronic hypercapnia, i.e., a PaCO₂ > 40 mm Hg, as advantageous for a patient with a problem with the “ventilatory pump” and reduced ventilatory reserve, e.g., an individual with severe emphysema? How might living with a higher PaCO₂ result in less shortness of breath?

B. Measurement of dead space

1. Anatomic dead space: In a healthy subject, can be estimated from a table of standard values matched to age, sex, and height, and body surface area. It equals approximately 1 ml of anatomic dead space per pound of body weight.

QUESTION 2: How would you measure anatomic dead space? What is the predominant gas in perfused versus non-perfused alveoli?

Can be measured using Fowler’s method, which utilizes a single inhalation of 100% oxygen and assesses the concentration of exhaled gases on the exhalation.

The first gas exhaled after the inhalation of oxygen (in the Fowler method) comes from the central airways. By measuring the volume of gas exhaled and the concentration of nitrogen in the gas, one can get a measure of the volume of the anatomic dead space (the gas coming from the anatomic dead space should contain only oxygen after taking in one breath of 100% oxygen; since one doesn’t fully empty alveoli with exhalation (remember: FRC is the volume of gas in the lung at the end of a quiet
exhalation), the gas coming from the alveoli will have a combination of oxygen and nitrogen – the nitrogen is present from the previous breath of normal atmospheric gas).

2. **Physiologic dead space**: Physiologic dead space is the combination of anatomic and alveolar dead space. It can be measured using the Bohr Method (a functional measurement of the volume of lung that does not participate in the elimination of CO₂), which is based on the principle that the volume of carbon dioxide in *mixed expiratory gas* (a collection of the gas you exhaled into a big bag over the course of several minutes) must come from alveoli that are both ventilated and perfused since there are negligible amounts of carbon dioxide in inspired air (alveoli that are ventilated but not perfused will contribute gas with no carbon dioxide to the exhaled gas collection). (Note: \( FE_{CO2} \)=fraction of mixed expired gas that consists of carbon dioxide; \( FI_{CO2} \)=fraction of inspired gas that consists of carbon dioxide; \( FA_{CO2} \)=fraction of alveolar gas that consists of carbon dioxide).

\[
FE_{CO2} \times VT = FI_{CO2} \times VDCO2 + FA_{CO2} \times VA
\]

Since the concentration of carbon dioxide coming from dead space is zero (fractional concentration of CO₂ in inspired gas is zero), and since alveolar ventilation equals tidal ventilation minus physiologic dead space (physiologic dead space is the sum of anatomic + alveolar dead space) ventilation:

\[
FE_{CO2} \times VT = FA_{CO2} (VT - VDCO2)
\]

Rearranging, and since \( FCO2 = \frac{PCO2}{P_{tot}} \):

\[
\frac{VDCO2}{VT} = \frac{PACO2 - PECO2}{PA_{CO2}}
\]

\( F = \) fractional concentration
\( E = \) mixed expired
\( I = \) inspired
\( A = \) alveolar

\( VDCO2 = \) dead space for CO₂ (physiologic dead space)
\( FA_{CO2} = \) fractional concentration of CO₂ in alveoli (both ventilated and perfused)

Since one cannot measure alveolar PCO₂ directly, one uses the arterial PCO₂ as equivalent to the alveolar CO₂ in alveoli that are both ventilated and perfused. The **assumption is made that the gas in the alveolus and the capillary perfusing the alveolus has come into equilibrium by the time the blood in the capillary exits the alveolus**. This assumption works well in healthy individuals, but is problematic in patients with severe lung disease.
C. Determinants of ventilation and perfusion.

1. In the upright posture, perfusion is primarily directed to the bases due to the effect of gravity.

2. Ventilation is also directed preferentially to the bases (assuming a breath is initiated at FRC). This is the consequence of varying pleural pressures from the bases to the apices. Because of the impact of gravity and mechanical interactions between the lung and the chest wall, pleural pressure is less negative at the bases than the apices (the pleural space is “squeezed” by the weight of the lung at the base). This means that, at FRC, the alveoli are more distended at the apex than the base of the lung. At this greater volume, the alveolus has a lower compliance than the smaller alveoli at the bases (recall the pressure-volume relationship for the lung from Lecture on compliance); the lung is made up of millions of alveoli and each one can be considered to have a pressure-volume curve similar to the lung as whole. As you begin to take a breath, ventilation tends to go to the alveoli at the base of the lung since the alveoli in this region reside at a more compliant portion of their pressure-volume curve.

Adding complexity to the discussion – the concept of Closing Volume: the amount of air in the lungs at which point the flow from the lower sections of the lungs becomes severely reduced or halts altogether during expiration. In the lecture on flow limitaiton, we introduced the concept of $P_{crit}$, and acknowledged that, because airways are not infinitely flexible, opening and closing of airways depends on transmural pressure and factors that affect the compliance and support of the airways.

Residual volume in young individuals is determined largely by the balance of forces of the lungs and chest wall. As individuals age, however, elastic recoil declines and the tethering of airways is reduced. As one actively exhales to residual volume, the small airways are more prone to narrow and collapse (to the extent that small airways may be lined with fluid, surface forces may also contribute to the propensity to collapse, in a manner similar to what we discussed with respect to alveoli). Gas is “trapped” behind the collapsed airways and residual volume increases. These collapsed airways at residual volume, depending on their compliance, may not open as soon as transmural pressure becomes positive.

**QUESTION 3:** How would distribution of ventilation in the lung differ when an inhalation is done from RV as compared to FRC in a 20 year old? In a 60 year old? Why?

3. Zones of the Lung: three general categories describing the relationship between alveolar pressure, pulmonary arterial pressure and pulmonary venous pressure. While both ventilation and perfusion go preferentially to the bases in the upright human, perfusion is affected by gravity to a greater extent than ventilation. Thus, there is “relatively” more perfusion than ventilation at the bases, and “relatively” more ventilation than perfusion at the apices.

**SEE FIGURE 2 below**
QUESTION 4: How does exercise affect ventilation-perfusion matching in the lung?

QUESTION 5: How would ventilation-perfusion matching change in outer space?

4. Pulmonary vessels, unlike those in the remainder of the body, constrict in the presence of alveolar hypoxia (more on the ways in which vascular tone is controlled in Dr. Beckman’s lecture in the Cardiovascular section). Poorly ventilated regions of lung have low oxygen levels, i.e., low PAO$_2$ (the oxygen that was in those alveoli is absorbed by the blood and not replenished from the outside world because ventilation to those units is poor). **Hypoxic pulmonary vasoconstriction** enables the body to direct blood to other portions of the lung that are being ventilated better, i.e., to improve the “match” between ventilation and perfusion.

Evidence suggests that hypoxic pulmonary vasculature vasoconstriction is mediated by hypoxia inducible factor-1 (HIF-1), which regulates the expression of genes that mediate adaptive responses. A nice review of this regulatory pathway (for those with a particular interest in or curiosity about this topic) is provided in a recent article in the New England Journal of Medicine 2011;365:537-547.

“(HIF-1) activity in vascular smooth-muscle cells (SMCs), leading to decreased expression of voltage-gated potassium channels (Kv1.5 and Kv2.1), increased expression of transient receptor-potential calcium channels (TRPC1 and TRPC6), and increased expression of sodium–hydrogen exchanger 1 (NHE1). The resulting alterations in the intracellular concentrations of potassium, calcium, and hydrogen ions trigger … depolarization and contraction, which lead to increased pulmonary vascular resistance.”

D. Carbon dioxide and hemoglobin

1. Relatively linear relationship between the partial pressure of carbon dioxide in the blood and the amount of carbon dioxide bound to hemoglobin (contrast with the sigmoid relationship between PaO$_2$ and the percentage of hemoglobin saturated with oxygen, which you studied in biochemistry/MCM).
2. The affinity of hemoglobin for carbon dioxide is dependent upon whether it is in the form of oxyhemoglobin or deoxyhemoglobin; deoxyhemoglobin binds carbon dioxide more avidly than oxyhemoglobin. With addition of oxygen, the curve is shifted to the right; with off-loading of oxygen, the curve is shifted to the left (Haldane effect). This allows the blood to load more carbon dioxide on to hemoglobin as capillaries traverse the tissues, and off-load carbon dioxide in the lungs when the capillary comes into contact with oxygen in the alveoli. The Haldane effect also contributes to the development of increased PaCO₂ in patients with chronic hypercapnia who are given supplemental oxygen (more about this issue in Pulmonary Lecture, Control of Ventilation).

**SEE FIGURE 3**

![Figure 3](image)

**FIGURE 3.** Relationship between partial pressure of carbon dioxide in the blood and carbon dioxide content. Much of the CO₂ content in the blood represents binding of carbon dioxide to hemoglobin. As the hemoglobin gives up oxygen to the tissue it binds carbon dioxide more effectively, i.e., can carry more carbon dioxide, The curve is shifted upward and to the left, primarily due to enhanced carbamino uptake and the binding of hydrogen ions to specific amino acid residues on the hemoglobin that stabilize the T conformation of the molecule. The arrow shows the change in carbon dioxide content that occurs as arterial blood passes through systemic capillaries and becomes venous blood. The shift in the curve facilitates a greater change in CO₂ content for a given increase in PCO₂, i.e., each milliliter of blood is able to carry and transport more carbon dioxide.

E. Physiologic causes of hypercapnia

1. Hypoventilation: Total ventilation is reduced leading to a reduction in alveolar ventilation. Examples - drug overdose, stroke, spinal cord injury.
2. Mismatching of ventilation and perfusion: Decreasing perfusion leads to areas of lung that are less well perfused and the potential to create alveoli that receive no perfusion but are still ventilated, i.e., increased physiologic dead space. Example: heart failure with reduced cardiac output.

3. Increased carbon dioxide production with inability to increase alveolar ventilation, either because of “control” or “ventilatory pump” problems. Example: severe emphysema patient who develops an infection and increased metabolic rate.

III. Gas exchange - oxygen uptake

A. Oxygen binding to hemoglobin.

1. Sigmoid curve rather than linear relationship exhibited by CO₂ and hemoglobin. Shape of curve facilitates release of oxygen in hypoxic tissues and uptake of oxygen in the alveolus. At the same time, it insures nearly fully saturated blood at levels of PO₂ that are below what a normal individual experiences at sea level, i.e., partially protects us from the hypoxemia associated with living at high altitude or with mild pulmonary diseases.

2. Multiple factors shift the curve: temperature, PCO₂, pH, and 2,3 diphosphoglycerate (DPG).

   **Bohr Effect**: Shift of the curve to the right with greater concentration of hydrogen ions in the blood, i.e., lower pH. The association of hemoglobin with hydrogen ions lowers the affinity of hemoglobin for oxygen. This allows the hemoglobin to release more oxygen to tissues that are not getting sufficient oxygen and are consequently relying upon anaerobic metabolism (which is associated with the production of lactic acid leading to a lower pH in the tissue).

SEE FIGURE 4 (below)

![FIGURE 4](image.png)

**FIGURE 4.** Oxygen-hemoglobin association/dissociation curve. The sigmoid shape of the curve allows the hemoglobin to stay almost fully saturated even as arterial PO₂ drops from 100 to 60 mm Hg. At the same time, it provides for rapid off-loading of oxygen to the tissues where PO₂ is approximately 45-50 mm Hg. Noted are various factors that shift the curve to the left or right. Shifts to the left imply that the hemoglobin is less likely to give up the oxygen to the tissue; shifts to the right facilitate oxygen availability to the tissue.
Carbon monoxide changes the shape and position of the curve in a way that reduces the delivery of oxygen to the tissues.

**QUESTION 6:** What do the factors that affect the oxygen-hemoglobin saturation curve have in common when one considers what causes a shift to the left, or a shift to the right?

**B. Ventilation and oxygenation**

1. **Alveolar Gas Equation:** Describes the relationship between inspired partial pressure of oxygen, alveolar carbon dioxide, and alveolar PO2. Once one knows the alveolar oxygen (PAO2), one can compare it to the arterial oxygen (PaO2) as measured with an arterial blood gas (a fairly simple blood test). The difference between the PAO2 and the PaO2 (A-aDO2 or the alveolar to arterial oxygen difference) defines whether there is a gas exchange problem. Normal A-aDO2 changes with age and approximated by the following relationship:

   Normal A-aDO2 ≤ age (0.3).

   NOTE: even in completely normal individuals, ventilation and perfusion are not perfectly matched; this mismatch, along with the fact that some deoxygenated blood returns to the left side of the heart (Thebesian and bronchial veins), contributes to the fact that A-aDO2 is greater than zero.

   a. Gases in the alveolus: nitrogen, oxygen, carbon dioxide, and water vapor (picked up from the epithelium lining the upper airways). Gas inhaled from the atmosphere has oxygen and nitrogen. The oxygen that is taken up from the alveolus and consumed by the tissues is replaced by carbon dioxide, which is the metabolic byproduct of aerobic metabolism. Thus, assuming a roughly 1/1 relationship between oxygen consumption and carbon dioxide production, the drop in alveolar oxygen should equal the rise in alveolar carbon dioxide. (Note: nitrogen is inert with respect to these metabolic processes.)

   b. If alveolar ventilation is reduced, the level of carbon dioxide in the alveolus is elevated (less CO2 being eliminated per unit time while production remains constant), and the fraction of oxygen in the alveolus is reduced (less oxygen being replenished in the alveolus while oxygen consumption remains constant). Hypoventilation leads to hypercapnia and to hypoxemia. **One can be hypoxemic even with normal lungs,** e.g., drug overdose.

   c. These concepts come together in the Alveolar Gas Equation:

   \[ \text{PAO}_2 = \text{FIO}_2 \left( \text{Patm} - \text{Pwater} \right) - \frac{\text{PCO}_2}{\text{R}} \]

   R = respiratory quotient (the ratio of carbon dioxide molecules produced to oxygen molecules consumed; eating a typical American diet, R=0.8. This value increases toward 1.0 with intake of carbohydrates and is decreases (toward 0.6-0.7) if one is eating and metabolizing primarily fat.
The first part of the equation \( FIO_2[Patm-Pwater] \) gives us the partial pressure of oxygen as the gas enters the alveolus. The second part of the equation \( PCO_2/R \) reflects the effect of the level of ventilation, and hence the rate of replenishment of oxygen in the alveolus, as well as the metabolic factors leading to the ratio between oxygen consumption and carbon dioxide production.

**QUESTION 7:** Explain what happens to the \( PaO_2 \) and the A-aDO2 when a healthy individual climbs to a high altitude.

2. Increasing ventilation only has marginal benefit on oxygen content of blood. Hemoglobin is nearly fully saturated at \( PO_2 \) of 60-65 mm Hg. Further increases in \( PaO_2 \) do not lead to significant increases in amount of oxygen carried by the blood.

**Oxygen content** in the blood is determined by the quantity of hemoglobin, the saturation of hemoglobin with oxygen, and the amount of dissolved oxygen in the blood. The amount of oxygen carried by hemoglobin far exceeds the amount that can be dissolved in the blood.

\[
O_2 \text{ content} = \text{Amount } O_2 \text{ Bound to Hgb} + \text{Amount } O_2 \text{ Dissolved in Blood}
\]

\[
O_2 \text{ content} = 1.35 \times (\text{Hgb})(\text{Oxygen saturation}) + 0.003(\text{PaO}_2)
\]

Each gram of hemoglobin can combine with approximately 1.35 (you will see values between 1.34 and 1.39) ml of oxygen. Thus, if person has 15 gm of hemoglobin per 100 ml of blood, there are 20.2 ml of oxygen bound to hemoglobin per 100 ml of blood (assuming the hemoglobin is 100% saturated with oxygen). This contrasts with the amount dissolved in blood: 0.3 ml of oxygen per 100 ml of blood (assuming \( PaO_2 \) of 100 mm Hg).

C. Supplemental oxygen…

1. Can overcome the hypoxemia of ventilation-perfusion (\( \dot{V}/Q \)) mismatch and hypoventilation. The low alveolar \( PO_2 \) seen in lung units that are hypoventilated will go up with increases in the fraction of oxygen in the inspired gas; even low ventilated units will receive some of the inspired gas, which now has high concentrations of oxygen.

2. May worsen hypercapnia by worsening \( \dot{V}/Q \) mismatch, i.e., by increasing alveolar \( O_2 \) in poorly ventilated units (units that were previously subject to hypoxic vasoconstriction). Vasoconstriction is reversed and blood is now sent once again to poorly ventilated regions of lung. Supplemental oxygen may improve \( PAO_2 \), but it does not change alveolar ventilation. Consequently, the body is less able to eliminate carbon dioxide when hypoxic pulmonary vasoconstriction is reversed and perfusion to poorly ventilated lung units is increased.

D. Shunt

1. Intra-Pulmonary shunt is an extreme form of \( \dot{V}/Q \) mismatch in which there is perfusion to alveoli, but no ventilation (i.e., \( \dot{V} = 0 \)).
The most classic form of shunt occurs when blood goes from the right side of the heart to the left side of the heart without ever passing through pulmonary capillaries, e.g., an arterio-venous malformation (AVM), which is an abnormal connection between pulmonary arterioles and venules, or a patent foramen ovale (PFO), which is a small defect in the wall between the right and left atria. In these situations, some deoxygenated blood goes from the right to the left side of the circulation without actually coming into contact with an alveolus.

A classical intra-pulmonary shunt is due to situations in which an alveolus is completely filled with fluid or is collapsed and there is still blood flow to the alveolus; thus, the lung unit receives no ventilation but, because of derangements in hypoxic pulmonary vasoconstriction that are associated with the disease process itself, the unit still receives some blood flow, i.e., hypoxic pulmonary vasoconstriction is not perfect.

If a substantial proportion of the body’s cardiac output (the number of liters/minute that the blood pumps) flows through a shunt, supplemental oxygen has a minimal effect on PaO₂ (the oxygen content of blood going through well ventilated units is already near maximum, and oxygen content of blood perfusing alveoli with no ventilation is not changed). We characterize a patient as having a clinically significant shunt if that patient is hypoxemic and supplemental oxygen does not raise the PaO₂ substantially. Thus, a patient may have a small number of collapsed, fluid filled alveoli but not be hypoxemic (either because hypoxic pulmonary vasoconstriction may redirect the blood to well ventilated alveoli, or because only a small proportion of cardiac output is flowing through these alveoli – in either case, little blood is flowing through the shunt), and we would not say that the patient is manifesting evidence of physiological shunt.

2. Clinically significant intra-pulmonary shunt implies associated abnormality in vasoregulation. Pulmonary arterioles normally should constrict if they flow through a region of lung that is hypoxic and, thereby, direct blood to better-ventilated portions of lung.

SEE FIGURE 5 (next page)
FIGURE 5. Relationships between various degrees of ventilation and perfusion on alveolar gas concentrations. **Top panel:** (A) represents normal ventilation and perfusion. Venous blood returns to the alveolus with PO$_2$=40 and PCO$_2$=45, exchanges oxygen and carbon dioxide with the alveolus, and exits with a PO$_2$=100, PCO$_2$=40. (B) represents an intrapulmonary “shunt.” There is no ventilation to the alveolus (note the obstruction in the airway leading to the alveolus). The partial pressures of oxygen and carbon dioxide in the blood are the same entering and exiting the alveolus since no gas exchange takes place. (C) represents “alveolar dead space.” There is no blood flow to the alveolus (note the obstruction in the artery leading to the alveolus). Thus, the alveolar gas is the same as atmospheric gas. **Bottom panel:** The curve shows the continuum of PO$_2$ (X-axis) and PCO$_2$ in the alveolus as ventilation/perfusion relationships vary from shunt (far left) to alveolar dead space (far right).

**QUESTION 8:** If a patient is hypoxemic due to a large intrapulmonary shunt, how does the oxygen content change with the addition of supplementary oxygen to the inspired gas? What are the physiological principles that explain this finding?

**QUESTION 9:** A patient has an intrapulmonary shunt and hypoxemia but is not hypercapnic. Why?
E. Diffusion

1. Exchange of gas between the alveolus and blood at the level of the alveolus occurs by diffusion.

2. When an individual is at rest, the exchange of oxygen and carbon dioxide occurs long before the red blood cell traverses the alveolus (NOTE: this is the reason we can assume that PaCO₂=PA CO₂ in the Bohr dead space derivation). Consequently, there is greater "reserve capacity" for diffusion, which means that diffusion problems are rarely a cause of hypoxemia at rest. See Figure 6 below.

**FIGURE 6.** Physiological gas transfer between alveolar gas and pulmonary capillary blood. Oxygen and carbon dioxide partial pressures in a volume of blood passing through a pulmonary capillary. Mixed venous blood enters the capillary with PO₂=40 and PCO₂=47 torr. Gas diffusion proceeds rapidly enough so that equilibration with alveolar gas is achieved before the end of the capillary.

**QUESTION 10:** Under what conditions will a diffusion abnormality lead to hypoxemia?

F. Summary of physiologic causes of hypoxemia:

1. Decreased inspiratory partial pressure of oxygen - e.g., altitude.
2. Hypoventilation.
4. Shunt.
5. Diffusion abnormality.
V. Summary

A. Consider the relationships between ventilation and perfusion; remember to distinguish alveolar ventilation from dead space ventilation.

B. Carbon dioxide and oxygen have different affinities for hemoglobin. Understand the significance of each for the delivery of oxygen to the tissues and the transport of carbon dioxide to the lungs.

C. Recall the three physiologic causes of hypercapnia. Understand why V/Q abnormalities have to be fairly severe before hypercapnia develops.

D. Recall the five physiologic causes of hypoxemia and the use of the alveolar gas equation to determine if there is a gas exchange abnormality. A gas exchange abnormality, i.e., a problem at the level of the alveolus and the pulmonary capillary, is present if the A-aDO2 is abnormal.

Summary Points

- Alveolar ventilation is the amount of air that enters or exits perfused alveoli each minute and is one of the key determinants of the PaCO2.
- Dead space refers to regions of the lung that receive air but do not participate in gas exchange.
- Physiologic dead space refers to the sum of anatomic dead space (airways) and alveolar dead space (alveoli that receive air but are not perfused).
- Total ventilation is the sum of alveolar and dead space ventilation.
- Physiological dead space can be measured with determination of the dead space to tidal volume ratio using the Bohr Method, which makes use of the principle that gas coming from dead space contains no carbon dioxide while gas coming from perfused alveoli has a PACO2 equivalent to the PaCO2.
- The carbon dioxide elimination relationship, or clearance equation for the lung, indicates that alveolar ventilation is inversely proportional to arterial PCO2, and directly proportional to carbon dioxide production.
- At FRC in the upright person, the alveoli at the apex of the lung are larger than at the base because of the distribution of the pleural pressure over the lung; the pleural pressure is lower (more negative) at the apex of the lung.
- During a normal tidal volume breath from FRC, the bases of the lung receive a greater proportion of the breath than the apices of the lung.
- The pulmonary circulation is a high compliance and low resistance system; thus, it can accommodate significant increases in blood flow with relatively small changes in pressure.
- In the normal person in the upright position, more blood flow goes to the bases than the apices of the lungs as a result of the effects of gravity.
• In the most superior (opposite gravity) portions of the lung, there may be no blood flow to some alveoli (alveolar dead space, Zone 1 of the lung). In these regions of lung, alveolar pressure may exceed pulmonary capillary pressure.

• The three zones of the lung describe the relative amounts of perfusion to different regions of the lung. These zones are derived from the relationships between alveolar, pulmonary arterial, and pulmonary venous pressures.

• The pulmonary arterioles respond to local hypoxia by constricting. This results in the redirection of blood flow to lung units with higher PAO₂.

• Optimal efficiency of gas exchange depends upon matching of ventilation and perfusion within the lung. Ventilation-perfusion mismatch (V/Q mismatch) is a major cause of hypoxemia in cardiopulmonary diseases.

• The carbon dioxide-hemoglobin dissociation curve is relatively linear. This relationship allows hyperventilation of normal alveoli to compensate for hypoventilation of diseased lung units.

• The Haldane Effect describes the shift to the right of the carbon dioxide-hemoglobin dissociation curve in the presence of oxygen. Carbon dioxide is displaced from hemoglobin and enters the blood as a dissolved gas. Thus, for a given CO₂ content, PaCO₂ is higher in the presence of high concentrations of oxygen.

• The physiological causes of hypercapnia include reduced alveolar ventilation (due to a decrease in total ventilation, a change in breathing pattern, or V/Q mismatch), and increased carbon dioxide production in the setting of minimal ventilatory reserve.

• The oxygen-hemoglobin dissociation curve has a sigmoid shape. This relationship insures that a mild decrease in alveolar PO₂ does not significantly affect hemoglobin saturation and the oxygen content of the blood, and that oxygen is released readily when blood reaches peripheral tissue.

• The vast majority of oxygen carried in blood is bound to hemoglobin.

• The oxygen-hemoglobin dissociation curve may shift to the right or the left based upon factors including body temperature, blood pH, and PaCO₂.

• The alveolar gas equation allows one to calculate the PAO₂. Utilizing this value and the PaO₂ obtained from an arterial blood gas, one can calculate the alveolar-arterial oxygen difference (A-aDO₂), a number that is essential in analyzing the physiological cause of hypoxemia. An abnormal A-aDO₂ indicates that there is a problem with the gas exchanger.

• There are five physiological causes of hypoxemia: decreased PIO₂, alveolar hypoventilation, V/Q mismatch, shunt, and abnormal diffusion. The physiological cause of hypoxemia can be determined in most cases with knowledge of the A-aDO₂, the response of the PaO₂ to supplemental oxygen, and with information on whether the hypoxemia is present at rest or only with exercise.

• Ventilation-perfusion mismatch is the most common physiological cause of hypoxemia. Mild to moderate V/Q mismatch is much more likely to produce hypoxemia than hypercapnia because of the different shapes of the oxygen-hemoglobin and carbon dioxide-hemoglobin dissociation curves.