WCHP Respiratory Physiology 2009-2010
Pathophysiology of Arterial Hypoxemia

Clinical rationale:

The final common feature of many forms of respiratory disease is *arterial hypoxemia*, defined as an arterial PO_2 that is less than 60 mm Hg while breathing room air at sea level (*Harrison's Principles of Internal Medicine, 16th edition*, Chapter 250, "Respiratory failure") and an arterial saturation that is less than 90%. The purpose of this section of the Respiratory System is to provide the student with an understanding of the basic pathophysiological mechanisms that may cause a reduction in arterial PO_2 and an appreciation of the signs, symptoms, and clinical tests that may help distinguish among these mechanisms. Arterial hypoxemia is, in turn, one of the causes of *tissue hypoxia*, along with reduced tissue blood flow, anemia, and toxic substances or drugs that impair aerobic metabolism at the cellular level. The *compensatory mechanisms* that help to prevent or minimize tissue hypoxia in the face of arterial hypoxemia will be included in this section.

Sources of information:

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

- *Harrison's Principles of Internal Medicine, 16th edition*, Chapter 234, "Disturbances of respiratory function, pp. 1498-1505. ***nota bene:*** This text is available free to students as **Harrison's Online** *via* the UNE "Libraries" website.
- Guyton and Hall, *Textbook of Medical Physiology* (11th editions), Chaps. 37, 38, 39, 42;
- Handouts, reprints or other supplementary materials provided by department or system faculty;
- The student's own lecture notes;

Learning outcomes:

Following study of this handout, reading of assigned pages sections in the required text, 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: arterial hypoxemia; ambient hypoxia; alveolar hyperventilation; alveolar hypoventilation; anatomical dead space; physiological dead space; alveolar dead space; diffusion capacity; anatomical shunt flow; physiological shunt flow; ventilation-perfusion mismatch;

2. List the five [5] possible pathophysiological causes of arterial hypoxemia;

3. Demonstrate an understanding of how ambient hypoxia, alveolar hypoventilation, decreased diffusion capacity, increased physiological shunt flow, and ventilation-perfusion mismatch actually cause a decrease in arterial PO_2;

4. Using arterial blood gas measurements and the *alveolar air equation*, calculate alveolar PO_2 and the A-a PO_2 difference, given information about the fractional concentration of oxygen in the ambient air, the barometric pressure, the arterial PO_2, and the alveolar (or arterial) PCO_2;

   Sample question: A hospitalized patient with respiratory disease is given supplemental oxygen sufficient to increase the fractional concentration of oxygen in the air she breathes to 30%. Arterial blood gas measurements on blood taken while she was breathing this gas mixture included the following: PO_2, 65 mm Hg: Hemoglobin concentration, 12 gm/dl; bicarbonate concentration, 27 mEq/L; pH, 7.30; PCO_2, 56 mm Hg. Barometric pressure is 756 mm Hg. What is this patient's A-a PO_2 difference, in mm Hg?

5. Using the *alveolar ventilation equation*, shown below, predict the direction of change in $PaCO_2$ (increase, decrease, no change) given information about changes in either alveolar ventilation or the rate of CO_2 production;

$$P_A CO_2 = \frac{\dot{V}_{CO_2}}{\dot{V}_A} \cdot 0.863$$

6. Identify the steady-state effects (increase, decrease, no change) of ambient hypoxia, alveolar hypoventilation, increased physiological shunt flow, and ventilation-perfusion mismatch on each of the following: inspired PO_2; alveolar PO_2; systemic arterial PO_2; systemic arterial PCO_2; and A-a PO_2 difference;

   Sample question: Which of the following would not be decreased in a patient with alveolar hypoventilation?
   - *a) Inspired PO_2*
   - *b) Alveolar PO_2*
   - *c) Pulmonary end-capillary PO_2*
   - *d) Systemic arterial PO_2*

7. Given a case study of a real or simulated patient with arterial hypoxemia that includes arterial blood gas values and other appropriate information, identify the possible cause(s) of arterial hypoxemia most likely present in the patient using the flow chart provided in this handout (adapted from *Harrison's Principles of Internal Medicine, 16th edition* [Figure 234-5]), and identify the physiological mechanisms (if any) by which the patient has compensated for the hypoxemia.

   Sample question: The following laboratory values and clinical findings were obtained on a 56-year-old male hypoxemic patient at SMMC breathing room air: arterial PO_2, 66 mm Hg; arterial PCO_2, 52 mm Hg; A-a PO_2 difference, 19 mm Hg; DL_{CO}, within normal limits; supplemental oxygen increased arterial PO_2 to 134 mm Hg. These results are most consistent with which of the following causes of arterial hypoxemia?
   - *a) Ambient hypoxia*
   - *b) Alveolar hypoventilation*
   - *c) Diffusion abnormality*
   - *d) Increased physiological shunt*

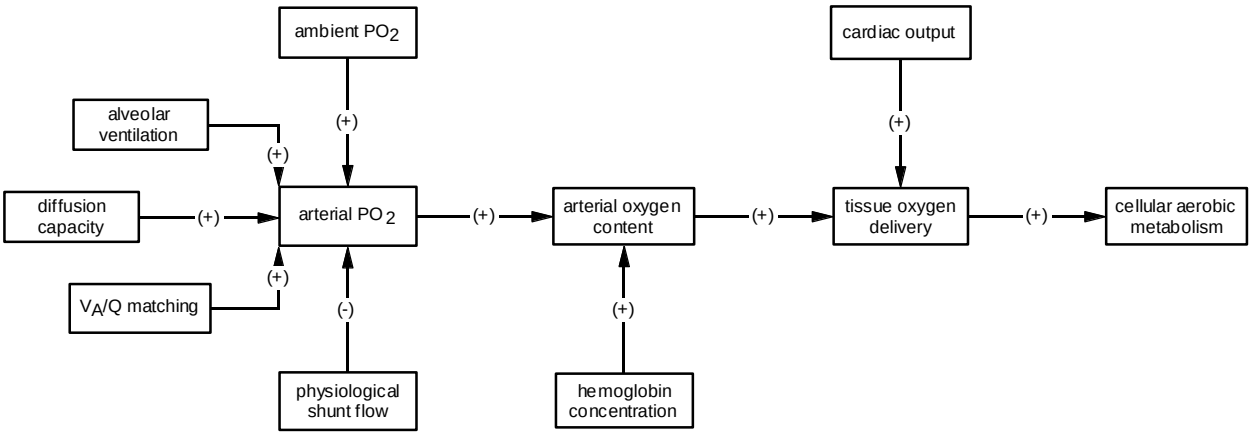
8. Identify at least three compensatory mechanisms for acute or chronic arterial hypoxemia, and recognize the physiological benefits of each;

9. Demonstrate an understanding of the term *cyanosis*, and recognize the distinction between *central cyanosis* and *peripheral cyanosis*;

10. Recognize or identify at least three causes of *tissue hypoxia*.

Introduction: determinants of arterial PO_2 and the importance of arterial PO_2 in tissue oxygen delivery:

The diagram below[1] summarizes the physiological determinants of arterial PO_2, and the role of arterial PO_2, along with hemoglobin concentration and cardiac output, in overall tissue oxygen delivery and in the maintenance of cellular aerobic metabolism.



The five [5] primary determinants of arterial PO_2 are on the left-hand side of the above diagram – the level of the *ambient PO_2*, the magnitude of *alveolar ventilation*, the *diffusion capacity* of the lung, the degree of *ventilation-perfusion matching*, and the magnitude of venous admixture, or *physiological shunt flow*. Increases in ambient PO_2, alveolar ventilation, diffusion capacity, and ventilation-perfusion matching will all increase arterial PO_2, and *vice versa*. An increase in the magnitude of the physiological shunt will decrease arterial PO_2. *Arterial PO_2* and the *hemoglobin concentration* together determine the magnitude of the *arterial oxygen content* (expressed as ml O_2/dl blood). The amount of oxygen actually delivered to the tissue, *tissue oxygen delivery* in the above diagram, is dependent on the combination of arterial oxygen content and *cardiac output*. Tissue oxygen delivery, in turn, supports cellular aerobic metabolism.

Causes of *arterial hypoxemia* (low arterial PO_2) can be visualized as changes in the variables on the left of the diagram, and the value of *increased hemoglobin concentration* as a physiological compensatory mechanism for maintaining arterial content can also be appreciated. Arterial hypoxemia (low *arterial* PO_2) is only one of the possible causes of *tissue hypoxia* (low *tissue* PO_2) due to decreased tissue oxygen delivery. Other causes of tissue hypoxia that can be visualized on the diagram above would be *anemia* (decreased hemoglobin concentration) and *decreased cardiac output*. Tissue hypoxia can therefore be the result of: 1) *respiratory diseases* that lower arterial PO_2, 2) *hematological disorders* that decrease the concentration of hemoglobin or otherwise render hemoglobin unable to bind oxygen (e.g., hemoglobinopathies, oxidation of hemoglobin to methemoglobin), and 3) *cardiovascular diseases* associated with decreased cardiac output. The student, therefore, should keep these causes of tissue hypoxia in mind when studying the pathophysiology of the respiratory, hematological, and cardiovascular systems.

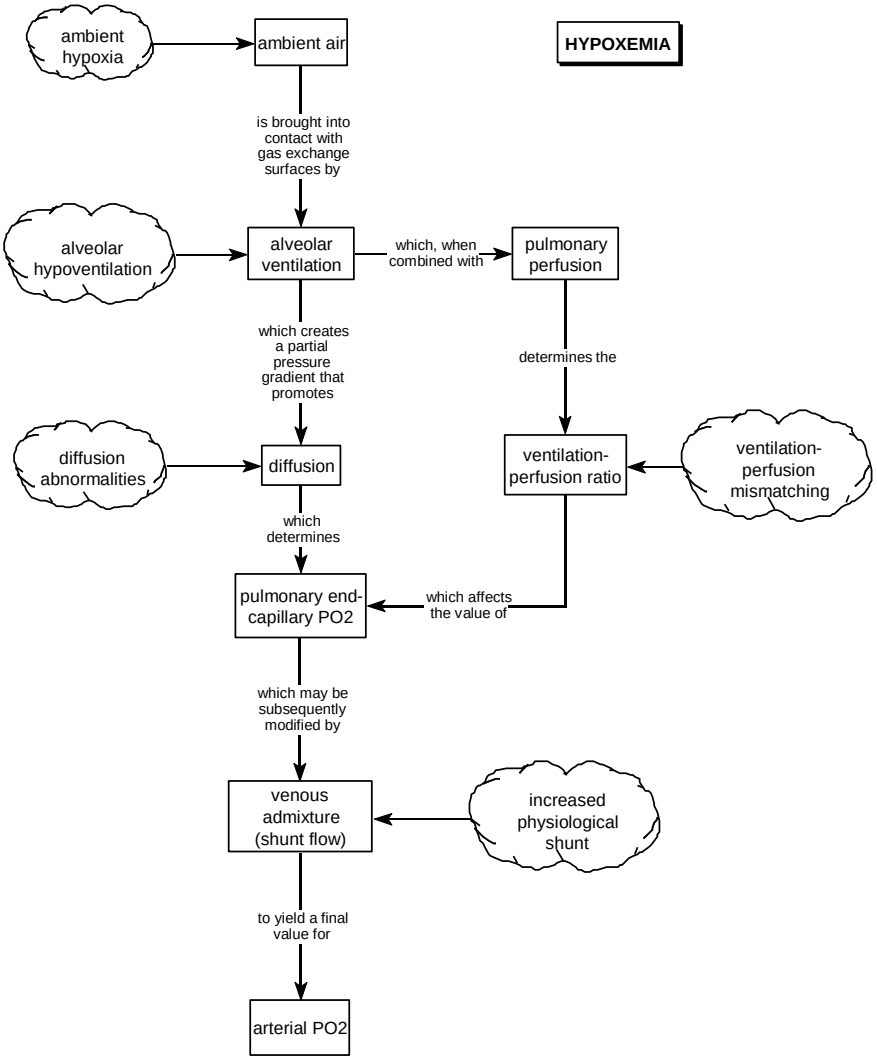
Overview of Pathophysiological Causes of Arterial Hypoxemia:

The following is an overview the five major causes of arterial hypoxemia (*ambient hypoxia*, *hypoventilation*, *diffusion abnormality*, *ventilation-perfusion mismatch*, and *increased physiological shunt*). For each of these five causes of hypoxemia, there are brief discussions of etiology, pathophysiological mechanism(s) by which arterial PO_2 is reduced, physiological compensatory mechanisms available, and response to oxygen therapy. The physiological compensations considered below are primarily the hypoxic ventilatory response (HVR), increased hemoglobin concentration, and decreased oxygen affinity mediated by 2,3-diphosphoglycerate (2,3-DPG). This outline is meant to

[1] In this diagram, cause and effect relationships are indicated by the direction of the arrows, and the nature of the influence of one variable on another is indicated by the symbol within the arrow. The symbol (+) inserted in an arrow means that the two variables connected by the arrow change in the *same* direction – if one increases, the other increases, and *vice versa*. For example, in the diagram, an increase in alveolar ventilation will increase arterial PO_2. The symbol (-) inserted into an arrow means that the two variables connected by the arrow change in *opposite* directions – if one increases, the other decreases, and *vice versa*. For example, in the diagram, an increase in the magnitude of the physiological shunt would decrease the arterial PO_2.

summarize, not *replace*, the lectures and readings on this topic; student understanding of hypoxemia is expected to be more comprehensive than the summary description provided here.

The overall framework for the following discussion is illustrated in the "oxygen flow" diagram below. As indicated by the boxes and their connecting arrows, **ambient air** is brought into contact with gas exchange surfaces in the lung by the process of **alveolar ventilation**, which creates a partial pressure gradient between alveolar gas and pulmonary capillary blood that promotes **diffusion** of oxygen across the respiratory membrane. Pulmonary end-capillary PO_2 is determined both by alveolar ventilation and pulmonary blood flow, *i.e.*, the **ventilation-perfusion ratio,** $\frac{\dot{V}_A}{\dot{Q}}$. Ultimately, arterial PO_2 is determined both by gas exchange in the lung and by the magnitude of physiological shunt flow, or **venous admixture**. The points at which each of the five causes of arterial hypoxemia interferes with this oxygen flow are indicated by the "cloud" symbols.



In short, *ambient hypoxia* causes arterial hypoxemia by reducing the PO_2 at each step of oxygen flow, starting with the ambient air. *Alveolar hypoventilation* reduces alveolar PO_2 even if the ambient PO_2 is normal, thereby lowering PO_2 at each subsequent step. A *decreased diffusion capacity* may lower end-capillary PO_2 even if ambient and alveolar PO_2 values are normal, and the decreased end-capillary PO_2 will ultimately reduce arterial PO_2. *Ventilation-perfusion mismatching* will decrease end-capillary PO_2 in those regions with low $\frac{\dot{V}_A}{\dot{Q}}$ ratios, thereby de-

creasing the overall oxygen content and PO_2 of pulmonary venous and systemic arterial blood. *Increased venous admixture* (*increased physiological shunt flow*) will decrease pulmonary venous and/or arterial PO_2 by mixing deoxygenated blood with the well-oxygenated blood from functional alveoli, thereby decreasing arterial PO_2 even if pulmonary end-capillary PO_2 is normal. More detailed discussions of each of these five [5] causes of arterial hypoxemia follow immediately below.

Ambient hypoxia:

Ambient hypoxia may be caused by a *reduction in total atmospheric pressure (P_B)*, such as that encountered at altitude, or by a *reduction in the fractional concentration of oxygen (FO_2)* in the ambient air by the addition of another gas to the air. In either case, since the partial pressure of oxygen in the ambient air is reduced, the inspired PO_2 is also reduced, leading to reductions in alveolar PO_2, pulmonary end-capillary PO_2, and eventually, arterial PO_2.

The hypoxic ventilatory response (HVR) to ambient hypoxia is usually present but limited in its effectiveness, since increased alveolar ventilation can only move the alveolar PO_2 closer to the inspired PO_2, which itself will remain low as long as the environmental conditions causing the ambient hypoxia remain. The HVR is a *hyperventilatory response* that will produce a decrease in alveolar and arterial PCO_2, resulting in the rapid development of a respiratory alkalosis that will be corrected in a few days, primarily by renal mechanisms, if the ambient hypoxia persists. The alkalosis may itself initially blunt the HVR, which may therefore not be fully manifested until renal mechanisms have restored arterial pH back toward normal. Increased hemoglobin concentration, increased 2,3-DPG, new blood vessel growth and increased tissue vascularity, and metabolic re-adjustments at the tissue level may produce a relatively successful adaptation to ambient hypoxia, and permanent human habitation is possible at altitudes as high as 4900 m (16000 ft).

A reduction in the fractional concentration of oxygen in the ambient air is rare, but occurs in some cases of natural disasters or industrial accidents, in which gases such as carbon dioxide or nitrogen are added to the ambient air in high concentrations. Suffocation due to rebreathing air within a confined, airtight enclosure also involves a progressive reduction in ambient PO_2. The usual and deliberate administration of anesthetic gases to a patient's inspired air during surgery, which would reduce the fractional concentration of oxygen in the inspired gas mixture, must be accompanied by the addition of oxygen to the air breathed by the patient to maintain the proper fractional concentration of oxygen.

The administration of supplemental oxygen *via* a facemask or nasal cannula will raise the F_IO_2 and P_IO_2, thereby raising alveolar PO_2, despite a low barometric pressure or the continued presence of another gas in the ambient air. Arterial hypoxemia caused by a decrease in ambient PO_2 alone is not accompanied by an increase in the alveolar-arterial PO_2 difference (A-a PO_2 difference).

Alveolar hypoventilation:

Alveolar hypoventilation may be caused by a large group of disorders, involving everything from the generation of efferent neuronal signals by the respiratory centers in the brainstem to diseases of the lungs. Examples are: depression of the respiratory center by drugs, trauma, or poor perfusion; damage to motor nerves leading to the ventilatory muscles; various muscular disorders leading to ventilatory muscle weakness; congenital or acquired malformations of the bony thorax; lung disorders that reduce pulmonary compliance or disturb lung architecture; and blockage of airways by foreign bodies, tumors, secretions, or reactive bronchoconstriction.

The effects of alveolar hypoventilation can be understood using the alveolar ventilation equation and the alveolar air equation. The *alveolar ventilation equation,*

$$P_A CO_2 = \frac{\dot{V}_{CO_2}}{\dot{V}_A} \cdot 0.863$$

demonstrates that alveolar (and therefore arterial) PCO_2 is directly proportional to the level of CO_2 production ($\dot{V}_{CO_2}$) and indirectly proportional to the level of alveolar ventilation ($\dot{V}_A$). If alveolar ventilation decreases in a human subject whose CO_2 production is constant, alveolar PCO_2 will increase.

The presence of alveolar hypoventilation and increased amounts of carbon dioxide in the alveolar gas will decrease the alveolar partial pressure of oxygen. The full version of the *alveolar air equation*,

$$P_AO_2 = (P_B - 47) \cdot F_IO_2 - \left(\frac{P_ACO_2}{R} \right) + P_ACO_2 \cdot F_IO_2 \cdot \left(\frac{1-R}{R} \right)$$

(in which the term $(P_B\text{-}47)\cdot F_IO_2$ represents P_IO_2), demonstrates that alveolar PO_2 is dependent on the level of inspired PO_2, the alveolar PCO_2, and the respiratory exchange ratio (R, or $\frac{\dot{V}_{CO_2}}{\dot{V}_{O_2}}$, typically 0.8). The alveolar air equation can be used to calculate the alveolar PO_2 that would result from alveolar hypoventilation and the resulting increase in alveolar PCO_2. A simplified and more user-friendly, version of the alveolar air equation can be generated in the following manner: 1) by dropping the last term, $P_ACO_2 \cdot F_IO_2 \cdot \left(\frac{1-R}{R} \right)$, which only amounts to about 2 mm Hg when breathing room air at sea level; 2) by substituting $PaCO_2$ (obtained from arterial blood gas measurements) for P_ACO_2, a reasonable assumption since alveolar and arterial PCO_2 values are usually very similar; and 3) by assuming that, *at a sea level barometric pressure of 760 mm Hg* and *without oxygen supplementation*, the term $(P_B\text{-}47)\cdot F_IO_2$, representing P_IO_2, is equal to about 150 mm Hg. The result is the following simplified expression:

$$P_AO_2 \approx 150 - \frac{PaCO_2}{R}$$

A very important concept for the student to understand is that the overall effect of a decrease in alveolar ventilation is a rise in alveolar (and arterial) PCO_2 and a fall in alveolar (and arterial) PO_2. This pattern of *hypoxemia combined with hypercapnia is the hallmark of alveolar hypoventilation* – any patient who has this combination of blood gas values should be assumed to have alveolar hypoventilation. The patient may have other causes of hypoxemia as well, since the causes of hypoxemia are *not* mutually exclusive, but the elevation of $PaCO_2$ in a hypoxemic patient means that some alveolar hypoventilation is present.

There can be no hypoxic ventilatory response (HVR) to the hypoxemia caused by alveolar hypoventilation, since failure to provide adequate ventilation is itself the problem. Increased hemoglobin concentration, increased 2,3-DPG, increased tissue vascularity, and cellular metabolic re-adjustments may help to preserve tissue metabolism in the heart, brain, and other vital organs if the alveolar ventilation persists. The administration of supplemental oxygen *via* a facemask or nasal cannula will raise the inspired PO_2, thereby raising alveolar, pulmonary end-capillary, and arterial PO_2 even if the alveolar hypoventilation continues. Arterial hypoxemia caused by a decrease in alveolar ventilation alone is not accompanied by an increase in the alveolar-arterial PO_2 difference (A-a PO_2 difference).

Diffusion abnormalities:

Diffusion abnormalities may be caused by pulmonary disorders affecting the length of the diffusion pathway (thickness of the respiratory membrane separating alveolar gas from pulmonary capillary blood) or the total alveolar surface area available for diffusion of O_2 and CO_2 between the alveolar gas and pulmonary capillary blood. Examples of disorders causing diffusion abnormalities are: pulmonary edema; pulmonary fibrosis; alveolar infiltrates; atelectasis; and emphysema. When thinking about diffusion abnormalities, the student should keep in mind *Fick's Law of Diffusion*,

$$J = -D \cdot \frac{A}{x} \cdot C$$

which states that the rate of diffusion of a substance (J) is directly proportional to the diffusion coefficient (D), the surface area available for diffusion (A), the diffusion distance (x), and the concentration gradient (C). The pulmonary diseases mentioned above affect the overall *diffusion capacity* of the lung, measured clinically using trace amounts of carbon monoxide as $D_{L_{CO}}$, and representing the product $D \cdot \frac{A}{x}$. Although the rate of diffusion is also affected by changes in the concentration gradient – or, for pulmonary gas exchange, the partial pressure gradient between alveolar gas and pulmonary capillary blood – diffusion abnormalities should be considered to be caused only by those disorders that affect the physical properties of the lung, such as surface area or diffusion distance. Since the diffusion capacity of the lung for carbon dioxide is much higher than that for oxygen (or for the carbon monoxide used to determine $D_{L_{CO}}$), diffusion abnormalities rarely affect end-capillary or arterial PCO_2, and have to be relatively severe even to begin to affect pulmonary end-capillary and arterial PO_2. For this reason, diffusion abnormalities are sometimes left off the list of clinical disorders causing arterial hypoxemia (as in the discussion of hypoxemia in *Harrison's Textbook of Medicine*).

The hypoxic ventilatory response (HVR) to hypoxemia caused by a severe diffusion abnormality is usually present and always appropriate. The HVR will increase alveolar ventilation and alveolar PO_2, thereby increasing the partial pressure gradient promoting oxygen diffusion into the pulmonary capillary and offsetting the reduced diffusion coefficient (see the discussion of *Fick's Law of Diffusion* above). Because CO_2 diffuses so rapidly, the HVR is likely to promote excess CO_2 diffusion out of the pulmonary capillary blood by reducing alveolar PCO_2, resulting in increased carbon dioxide excretion and an initial respiratory alkalosis, which will be corrected within a few days by non-respiratory mechanisms if the diffusion abnormality persists. If the diffusion problem and the resulting hypoxemia are chronic, the same long-term compensatory mechanisms mentioned above for ambient hypoxia and alveolar hypoventilation will be utilized to help maintain tissue oxygenation.

The administration of supplemental oxygen *via* a face mask or nasal cannula will raise the inspired PO_2, thereby increasing alveolar PO_2, increasing the partial pressure gradient, and increasing the diffusion rate across the respiratory membrane, even if the structural problem causing the diffusion abnormality persists. Arterial hypoxemia caused by a diffusion abnormality may be accompanied by an increase in the alveolar-arterial PO_2 difference (A-a PO_2 difference), since there would not be sufficient time for equilibration between the partial pressures of oxygen in the alveolar gas and pulmonary capillary blood.

Ventilation-perfusion abnormalities:

Ventilation-perfusion abnormalities may be caused by vascular disorders affecting perfusion of regions within the lung, by airway disorders that affect ventilation of regions within the lung, or by pathological processes that distort the normal lung architecture and affect the distribution of both ventilation and perfusion.

The bases for understanding how arterial hypoxemia might be caused by ventilation-perfusion disturbances are the *alveolar ventilation equation* (see above), the *alveolar air equation* (see above), and the *oxygen dissociation curve*. According to the *alveolar ventilation equation*, regions of the lung with a relative increase in alveolar ventilation (increased ventilation-perfusion ratio) will have a low alveolar PCO_2 and, according to the *alveolar air equation*, an increase in alveolar PO_2. In contrast, regions of the lung with a relatively low level of alveolar ventilation (decreased ventilation-perfusion ratio) will have an increased alveolar PCO_2 and a reduction in alveolar PO_2. The pulmonary end-capillary PO_2 of blood from regions of the lung with *increased* ventilation-perfusion ratios will therefore be increased, but this increase in PO_2 will *not* result in a significant increase in oxygen content. The reasons for this are: 1) that the oxygen binding sites on hemoglobin are nearly completed filled (or "saturated") even at normal end-capillary PO_2 levels, and 2) that oxygen solubility in body fluids is low. In contrast, the pulmonary end-capillary blood from regions of the lung with *decreased* ventilation-perfusion ratios will have a low PO_2, which will translate into a *reduction in end-capillary oxygen content* because of the shape of the oxygen dissociation curve. Since the pulmonary venous system collects and mixes end-capillary blood from all regions of the lung, the oxygen content of the combined pulmonary venous blood heading into the left atrium will represent the weighted average of the oxygen content of blood from high, normal, and low $\frac{\dot{V}_A}{\dot{Q}}$ regions. Since there is no significant increase in oxy-

gen content in blood draining high $\frac{\dot{V}_A}{\dot{Q}}$ regions, these regions cannot offset the reduction in oxygen content in blood from low $\frac{\dot{V}_A}{\dot{Q}}$ regions, and as a result the combined pulmonary venous blood will have *an overall reduction in oxygen content and PO_2.* The greater the ventilation-perfusion heterogeneity within the lung, the more prominent is the effect of the low $\frac{\dot{V}_A}{\dot{Q}}$ regions, and the lower the arterial PO_2 will become.

The hypoxic ventilatory response will increase the overall level of alveolar ventilation, will generally raise alveolar PO_2 values, and may normalize or even decrease arterial PCO_2, but may not be able to compensate fully in areas of the lung where ventilation is decreased by disorders causing significant airway obstruction. In addition, in some patients with obstructive disorders (such as smokers with severe chronic bronchitis), the increased work of breathing due to the increased airway resistance may blunt or even prevent the hypoxic ventilatory response. This may result in persistent arterial hypoxemia (and cyanosis) accompanied by an increased arterial PCO_2 caused by alveolar hypoventilation in the low $\frac{\dot{V}_A}{\dot{Q}}$ regions. The *hypoxic vasoconstrictor response* triggered in the low $\frac{\dot{V}_A}{\dot{Q}}$ regions of these patients may also raise pulmonary vascular resistance and pulmonary artery pressure, causing pulmonary hypertension, and an increased right ventricular afterload. The other expected compensations to chronic hypoxemia (increased hemoglobin and 2,3-DPG concentrations, increased tissue vascularity, and metabolic reorganization) may help to preserve tissue oxygenation in these patients.

The administration of supplemental oxygen *via* a facemask or nasal cannula is very likely to raise arterial PO_2 in patients with $\frac{\dot{V}_A}{\dot{Q}}$ abnormalities, but the improvement may be slow since the alveolar PO_2 in the most poorly ventilated regions of the lung will not increase immediately. Arterial hypoxemia caused by ventilation-perfusion mismatching alone is accompanied by an increase in the alveolar-arterial PO_2 difference (A-a PO_2 difference).

Increased physiological shunt flow:

Increased physiological shunt flow (increased venous admixture) may be caused by a pathological or pathophysiological process whereby deoxygenated blood mixes with oxygenated blood from regions of the lung after gas exchange between alveoli and pulmonary capillary blood has occurred. Examples are: blood that has perfused nonventilated alveoli within the lung; right-to-left intracardiac shunts (*e.g.*, cyanotic heart disease); and pulmonary vascular malformations such as arteriovenous fistulas.

Normal anatomical shunt flow results from mixing of some bronchial venous blood with pulmonary venous blood and from coronary venous blood emptying directly into the left ventricle *via* the Thebesian veins, and is largely responsible for the normal A-a PO_2 difference in healthy human subjects. The further admixture of deoxygenated blood with oxygenated pulmonary venous blood *via* pathological intrapulmonary or intracardiac shunt flow will reduce the oxygen content and PO_2 of the arterial blood even more. *The greater the physiological shunt flow ($\dot{Q}_S$) compared to total pulmonary blood flow ($\dot{Q}_T$), the lower will be the resulting systemic arterial content and PO_2.* The magnitude of the shunt fraction, $\frac{\dot{Q}_S}{\dot{Q}_T}$, (in principle, how much mixed venous blood would have to be added to "ideal" pulmonary end-capillary blood to yield the measured arterial oxygen content) can be calculated from the ideal end-capillary, mixed venous, and arterial oxygen contents using the *shunt equation,*

$$\frac{Q_S}{Q_T} = \frac{CiO_2 - CaO_2}{CiO_2 - CvO_2}$$

which is based on the principles of dilution and conservation of mass. The ideal end-capillary oxygen content (CiO_2) can be derived from the alveolar PO_2 (calculated using the *alveolar air equation [see above]*) and a standard *oxygen dissociation curve*, and the arterial and mixed venous oxygen contents (CaO_2 and CvO_2, respectively) can be calculated from appropriate blood samples. Because of the non-linear relationship between blood PO_2 and blood oxygen content (manifested in the sigmoidal shape of the oxygen dissociation curve) and because PO_2 represents only the chemical activity of dissolved oxygen, total oxygen content (ml O_2/dl blood, including dissolved and hemoglobin-bound oxygen) must be used in calculating the shunt fraction, not simply PO_2.

The *hypoxic ventilatory response* is *ineffective* at correcting the hypoxemia caused by increased physiological shunt flow, since the problem is increased venous admixture *after* gas exchange and oxygenation has already taken place. Similarly, *the administration of supplementary oxygen is usually ineffective* at correcting the hypoxemia, except when the shunt fraction is relatively low and the amount of additional dissolved oxygen in the pulmonary venous blood is enough to offset the small amount of venous admixture. The usual adaptations to chronic hypoxemia would take place in the presence of a chronically increased physiological shunt flow. Arterial hypoxemia caused by increased venous admixture alone is accompanied by an increase in the alveolar-arterial PO_2 difference (A-a PO_2 difference).

Arterial Hypoxemia and Cyanosis:

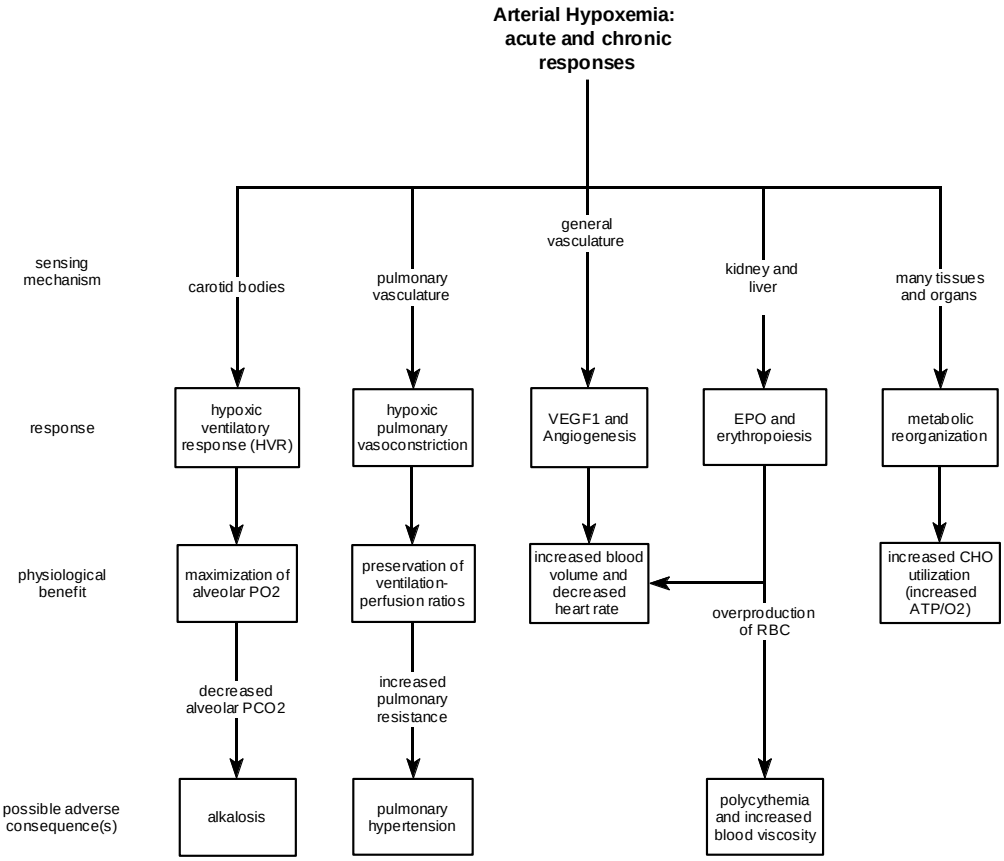
Patients with arterial hypoxemia often show signs of *cyanosis*, defined as the bluish color of non-pigmented skin and mucous membranes that results from an increased concentration of deoxygenated hemoglobin in the capillary beds of those areas. The degree of observable cyanosis is generally dependent on the concentration of deoxyhemoglobin, the depth of skin pigmentation, the thickness of the skin, and the extent of filling of the cutaneous capillaries. Cyanosis should be sought in the non-pigmented areas of the body, such as mucous membranes and nail beds.

An easy way for the student to appreciate the significance of cyanosis is to remember that mixed venous blood in a healthy human subject at rest has a PO_2 of about 40 mm Hg and a percent saturation of about 75% - and is clearly colored a deep bluish-purple. Normal arterial blood has a percent saturation of 90% or more - and is red. If arterial or capillary blood is deoxygenated enough to give a bluish tint to the skin, its PO_2 must be approaching the normal mixed venous PO_2 of 40 mm Hg, and its percent saturation must be approaching the mixed venous value of 75%! The student should also appreciate that it is the *absolute concentration of deoxyhemoglobin* in the blood that correlates best with the degree of observable cyanosis, rather than the relative amount of deoxygenated hemoglobin (as indicated by the oxygen saturation). Cyanosis may therefore not be as evident in a severely anemic patient with significant arterial desaturation (SaO_2 ~75%) as it is in a patient with a normal hemoglobin concentration with less severe arterial desaturation (SaO_2 ~80%).

There are two major types of cyanosis - *central* and *peripheral*. *Central cyanosis* represents desaturation of all the arterial blood sent out to peripheral tissues and results most commonly from arterial hypoxemia. Other causes might be the presence of an abnormal hemoglobin (hemoglobinopathy) or the chemical reduction of normal hemoglobin to *methemoglobin* or *sulfhemoglobin*. Central cyanosis is noticed in both mucous membranes and skin. *Peripheral cyanosis*, on the other hand, is due to the *increased extraction of oxygen* from blood in poorly perfused peripheral tissues, and may therefore occur in the skin in severe cold exposure, shock, congestive heart failure, and peripheral vascular disease. These are all situations in which mean arterial pressure, coronary perfusion, and cerebral perfusion are maintained at the expense of decreases in blood flow to other tissues (*e.g.*, skin, kidney, gut) involved in overall homeostasis. In peripheral cyanosis, the mucous membranes are typically normal in color (pink). Clinical differentiation of central and peripheral cyanosis is often not easy, since both could occur in a patient with a combination of cardiac and pulmonary disease.

Further discussion of physiological compensatory mechanisms in arterial hypoxemia:

Responses to arterial hypoxemia may be acute or chronic, depending on the duration of the hypoxemia. The time course of the responses ranges from seconds, in the case of the hypoxic ventilatory response (HVR), to weeks, in the case of tissue metabolic reorganization. A summary of acute and chronic responses to arterial hypoxemia, the sensing mechanism(s) responsible, the physiological benefit(s) of the responses, and the possible adverse consequence(s) of the responses, is provided in the figure below.



Hypoxic ventilatory response (HVR):

The hypoxic ventilatory response occurs very rapidly in response to a decrease in arterial PO_2, and when PaO_2 drops below 60-65 mm Hg, the ventilatory response is pronounced. The HVR is mediated by the PO_2-sensing mechanism in the *peripheral chemoreceptors*, the carotid and aortic bodies. Increased afferent inputs from these receptors to the respiratory center cause increases in both respiratory frequency and tidal volume, resulting in an increase in alveolar ventilation. The increased alveolar ventilation is associated with an increase in alveolar (and therefore pulmonary capillary) PO_2, thereby increasing the oxygen saturation of the available hemoglobin in the pulmonary capillary blood. The increased in ventilation, since it is driven by low PO_2, causes alveolar and arterial PCO_2 to decrease, and is therefore a hyperventilatory response that results in an *acute respiratory alkalosis*. The alkalosis initially blunts the ventilatory response to the hypoxemia through its effect on the *central chemoreceptors*; only after a few days, when renal mechanisms have restored ECF and CSF hydrogen ion concentration back toward normal, will the hypoxic ventilatory response be fully manifested.

Hypoxic pulmonary vasoconstriction:

In contrast to the peripheral vasculature, where tissue hypoxia is associated with vasodilation and increased blood flow, the pulmonary vasculature responds to decreases in local PO_2 with vasoconstriction. This is a rapid, intrinsic, local response of the pulmonary vasculature, independent of innervation or circulating vasoactive agents.

The physiological benefit of hypoxic pulmonary vasoconstriction is the diversion of pulmonary blood flow away from poorly ventilated regions (the usual reason for decreased PO_2 in areas within the lungs) and toward better-ventilated regions where the local PO_2 is high. This is an effective mechanism for preserving ventilation-perfusion ratios within the lung when there are pockets of decreased ventilation scattered throughout the lung volume. When the hypoxia within the lung is global, as it would be with ambient hypoxia or decreased alveolar ventilation, the hypoxic vasoconstrictor response is also global, resulting in overall increases in pulmonary vascular resistance, pulmonary vascular pressures, and right ventricular afterload.

Increased angiogenesis:

Hypoxia is a potent stimulus for the release of various cytokines, such as vascular epithelial growth factor (VEGF-1), that promote the growth and development of new blood vessels, known as *angiogenesis*. The primary physiological benefit of new blood vessel growth centers on the decrease in diffusion distance within tissues associated with increased tissue vascularity and increased capillary density. Even if tissue capillary PO_2 remains low, the shorter diffusion distance means that oxygen can still reach tissue cells and aerobic metabolism can be maintained. Another consequence of angiogenesis is the increase in total vascular capacity associated with new blood vessel growth, which, along with increased erythropoiesis [see below], allows circulating blood volume to increase.

Increased erythropoiesis:

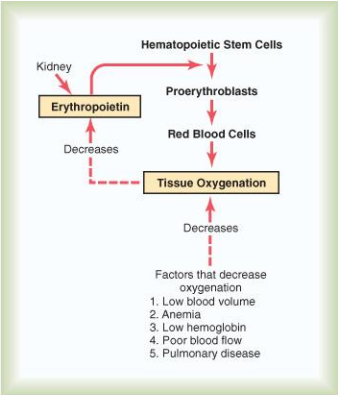
Arterial hypoxemia is a potent stimulus for the release of erythropoietin from the perivascular interstitial cells within the cortex of the kidney, which is responsible for increases in bone marrow erythrocyte production, circulating red cell mass, hematocrit, and hemoglobin concentration. The physiological benefit of this erythropoietic response is that the increase in oxygen transport capacity will increase arterial oxygen content even if arterial PO_2 remains low. The combined beneficial effects of increases in angiogenesis and erythropoiesis are increased overall blood volume, increased oxygen-carrying capacity, increased tissue vascularity, shorter diffusion distances, and the maintenance of tissue oxygen delivery even with the continued presence of arterial hypoxemia. The most likely adverse consequence of increased erythropoiesis is the increase in blood viscosity (and therefore total peripheral resistance) associated with increased hematocrit.

The cytokine controlling erythrocyte production is erythropoietin, a circulating glycoprotein produced by interstitial cells in the peritubular capillary bed of the kidneys (~90-95% of the total) and by perivenous hepatocytes in the liver (~5-10% of the total). Erythropoietin increases the number of erythropoietin-sensitive stem cells in the bone marrow that are converted into red cell precursors and eventually to mature erythrocytes. The erythropoietin receptor on erythrocyte precursors has tyrosine kinase activity, and it activates a series of other intracellular kinases that increase the proliferation, growth, and development of erythrocyte precursors. Erythropoietin belongs to the same family of cytokines as growth hormone and prolactin.

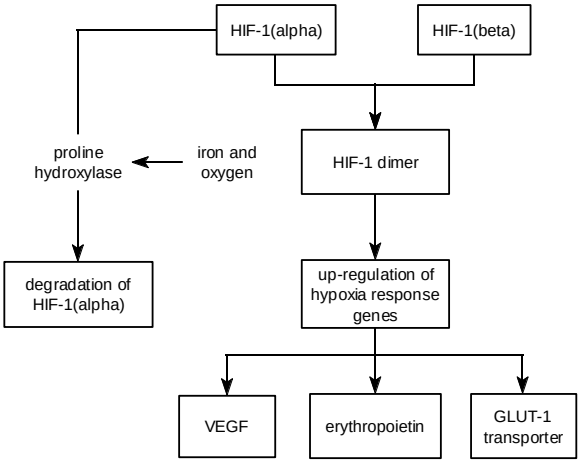
The usual stimulus for the release of erythropoietin is tissue hypoxia, and the release of erythropoietin appears to be directly related to the rate of tissue oxygen delivery. Oxygen delivery is the product of cardiac output ($\dot{Q}$) and arterial oxygen content (CaO_2), and the latter is, in turn, dependent on hemoglobin concentration ([Hb]) and the arterial partial pressure of oxygen (PaO_2). These relationships can be summarized as:

$$\text{Rate of erythropoietin release} = f(\dot{Q}, [Hb], PaO_2)$$

Erythropoietin increases in the presence of arterial hypoxemia, decreased hemoglobin concentration, and decreased cardiac output as shown in the figure below, reproduced from Guyton & Hall's *Textbook of Medical Physiology, 11th edition*. The autologous transfusion of red cells by unscrupulous athletes in attempts to improve athletic performance would increase hemoglobin concentration and decrease circulating erythropoietin concentration. Recombinant erythropoietin is also available for clinical use in the treatment of the anemias associated with renal failure and cancer chemotherapy. Other stimuli for erythropoietin secretion include androgens (which, along with menstrual blood loss, are responsible for the differences in hematocrit and hemoglobin concentration between men and women), alkalosis (*e.g.*, secondary to the hyperventilation that occurs at high altitude), and β-adrenergic stimulation.



The link between erythropoietin concentration and hypoxia is the hypoxia-inducible factor (HIF-1), a heterodimeric transcription factor consisting of alpha and beta subunits. HIF-1α is subject to degradation by proline hydroxylase in the presence of oxygen and iron, whereas the HIF-1β subunit is constitutively expressed. When hypoxia is present, HIF-1α increases in concentration, combines with the HIF-1β subunit to form the dimer, which then activates a number of HIF-1-dependent target genes, such as those for erythropoietin, vascular endothelial growth factor (VEGF), and the GLUT-1 glucose transporter. An outline of the control of hypoxia-sensitive genes is shown in the diagram below. HIF-1 is a master regulator of overall oxygen homeostasis through its effects on erythropoiesis, energy metabolism, and vascular remodeling.



Decreased hemoglobin-oxygen affinity:

Arterial hypoxemia that lasts for more than a few days is associated with a decrease in oxygen affinity, measured as an increase in P_{50} and caused by an increase in intracellular 2,3-diphosphoglycerate (a.k.a., 2-3 biphosphoglycerate). The 2,3-DPG (or 2,3-BPG, if you prefer) molecules bind to the hemoglobin tetramer between the β-chains and stabilize the tetramer in the low-affinity, "deoxy" conformation. This shifts the position of the oxyhemoglobin dissociation curve (ODC) to the right, favoring tissue oxygen delivery, an obvious physiological benefit in the presence of decreased delivery of oxygen to the tissues. With very high concentrations of 2,3-DPG, however, the shift in the position of the ODC begins to affect oxygen loading in the lung, which is especially significant when the cause of the arterial hypoxemia is associated with a reduced alveolar PO_2 (*i.e.*, ambient hypoxia or alveolar hypoventilation). This effect of decreased oxygen affinity on oxygen loading limits the effectiveness of further increases in 2,3-DPG, and is a major factor in establishing the altitude at which humans can permanently live and work.

Tissue metabolic reorganization:

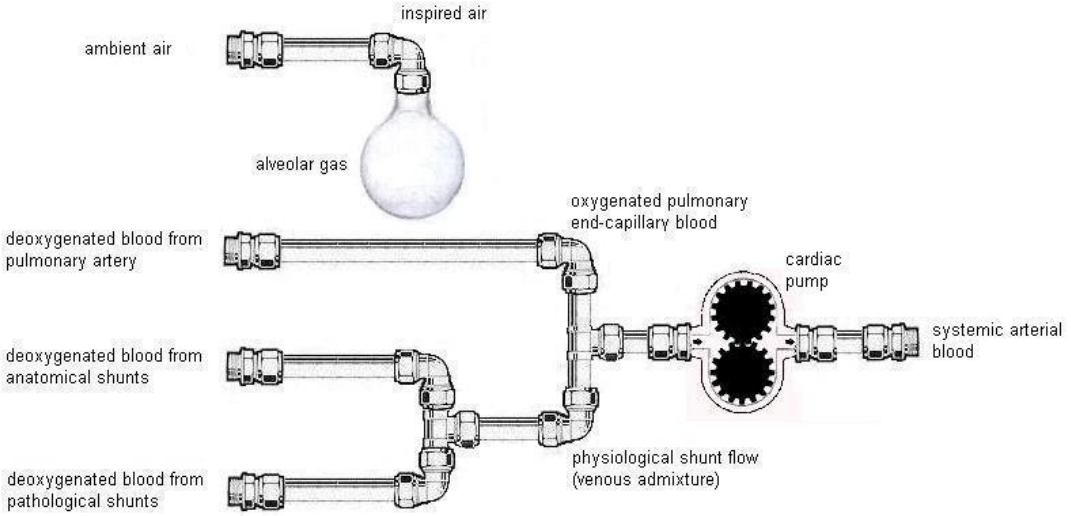
Metabolic adjustments in tissues appear to focus on adjustments in metabolic fuel preference, such as an increased preference for carbohydrate as an energy supply and an up-regulation of oxidative versus glycolytic metabolic pathways, both of which increase energy yield as moles of ATP produced per mole of oxygen utilized or per mole of carbon substrate used.

Evolutionary biology, hypoxia tolerance, and exercise performance

The figure above outlining acute and chronic responses to arterial hypoxemia, and the preceding discussion of various physiological adaptations to hypoxemia, are based in part on an evolutionary consideration of the very closely related human adaptations to hypoxia tolerance and to endurance exercise, as described in the following articles: Hochachka, PW, HC Gunga, and K Kirsch. Our ancestral physiological phenotype: an adaptation for hypoxia tolerance and for endurance performance? *Proc Natl Acad Sci* 95:1915-1920, 1998 and Hochachka, PW. Mechanism and evolution of hypoxia-tolerance in humans. *J Exp Biol* 201: 1243-1254, 1998. The suite of physiological and metabolic traits that provide for both hypoxia tolerance and the capacity for endurance exercise are similar, because both work for extending endurance or tolerating hypoxia. These traits most likely represent the "ancestral" condition for humans, and could have developed during a critical point in human evolution when the local environment was becoming higher, colder, and drier, conditions in which these adaptations would have been advantageous.

Clinical assessment of compensations to arterial hypoxemia:

Routine clinical assessment of some of the above compensations to acute or chronic arterial hypoxemia would be difficult. However, a comprehensive physical examination of a patient with symptoms of respiratory disease may reveal signs of increased ventilatory activity (usually observed as *increased respiratory frequency*), and arterial blood gas measurements on such a patient would confirm the presence of a *hypoxic ventilatory response* (HVR) if a *decrease in arterial* PCO_2 were present. The combination of PCO_2 and hydrogen ion measurements (pH) would also allow determination of whether the HVR is associated with an *acute or chronic alkalosis*, which might shed some light on the time course of the respiratory problem. The *absence of an HVR and an elevated* PCO_2 *mean that alveolar hypoventilation is present* in the patient, and is at least one of the causes of the patient's hypoxemia. In addition, arterial blood gas measurements would also reveal an erythropoietic response, if one were present, by an *increase in hemoglobin concentration*. On the other hand, measurements of 2,3-DPG or P_{50} are rarely done on patients with respiratory disease, except for research purposes, and measurements of angiogenesis and angiogenic factors, tissue vascularity, and metabolic substrate preferences are also research, not clinical, tools.



This schematic diagram (or a blackboard version of it) will be used in classroom discussions of the causes of arterial hypoxemia. The upper portion of the diagram represents ventilation, which moves ambient air into the conducting system and eventually to the alveolar gas. Deoxygenated blood from the pulmonary artery is carried into the pulmonary capillary bed and placed in close contact with the alveolar gas. Diffusion of oxygen between the pulmonary capillary blood and alveolar gas normally produces well-oxygenated pulmonary end capillary blood that enters the pulmonary venous circulation. Even in healthy human subjects, some deoxygenated bronchial venous blood also mixes into the pulmonary venous blood *via* anatomical shunt flow, decreasing its oxygen content and PO_2. Pulmonary disease, arteriovenous malformations within the lung, or intracardiac shunts may also result in deoxygenated blood being added to the well-oxygenated blood from the normal pulmonary capillaries, further decreasing oxygen content and PO_2. The combination of normal anatomical shunt flow and these pathological sources of venous admixture is called physiological shunt flow. Ventilation-perfusion heterogeneity results in lung units having different ventilation-perfusion ratios, and therefore different pulmonary end-capillary values for oxygen content and PO_2. When blood from these heterogeneous lung units mixes together in the pulmonary circulation, the values for oxygen content and PO_2 are below normal.

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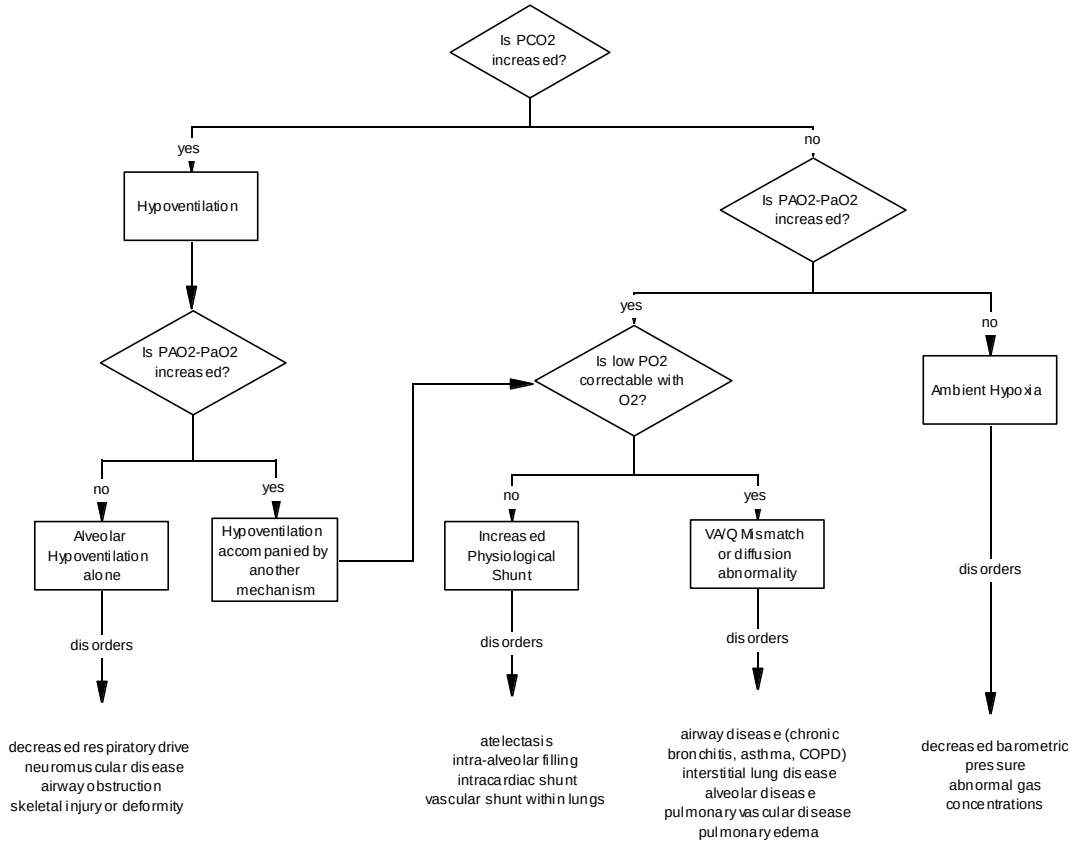
Summary Table of Arterial Blood Gas Findings for the Causes of Hypoxemia

The five major causes of arterial hypoxemia can be distinguished from one another by differences in arterial blood gas values and by the level of improvement seen with the administration of supplemental oxygen. The table below will serve as a qualitative summary of changes observed in each of the five situations *when they occur alone*. The student should remember that the various causes of hypoxemia are NOT *mutually exclusive*, and can occur in various combinations. To determine which of the causes of hypoxemia are present together in a patient, use the diagnostic flow chart reproduced on the next page of this handout.

Students should fill out the table by indicating, for each of the five [5] causes of hypoxemia *considered individually*, the qualitative direction of the changes (increase, ↑; decrease, ↓; no change, 0) in each of the four [4] variables listed in the column headings. Assume that these variables are measured and/or calculated for a real human subject who has utilized any appropriate or available compensatory mechanisms. ***Again, the student should keep in mind that this chart analyzes the five causes of hypoxemia considered individually, but real patients often have more than one cause for their arterial hypoxemia and the causes of hypoxemia are NOT mutually exclusive!***

	P_AO_2	P_aO_2	P_aCO_2	A-a PO_2 Difference	Response to ↑ F_IO_2
Alveolar hypoventilation alone		low			
Diffusion abnormality alone		low			
Increased physiological Shunt alone		low			
VA/Q mismatching alone		low			
Ambient hypoxia alone		low			

Hypoxemia Diagnostic Flow Chart:



Above is very useful flow chart (based on *Harrison's Principles of Internal Medicine, 16th edition*, Figure 234-5) describing the differentiation of the various pathophysiological causes of arterial hypoxemia using arterial blood gas measurements and a few calculations. Students will be expected to be able to do each of the following: 1) apply this flow chart or algorithm to data from real or simulated case histories describing patients with arterial hypoxemia; 2) determine which of the pathophysiological causes of arterial hypoxemia might be present; and 3) defend their choice(s) with specific data from the patient or case and/or calculations based on that data.

In order to use the above flow chart properly, students must know: 1) normal values for arterial PO_2 and PCO_2; 2) how to calculate alveolar PO_2 using the alveolar air equation; 3) how to calculate the *actual* A-a PO_2 difference using arterial blood gas data and the calculated alveolar PO_2; and 4) how to estimate the *expected* A-a PO_2 difference given the patient's age.