WCHP Respiratory Physiology 2009-2010
PULMONARY GAS EXCHANGE

Clinical rationale and overall goal:

The uptake of oxygen from the inspired air and the excretion of carbon dioxide in the expired air are dependent on diffusion of these gases across the respiratory membrane. The over goal of this classroom session is to provide the student with an understanding of the basic principles of diffusional pulmonary gas exchange, the concept of the ventilation-perfusion ratio, and the concept of venous admixture (shunting), all of which are essential for understanding the genesis of the typical normal arterial PO_2 and the pathogenesis of arterial hypoxemia.

Sources of information:

The sources of information that will be sufficient for the individual student to master the specific objectives listed below include the following:

- The required text: Guyton & Hall, *Textbook of Medical Physiology 11th edition*, Chap. 39;
- handouts, reprints or other supplementary materials provided by department faculty;
- lecture notes;

Nota bene: Students are expected to be prepared for class by having read the relevant sections in the text(s) prior to the classroom sessions on individual topics, to take their own notes during classroom sessions, to participate actively in any large-group or break-out group activities, and to try all online quizzes. Students are encouraged to contact the instructor via email (jnorton@une.edu) with any questions. Students are strongly discouraged from using class notes provided by a note service as the sole or even the primary source of information in this course.

Learning objectives:

Following study of appropriate sections in the assigned texts (or similar sections in other texts available to the student and approved by the instructor) and attendance at the lectures on this topic, the student should be able to:

1. Define or otherwise indicate an understanding of the following words or phrases: ideal gas law; partial pressure (P); solubility coefficient for O_2 and CO_2; respiratory membrane; pulmonary diffusion capacity (D_L); diffusion rate; alveolar gas; ventilation-perfusion ratio, $\frac{\dot{V}_A}{\dot{Q}}$; A-a PO_2 difference.

2. Recognize the standard notations used in Respiratory Physiology for quantities (pressure, fractional concentration, content, etc.), locations (arterial, alveolar, inspired, etc.), and rates (minute ventilation, alveolar ventilation, *etc.*); *For example: write the correct notation for the partial pressure of nitrogen in mixed venous blood.*

3. Demonstrate an understanding of the concept of partial pressure it applies to gas mixtures (*e.g.*, alveolar air) and gasses dissolved in aqueous solutions (*e.g.*, pulmonary capillary blood);

4. Recognize the typical fractional concentrations and partial pressures of oxygen and carbon dioxide in ambient air, inspired air, alveolar air, and expired air, and recognize typical values for partial pressures of oxygen and carbon dioxide in mixed venous blood and arterial blood;

5. Demonstrate an understanding of the determination of *pulmonary diffusing capacity* using carbon monoxide ($D_{L_{CO}}$), illustrated by the expression below, and identify its significance in pulmonary gas exchange;

$$D_{L_{CO}} = \frac{\dot{V}_{CO}}{P_{A_{CO}}}$$

6. Describe the most likely effect (increase, decrease, no change) of each of the following on $D_{L_{CO}}$: anemia; exercise; pneumonectomy; pulmonary edema; pulmonary fibrosis; emphysema;

7. Demonstrate an understanding of the origin and physiological significance of regional differences in ventilation-perfusion ratios that exist in the lung of a healthy, normal human subject standing upright;

8. Indicate the effects (increase, decrease, no change) of changes in the magnitude of venous admixture (physiological shunting) on arterial partial pressures of oxygen and carbon dioxide in an otherwise healthy human subject;

9. Indicate the effects (increase, decrease, no change) of changes in the ventilation-perfusion ratio, $\frac{\dot{V}_A}{\dot{Q}}$, on alveolar and arterial partial pressures of oxygen and carbon dioxide in an otherwise healthy human subject;

10. Demonstrate an understanding of the causes of the *alveolar-arterial PO_2 difference* (A-a PO_2 difference) commonly seen even in healthy human subjects;

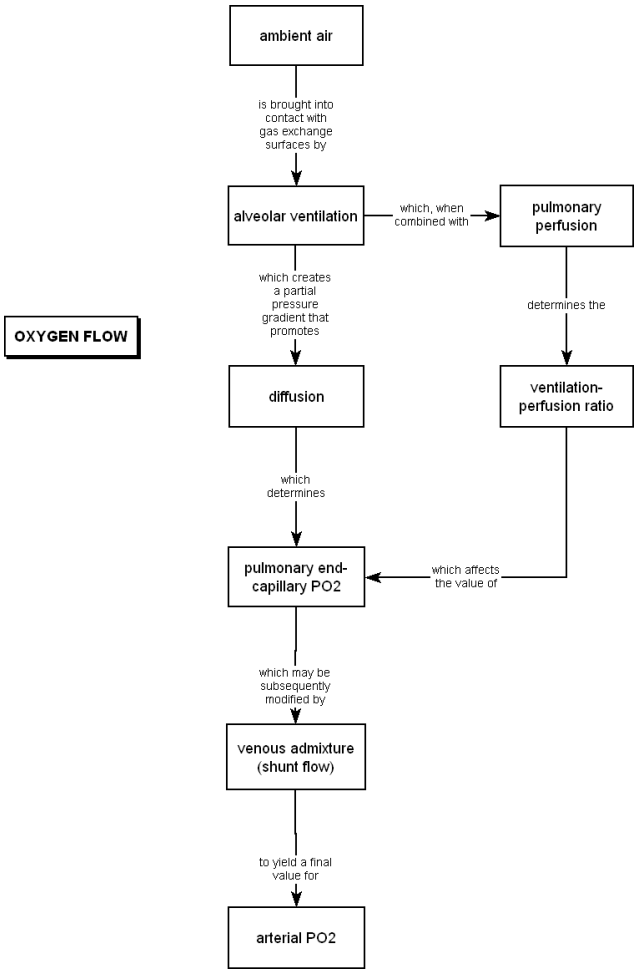
11. Given values for inspired PO_2 and/or F_IO_2, barometric pressure, respiratory exchange ratio, and arterial (or alveolar) PCO_2 provided in a real or simulated patient case study, calculate the simplified version of the alveolar PO_2 using the *alveolar air equation* shown below, and use this calculated alveolar PO_2 to calculate the *A-a O_2 difference*;

$$P_AO_2 = (P_B - P_{H_2O}) \cdot F_IO_2 - \frac{P_ACO_2}{R}$$

The pathway for Oxygen

The diagram below summarizes the pathway for oxygen from the ambient air to the arterial blood, and will serve as the framework for the subsequent discussions of pulmonary gas exchange and the pathophysiology of hypoxemia. Students should be familiar with the terms and concepts inherent in this diagram, and following the arrows from block to block will provide a narrative of the factors that affect PO_2 at each step of the way.

Ambient air is brought into contact with gas exchange surfaces within the lung by *alveolar ventilation*, a topic already discussed in some detail in previous handouts and lectures. Deoxygenated blood from systemic tissues is brought into contact with the gas exchange surfaces within the pulmonary capillaries of the lung by *pulmonary blood flow*, also discussed in detail previously. The relatively high partial pressure of oxygen in the alveolar gas promotes *diffusion* of oxygen across the respiratory membrane into the initially deoxygenated pulmonary capillary blood, until diffusion equilibrium between the alveolar gas and pulmonary capillary blood is achieved. The factors affecting the rate of diffusion of oxygen (and carbon dioxide) across the respiratory membrane, and the measurement of pulmonary diffusing capacity using carbon monoxide, will be discussed below.



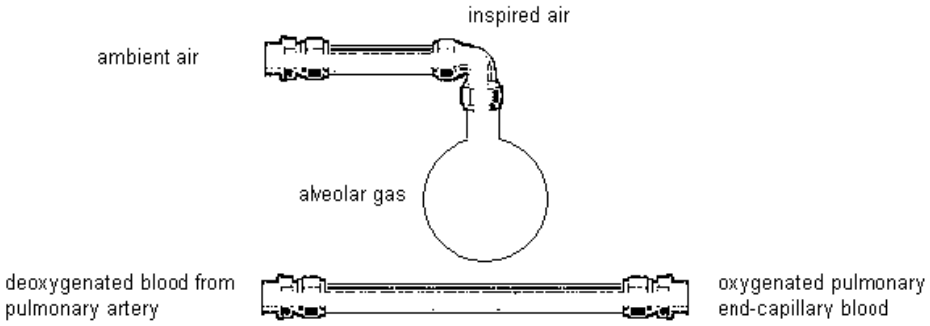
The ratio of alveolar ventilation to pulmonary blood flow, the ventilation-perfusion ratio or $\frac{\dot{V}_A}{\dot{Q}}$, in addition to the diffusing capacity of the lung, D_LCO, is an important determinant of the partial pressure of oxygen in the alveolar gas, at the ends of the pulmonary capillaries, and in the arterial blood. The mechanism(s) by which the *ventilation-perfusion ratio* affects the PO_2 in these locations will be discussed in detail below.

Finally, the mixing of deoxygenated blood into the oxygenated pulmonary venous blood, described as *venous admixture* or *shunt flow*, affects the ultimate value for arterial PO_2, and normal (anatomical) venous admixture as well as abnormal sources of venous admixture will be discussed below.

Diffusion across the respiratory membrane and the measurement of pulmonary diffusing capacity

Partial pressure gradients between the alveolar gas and the pulmonary capillary blood drive the diffusion of oxygen and carbon dioxide. Movement of oxygen involves sequential diffusion through the various components of the respiratory membrane, through the plasma, and into the erythrocyte, where the oxygen binds to hemoglobin and is taken out of solution.

The diagram below will be used in classroom discussions of the diffusion of oxygen and carbon dioxide within the lung and in the determination of pulmonary diffusion capacity. *Ambient air* (the air we walk around in) that has been brought into the conducting system, warmed, and humidified is called *inspired air*; air carried all the way into alveoli is called *alveolar gas*. Deoxygenated blood is brought into the lung *via* the pulmonary artery and into the *pulmonary capillaries*, which are separated from the alveolar gas by the *respiratory membrane*. Normally, the alveolar gas and pulmonary capillary blood quickly reach diffusion equilibrium, and the partial pressures in the alveolar gas and the pulmonary end-capillary blood are the same.



The rate of diffusion of a gas through the respiratory membrane ($\dot{V}_{gas}$) is directly proportional to the diffusion coefficient of the lung (D), the partial pressure gradient (P) and the total surface of the membrane (A), and is inversely proportional to the length of the diffusion pathway, *i.e.*, the thickness of the membrane (x). This can be described mathematically as follows:

$$\dot{V}_{gas} = \frac{D \cdot A}{x} \cdot P$$

The diffusion coefficient, D, incorporates such physical and chemical factors as temperature, molecular weight of the substance diffusing, the solubility of the substance diffusing in the medium, etc. The expression above can be more directly related to pulmonary gas diffusion by replacing the term $D \cdot \frac{A}{x}$ with $D_{L_{gas}}$, the diffusing capacity of the lung for that gas; and by replacing the partial pressure gradient term, P, with the full expression describing the alveolar-capillary partial pressure gradient, $P_{A_{gas}} - P_{c_{gas}}$, to yield the following:

$$\dot{V}_{gas} = D_{L_{gas}} \cdot \left(P_{A_{gas}} - P_{c_{gas}} \right)$$

This expression can be rearranged algebraically to yield an expression that reveals how the diffusing capacity of the lung might be measured:

$$D_{L_{gas}} = \frac{\dot{V}_{gas}}{P_{A_{gas}} - P_{c_{gas}}}$$

Measurement of the movement of a gas across the respiratory membrane, $\dot{V}_{gas}$, can be made by comparing the concentration of the gas in the inspired and expired air at a given level of minute ventilation. The alveolar partial

pressure of a gas, $P_{A_{gas}}$, can be measured as the partial pressure of an end-tidal air sample. The problem arises with the pulmonary capillary partial pressure of a gas, $P_{c_{gas}}$, which is technically difficult to measure and mathematically difficult to calculate. For oxygen and carbon dioxide, the capillary partial pressures change as the blood flows through the capillary, so the concentration gradient is also changing. The solution to this problem is to use a gas for which the pulmonary capillary partial pressure can be known or estimated with some certainty, and the gas of choice is carbon monoxide, CO. The affinity of hemoglobin for carbon monoxide is 250 times higher than the affinity of hemoglobin for oxygen, and any carbon monoxide that diffuses into the pulmonary capillary is quickly taken up by hemoglobin and removed from solution. Since it is only dissolved gas that contributes to partial pressure, the capillary partial pressure of CO will remain close to zero [0]. The use of trace amounts of CO will allow $\dot{V}_{CO}$ and $P_{A_{CO}}$ to be measured directly, and the partial pressure gradient promoting diffusion of carbon monoxide across the respiratory membrane can be calculated by assuming that $P_{c_{CO}}$ is zero [0]. The above equation then becomes:

$$D_{L_{CO}} = \frac{\dot{V}_{CO}}{P_{A_{CO}}}$$

Since oxygen (O_2) and carbon dioxide (CO_2) are similar in composition, molecular weight, and physical properties to carbon monoxide (CO), measurements of D_LCO can be used to predict the diffusion capacity of the lung for oxygen and carbon dioxide. The diffusion capacity of the lung for oxygen, D_LO_2, is about the same as D_LCO, but pulmonary diffusion capacity for carbon dioxide, D_LCO_2, is much higher, due to the relatively high solubility of carbon dioxide in body fluids. For this reason, respiratory diseases that affect the surface area available for diffusion in the lung, or the thickness of the respiratory membrane, have a greater effect on the diffusion of oxygen than carbon dioxide. Carbon dioxide retention is rarely a problem even when there is a severe reduction in pulmonary diffusion capacity that impairs the movement of oxygen into the pulmonary capillary blood. Normal values for D_LCO have been established for patient populations with respect to age, sex, and body weight; a typical value for D_LCO is 25 ml/min/mm Hg.

Although the description provided above is the most direct way of explaining pulmonary diffusing capacity, D_LCO may also be described mathematically by the following expression, which is found in many textbooks of Physiology and which should, for completeness, be mentioned here:

$$\frac{1}{D_{L_{CO}}} = \frac{1}{D_{m_{CO}}} + \frac{1}{\theta \cdot V_c}$$

This expression for D_LCO provide separate terms for the diffusion capacity of the respiratory membrane, D_mCO, and for the rate of uptake of carbon monoxide by red blood cells, $\theta \cdot V_c$, which is dependent on the rate of combination of carbon monoxide with hemoglobin (θ) and the volume of blood in the pulmonary capillaries (V_c). The expression actually describes the total resistance to movement of carbon monoxide as the sum of two resistances, one at the respiratory membrane and the other associated with the combination of CO with hemoglobin. The student should be reminded here that D_LCO is a measure of CO *conductance*, and that *resistance is the inverse of conductance*, as follows:

$$\text{resistance} = \frac{1}{\text{conductance}}$$

The total resistance to CO movement can therefore be described as $\frac{1}{D_{L_{CO}}}$, the resistance at the respiratory membrane as $\frac{1}{D_{m_{CO}}}$, and the reaction of CO with hemoglobin as $\frac{1}{\theta \cdot V_c}$.

Ventilation-perfusion ratio

Alveolar ventilation equation:

A discussion of the effects of ventilation-perfusion ratios on pulmonary gas exchange and alveolar partial pressures for oxygen and carbon dioxide best begins with a consideration of carbon dioxide. The *alveolar ventilation equation* relates the rate of carbon dioxide production ($\dot{V}_{CO_2}$), the rate of alveolar ventilation ($\dot{V}_A$), and the alveolar partial pressure of carbon dioxide, P_ACO_2, as follows:

$$P_ACO_2 = \frac{\dot{V}CO_2}{\dot{V}_A} \cdot K$$

In the equation above, the rate of CO_2 production is expressed as ml/min, STPD; the rate of alveolar ventilation is expressed as L/min, BTPS, and alveolar PCO_2 is expressed as mm Hg. K is a constant, with a value of 0.863, which corrects for differences among these units. In this form, the alveolar ventilation equation correctly places the two independent determinants of alveolar PCO_2 – alveolar ventilation and the rate of CO_2 production – correctly together on the right-hand side of the equation, where independent variables usually reside. For example, alveolar PCO_2 (and therefore arterial PCO_2) can be increased either by increasing the rate of CO_2 production, or by decreasing the rate of alveolar ventilation.

Alveolar air equation:

At the same time carbon dioxide is added to the alveolar gas, oxygen is being removed from it. The alveolar air equation is used to calculate a value for alveolar PO_2 given knowledge of the barometric pressure, the alveolar PCO_2, and the respiratory exchange ratio, R. The full form of the alveolar air equation is the following:

$$P_AO_2 = P_IO_2 - \frac{P_ACO_2}{R} + \left[P_ACO_2 \cdot F_IO_2 \cdot \frac{1-R}{R} \right]$$

The equation above can be simplified greatly, however, since the magnitude of the last term in brackets is only a few mm Hg. The simplified form of the alveolar air equation that students should use in this course and in the discussions of the pathophysiology of arterial hypoxemia is the following:

$$P_AO_2 = P_IO_2 - \frac{P_ACO_2}{R}$$

where

$$P_IO_2 = (P_B - P_{H_2O}) \cdot F_IO_2$$

In the expression immediately above, F_IO_2 represents the fractional concentration of oxygen in the ambient air, or 21%. At sea level, with a normal barometric pressure of 760 mm Hg, P_IO_2 becomes (760-47)·0.21, or about 150 mm Hg.

The logic behind the alveolar air equation is the following: as inspired air enters the alveoli, oxygen is removed from it, and carbon dioxide is added to it. The alveolar PO_2 is therefore lower than the inspired PO_2, and the alveolar PCO_2 is higher than the inspired PCO_2. If we know the ratio of exchange of oxygen and carbon dioxide (the respiratory exchange ratio, R), we can predict the magnitude of the drop in PO_2 between inspired air and alveolar gas from the corresponding increase in PCO_2, using the term PCO_2/R. Subtracting this calculated change in PO_2 from the actual inspired PO_2 will yield a very good approximation of the alveolar PO_2.

Since complete equilibrium normally occurs between carbon dioxide partial pressures in alveolar gas and pulmonary capillary blood, and since there is little change in PCO_2 between the pulmonary end-capillary blood and arterial blood, the arterial PCO_2 obtained from arterial blood gas analysis can be used in the alveolar air equation above in place of the term for alveolar PCO_2. It is possible, therefore to determine with some certainty the alveolar

partial pressure of oxygen and carbon dioxide and oxygen from the information obtained in an arterial blood gas study.

For example, arterial blood gas values obtained from a patient breathing room air at sea level (barometric pressure, 756 mm Hg) include the following: arterial PO_2, 86 mm Hg; arterial PCO_2, 42 mm Hg; pH, 7.38; bicarbonate, 24 mEq/L. Inspired PO2 would be calculated as (756-47)·0.21, or 149 mm Hg. Alveolar PO_2, calculated from the simplified version of the alveolar gas equation above, assuming a respiratory exchange ratio of 0.8, would be $149 - \frac{42}{0.8}$, or 96.5 mm Hg.

Effects of changes in ventilation on alveolar gas partial pressures:

The physiological principles described in the alveolar ventilation equation and the alveolar air equation allow prediction of the effects of changes in ventilation on alveolar, and therefore arterial, partial pressures of oxygen and carbon dioxide. For example, an increase in alveolar ventilation without an increase in carbon dioxide production or pulmonary blood flow will cause alveolar PCO_2 to decrease, according to the alveolar ventilation equation. The decrease in alveolar PCO_2 will be accompanied by an increase in alveolar PO_2, according to the alveolar air equation. Conversely, a decrease in alveolar ventilation, without an increase in carbon dioxide production or pulmonary blood flow, will cause alveolar PCO_2 to rise and alveolar PO_2 to fall. These changes in alveolar gas composition with changes in alveolar ventilation will be reflected in corresponding changes in the arterial partial pressures of these gases.

An important point to make here relates to the definitions of the commonly used terms *hyperventilation* and *hypoventilation*. *Hyperventilation* is defined as a level of alveolar ventilation that leads to a *decrease* in alveolar and arterial PCO_2. *Hypoventilation*, conversely, is defined as a level of alveolar ventilation that results in an *increase* in alveolar and arterial PCO_2. In other words, hyperventilation and hypoventilation cannot be used to describe simply increased ventilation and decreased ventilation; the use of these terms must be restricted to levels of ventilation that produce changes in PCO_2. Thus, the increase in ventilation seen in an exercising human subject who maintains a normal arterial PCO_2 cannot be called hyperventilation, but rather must be described as *tachypnea* and *hyperpnea*.

Effects of changes in blood flow (perfusion) on alveolar gas partial pressures:

Gas exchange in the lung is affected not only by changes in ventilation, but also by changes in pulmonary blood flow. The alveolar PO_2 can be considered to represent a balance between the rate at which oxygen is brought into the alveoli by alveolar ventilation and the rate at which oxygen is removed from alveolar gas by diffusion into the pulmonary capillary blood. Likewise, alveolar PCO_2 can be considered to represent a balance between the rate at which CO_2 is removed from the alveolar air by alveolar ventilation and the rate at which CO_2 is added to alveolar gas by diffusion from the pulmonary capillary blood. For example, with no change in ventilation, a decrease in pulmonary blood flow will cause alveolar PO_2 to rise and alveolar PCO_2 to fall, since the decreased blood flow will not remove as much oxygen from, or add as much carbon dioxide to, the alveolar gas.

Effects of changes in the ventilation-perfusion ratio on alveolar gas partial pressures:

The effects of changes in ventilation and pulmonary blood flow on alveolar partial pressures of oxygen and carbon dioxide can be combined into a consideration of the effects on alveolar gas pressures of changes in the ventilation-perfusion ratio, or $\frac{\dot{V}_A}{\dot{Q}}$. A relatively simple way for the student to understand the effects of changes in $\frac{\dot{V}_A}{\dot{Q}}$ on gas exchange is the following: alveolar ventilation brings into the area of gas exchange inspired air, which has a high PO_2 and essentially no CO_2; pulmonary blood flow brings into the region of gas exchange deoxygenated blood with a low PO_2 and a high PCO_2. If ventilation is greater than perfusion, the alveolar gas partial pressures become more like those in inspired air, with a higher PO_2 and lower PCO_2; if perfusion is relatively greater than ventilation, the alveolar gas partial pressures for oxygen and carbon dioxide become more like those in venous blood, with a lower PO_2 and higher PCO_2. The absolute values for ventilation and perfusion are less important in this analysis than the relative amount of each as expressed in the ventilation-perfusion *ratio*.

Pulmonary venous blood leaving a region of the lung with a high ventilation-perfusion ratio would, therefore, have a higher PO_2 and lower PCO_2 than would pulmonary blood leaving a region of the lung with a normal or low

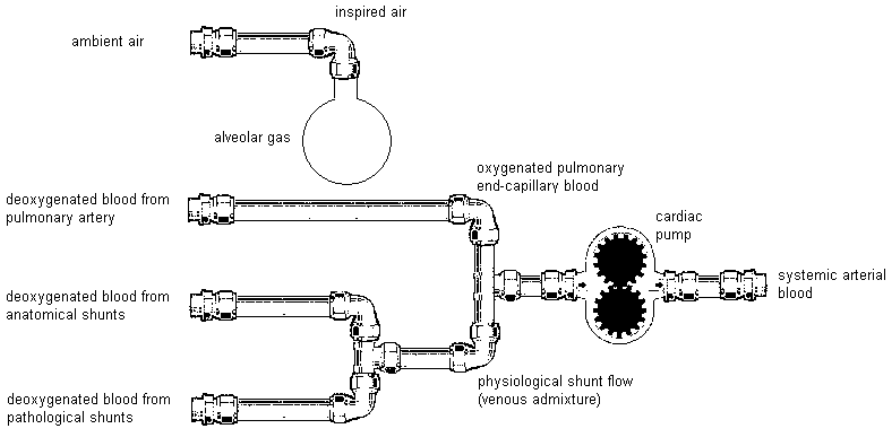
ventilation-perfusion ratio. This would occur regardless of whether the increase in the ventilation-perfusion ratio was due to an increase in ventilation or a decrease in perfusion (or both!). Similarly, pulmonary venous blood leaving a region of the lung with a low ventilation-perfusion ratio would, therefore, have a lower PO_2 and higher PCO_2 than would pulmonary blood leaving a region of the lung with a normal or high ventilation-perfusion ratio. This would also occur regardless of whether the decrease in the ventilation-perfusion ratio was due to a decrease in ventilation or an increase in perfusion (or both!).

Venous admixture, or shunt flow

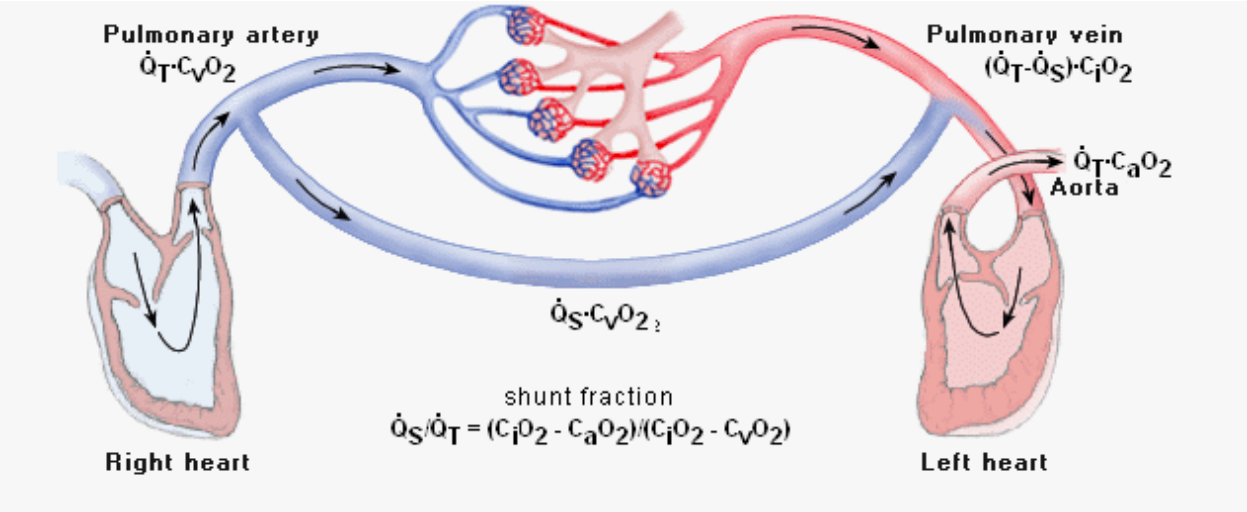
The lung receives blood flow from two sources. First, deoxygenated blood from the pulmonary artery is carried into the pulmonary capillaries and placed in close contact with the alveolar gas. Diffusion of oxygen between the alveolar gas and pulmonary capillary blood normally produces well-oxygenated end-capillary blood that enters the pulmonary venous circulation. Second, oxygenated blood in the bronchial arteries nourishes the structures of the lung, and in the process becomes deoxygenated. This bronchial venous blood is normally carried back to the right side of the heart by the azygos vein.

The separation between these two circulations is not complete, however. Even in healthy human subjects, there is some admixture of deoxygenated blood from the bronchial venous circulation with well-oxygenated pulmonary venous blood *via* what is called *anatomic shunt flow*. Additional anatomic venous admixture or shunt flow occurs in the heart, where the Thebesian vessels empty deoxygenated blood from the coronary circulation directly into the left ventricular chamber.

The amount of venous admixture or shunt flow can be increased in pathological situations, such as those associated with blockage of alveolar ventilation, including atelectasis, filling of alveoli with fluid or inflammatory cells, or blockage of a bronchus or bronchiole supplying a portion of the respiratory tree. In these cases, there would be no alveolar ventilation in these regions, the ventilation-perfusion ratio would be zero [0], and the pulmonary capillary blood perfusing these alveoli would not become oxygenated. This unaltered, deoxygenated blood from pulmonary capillaries perfusing non-ventilated alveoli would mix with normally oxygenated blood from other regions of the lung, producing an increase in the total amount of venous admixture. Other sources of increased venous admixture are arteriovenous malformations within the lung and intracardiac shunts that allow mixing within the heart of deoxygenated blood from the right atrium or ventricle with oxygenated blood in the left side of the heart. The sum of the normal anatomic shunt flow and the additional abnormal shunt flow from non-ventilated areas of the lungs, arteriovenous malformations, or intracardiac shunts is described as the *physiologic shunt flow*. In healthy human subjects with no non-ventilated alveoli or intracardiac right-to-left shunts, the physiologic shunt flow is very close to, or identical to, the anatomic shunt flow. The diagram below will be used in class to illustrate the possible anatomic and pathologic sources of venous admixture that comprise the physiological shunt flow, and illustrates how the physiologic shunt flow is mixed with oxygenated blood from ventilated, perfused alveoli and carried out into the peripheral circulation.



A somewhat more anatomical diagram (but still somewhat cartoonish) describing venous admixture or shunt flow is shown below.



This figure illustrates the effects of increased physiological shunts on arterial PO_2 and oxygen content, and provides a visualization of the rationale behind the shunt equation. The rate at which oxygen is brought into the lung is calculated as the product of pulmonary blood flow ($\dot{Q}_T$) and pulmonary arterial oxygen content (C_vO_2). The rate at which oxygen is sent out to the peripheral tissues is calculated as the product of systemic blood flow ($\dot{Q}_T$) and systemic arterial oxygen content (C_aO_2). The arterial oxygen content is determined by the relative contributions of pulmonary capillary blood flow and physiological shunt flow. The shunt flow contribution is expressed as the product of shunt flow ($\dot{Q}_S$) and mixed venous oxygen content (C_vO_2). The oxygen content of the end-capillary blood (C_iO_2) is described as "ideal" because it represents diffusion equilibrium between the alveolar gas and the pulmonary capillary blood. The contribution of normal pulmonary venous blood to systemic arterial blood can be expressed the product of capillary blood flow (total flow minus shunt flow, or $\dot{Q}_T - \dot{Q}_S$) and the ideal end-capillary oxygen content (C_iO_2). Combining all of these quantities yields the shunt flow equation (also described in a previous handout and/or lecture):

$$\frac{\dot{Q}_S}{\dot{Q}_T} = \frac{C_iO_2 - C_aO_2}{C_iO_2 - C_vO_2}$$

The rationale behind the shunt equation is the dilution principle, and the determination of the magnitude of a physiologic shunt can be expressed as a question – "How much deoxygenated blood, with a low oxygen content equal to that of mixed venous blood (C_vO_2), would have to be added to ideal pulmonary end-capillary blood with a high oxygen content (C_iO_2) to yield the actual arterial oxygen content (C_aO_2)?"