

Causes of Hypoxemia

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Required Reading: Respiratory Physiology: A Clinical Approach, Shwartzstein & Parker, Ch. 5.

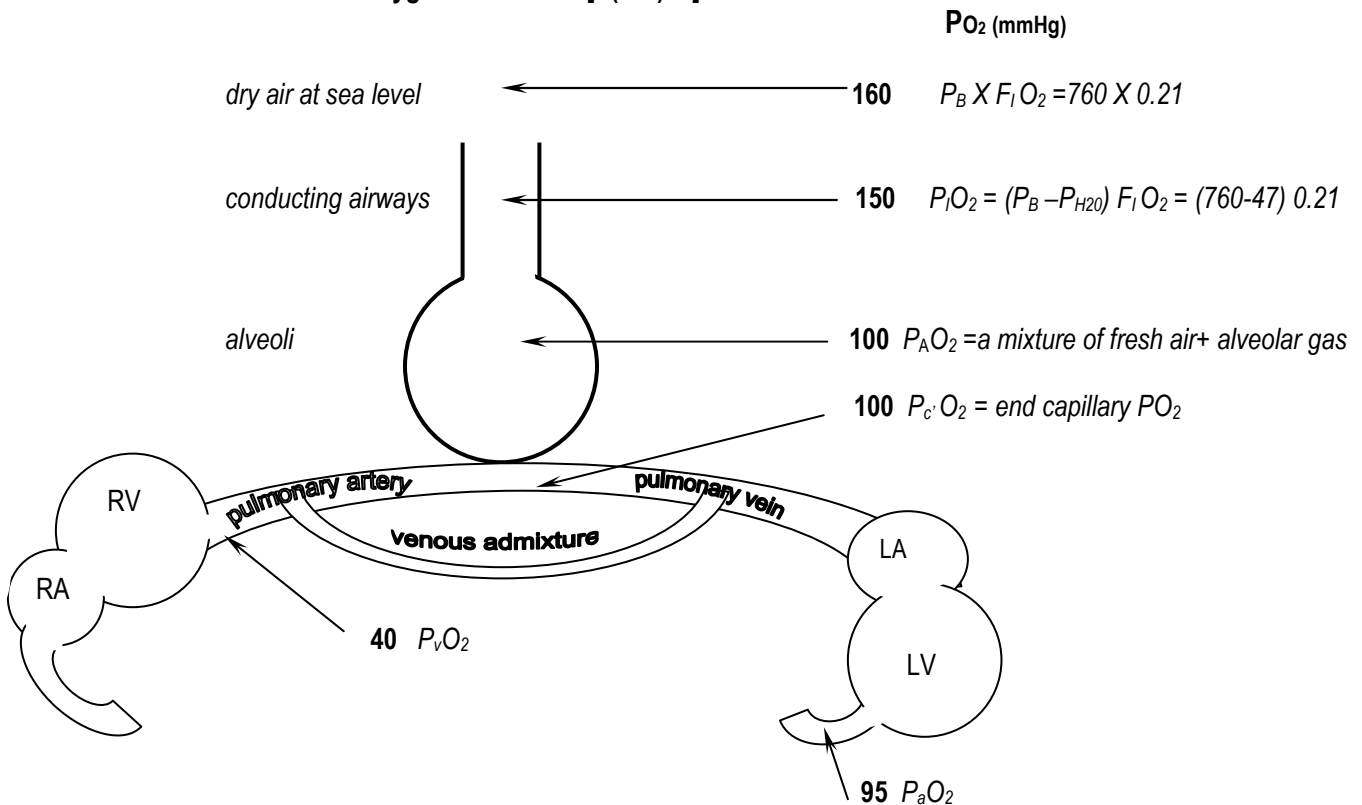
Objectives

1. Define and distinguish between hypoxia, hypoxemia, anoxia and asphyxia.
2. Be able to calculate the A-a gradient, define its normal range, and describe its significance in distinguishing between the common causes of hypoxia.
3. Describe the clinically important causes of arterial hypoxemia.

1. Definitions

- **anoxia:** Absence of oxygen supply. No oxygen.
- **asphyxia:** Absence of O₂ and accumulation of CO₂.
- **hypoxia:** Low oxygen in the body, often specified e.g. tissue hypoxia, alveolar hypoxia
- **hypoxemia:** Low oxygen in the blood. Specifically, hypoxemia is determined by measuring the partial pressure of oxygen in the arterial blood [P_aO₂].

2. The Alveolar-Arterial Oxygen Difference [P(A-a)O₂]



- **Normal range:** ≤ 10 mmHg **breathing room air** [$F_I O_2 = 0.21$] in young adults. The normal $P(A-a)O_2$ exists due to venous admixture. In the healthy individual, the normal anatomic shunt and the regional differences in V_A/Q in the lungs result in venous admixture.

The normal range for $P(A-a)O_2$ increases with age [an approximate formula: $A-a \text{ gradient} = (\text{Age}/4) + 4$]. This increase is due to the age-dependence of normal P_aO_2 . P_aO_2 declines slightly over the years and reflects the change in V_A/Q ratio of the aging lungs

Normal A-a gradient $A-a \text{ gradient} = (\text{Age}/4) + 4$

Increased age affects A-a gradient (at sea level on room air)

1. Age 20 years: 4 to 17 mmHg
2. Age 40 years: 10 to 24 mmHg
3. Age 60 years: 17 to 31 mmHg
4. Age 80 years: 25 to 38 mmHg

- **Determination:** P_aO_2 and P_aCO_2 are measured by sampling arterial blood [arterial blood gases, a.k.a. ABG]. P_aO_2 is calculated using the alveolar-air equation. $P(A-a)O_2$ is determined by the difference in the calculated P_AO_2 and the measured P_aO_2 .

3. Five Causes of Hypoxemia [$\downarrow P_aO_2$]

The mechanisms that cause hypoxemia can be divided into those that increase $P(A-a)O_2$ and those where $P(A-a)O_2$ is preserved.

I) HYPOVENTILATION (low alveolar ventilation)

- $P(A-a)O_2$ is normal
- P_aCO_2 is elevated (hypercapnia)
- Increasing the fraction of inspired oxygen ($F_I O_2$) can alleviate the hypoxemia and the hypercapnia can be corrected by mechanically ventilating the patient to eliminate CO_2 .

Causes of Hypoventilation

1. Depression of CNS by drugs
2. Inflammation, trauma or hemorrhage in the brainstem
3. Abnormal spinal cord pathway
4. Disease of the motoneurons of the brain stem/spinal cord
5. Disease of the nerves supplying the respiratory muscles.
6. Disease of the neuromuscular junction
7. Disease of the respiratory muscles
8. Abnormality of the chest wall
9. Upper airway obstruction

A list of examples of specific abnormalities for categories listed above can be found in Table 7-3 in Pulmonary Pathophysiology by Ali, Summers & Levitzky available at the library.

II) LOW INSPIRED OXYGEN [$\downarrow P_I O_2$]

$$P_I O_2 = (P_B - P_{H_2O}) F_I O_2$$

Examples

- A decrease in barometric pressure [e.g. breathing at high altitude].
- A decrease in F_{iO_2} – accidental [e.g. anesthetist does not supply enough oxygen or improper installation of oxygen supply lines or a leak in the breathing circuit].

- $P(A-a)O_2$ normal
- P_aCO_2 is decreased. This reduction in P_aCO_2 (hypocapnia) is due to hyperventilation in response to hypoxemia. Peripheral chemoreceptors sense the low arterial PO_2 and initiate an increase in ventilation through their input to the medullary respiratory centre.

III) RIGHT TO LEFT SHUNT

- $P(A-a)O_2$ is elevated
- P_aCO_2 is normal

Anatomic shunt: when a portion of blood bypasses the lungs through an anatomic channel.

In healthy individuals

- i) A portion of the bronchial circulation's (blood supply to the conducting zone of the airways) venous blood drains into the pulmonary vein.
- ii) A portion of the coronary circulation's venous blood drains through the thebesian veins into the left ventricle.

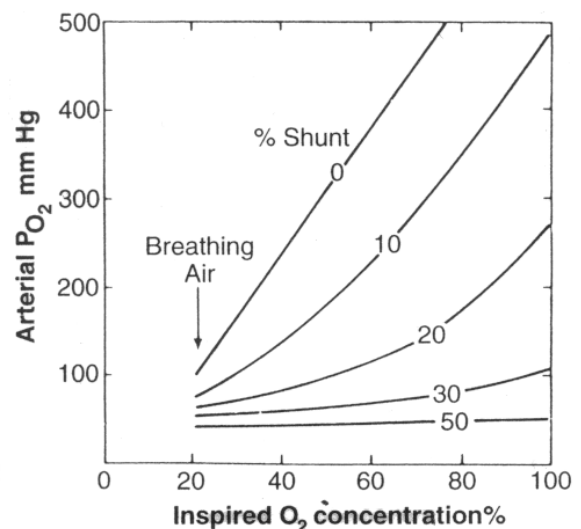
note: i & ii represent about 2% of the cardiac output and account for 1/3 of the normal $P(A-a)O_2$ observed in health.

Congenital abnormalities

- i) intra-cardiac shunt [e.g. *Tetralogy of Fallot: ventricular septal defect + pulmonary artery stenosis*]
- ii) intra-pulmonary fistulas [direct communication between a branch of the pulmonary artery and a pulmonary vein].

Physiologic shunt: In disease states, a portion of the cardiac output goes through the regular pulmonary vasculature but does not come into contact with alveolar air due to filling of the alveolar spaces with fluid [e.g. *pneumonia, drowning, pulmonary edema*]

The key clinical feature of a R-L shunt is that the accompanying hypoxemia (low partial pressure of arterial oxygen) can not be corrected with administration of supplemental oxygen. This is because the shunted blood is not exposed to the supplemental oxygen, remains low in oxygen lowering the overall arterial PO_2 . This depression is marked because of the shape of the oxygen dissociation curve. * **However, if the amount of shunt is relatively small (see figure on the right) useful gains in oxygen content of the blood can be made by administering supplemental oxygen. For this reason, supplemental oxygen is never withheld from patients with hypoxemia.**



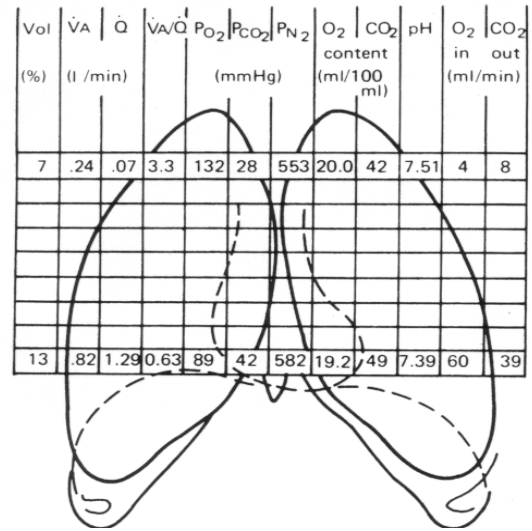
IV) VENTILATION-PERFUSION INEQUALITY (a.k.a. ventilation-perfusion mismatch, both the symbols V/Q and V_A/Q are often used in medical texts)

- P_aCO_2 is normal
- $P(A-a)O_2$ is elevated

❖ V_A/Q inequality is the most common cause of hypoxemia in disease states.

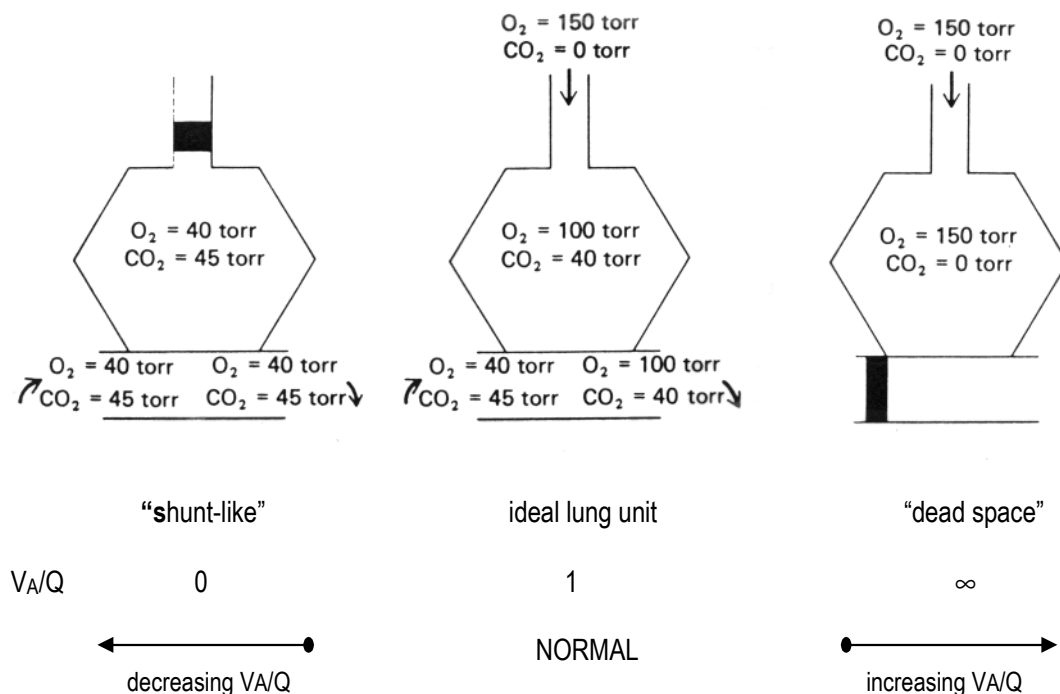
Alveolar ventilation brings oxygen into the lungs and removes carbon dioxide from it. Mixed venous blood brings carbon dioxide into the lungs and takes up alveolar oxygen. The alveolar P_{O_2} and P_{CO_2} are thus determined by the relationship between alveolar ventilation and perfusion. Changing the ratio of alveolar ventilation to perfusion (V_A/Q), will therefore change in the alveolar P_{O_2} and P_{CO_2} . Alveolar ventilation is normally 4-6 L/min and pulmonary blood flow has a similar range. Therefore, the normal range of ventilation-perfusion ratio [V_A/Q] for the whole lung is 0.8-1.2.

Consider a hypothetical scenario where all the pulmonary blood flow is directed to the right lung and all the alveolar ventilation is directed to the left lung. Although the whole lung V_A/Q ratio would be within the normal range, at the alveolar-capillary level there would be no gas exchange. Therefore, ventilation-perfusion must be matched at the individual alveolar-capillary level for gas exchange to be adequate.



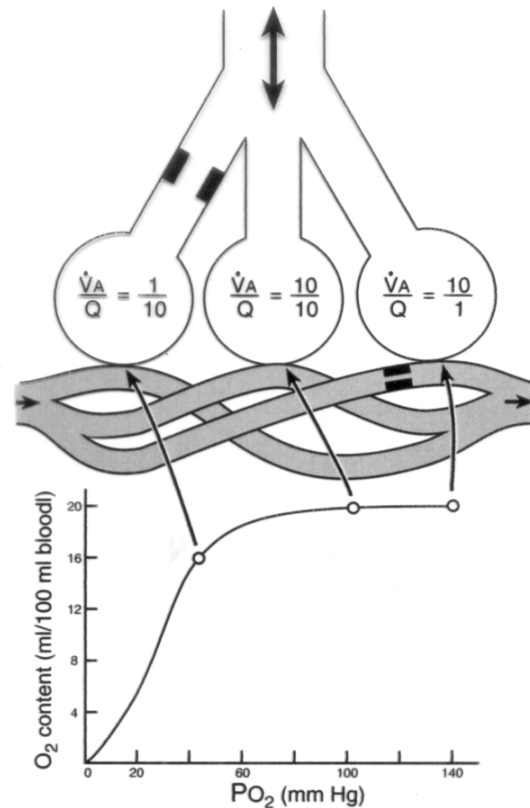
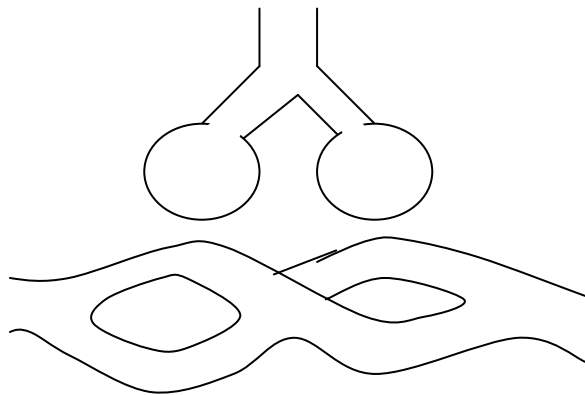
There are regional variations in the V_A/Q ratio in the healthy upright lung. The V_A/Q ratio decreases from the top to the bottom of the upright lung. This normal pattern accounts for approximately 2/3 of the normal $P(A-a)O_2$ seen in healthy individuals and does not present any gas exchange problem.

In disease states, there is a progression of disorganization in the normal pattern of V_A/Q inequality. The figure below shows the effect of altering the ventilation perfusion ratio on the alveolar P_{O_2} and P_{CO_2} in a lung unit. For clarity, only the extreme values of low and high V_A/Q mismatch are depicted.



- Because of the S shape of the oxygen-hemoglobin dissociation curve, a lung unit with a high V_A/Q will have little effect on arterial PO_2 and O_2 content. However, mixing blood from a lung unit with low V_A/Q will have a dramatic effect on oxygenated blood leaving the lungs.

Example



V) DIFFUSION IMPAIRMENT

- P_aCO_2 is normal
- $P(A-a)O_2$ is normal at rest but may be elevated during exercise.
- ❖ a rare observation in the clinical setting
- In healthy individuals, the transit time for red blood cells in the pulmonary capillary exceeds that required for the PO_2 in the mixed venous blood to reach equilibrium with the alveolar gas. During exercise, when there is an increase blood flow, this transit time is decreased but there remains sufficient time for the PO_2 in the mixed venous blood to reach equilibrium with the alveolar gas. The exception to this is the elite athlete who achieves very high cardiac outputs during exercise resulting in a large decrement in pulmonary transit time.
- In disease states, impaired diffusion may occur when there is an increase in the thickness of the physical separation between alveolar gas and pulmonary capillary blood and a shortened pulmonary transit time. Both of these conditions exist in a patient with an interstitial lung disease performing exercise.

This table is provided as an aid for review of the material presented in the lecture and additional material that you read on your own on this topic.

IT IS IMPORTANT to appreciate that hypoxemia refers to low partial pressure of oxygen in the blood and not low oxygen content of blood. Factors such related to hemoglobin such as anemia, hemoglobinopathies and carbon

monoxide poisoning that lower oxygen content as well factors such as stagnation of blood and histotoxic poisons such as cyanide that lead to tissue hypoxia are not considered as causes of hypoxemia since PaO₂ in these cases is normal.

IT IS ALSO IMPORTANT to appreciate that in a given patient mixed causes of hypoxemia occur frequently and it is often impossible to define precisely the extent of the contribution of each mechanism in the acutely ill patient. In terms of treatment however the patient is always given supplemental oxygen with due cautions.

Summary	arterial blood		venous blood		P(A-a)O ₂	Does supplemental oxygen (↑F _I O ₂) increase PaO ₂ substantially?
	PO ₂	PCO ₂	PO ₂	PCO ₂		
Hypoxemia						
Hypoventilation	↓	↑	↓	↑	normal	yes
↓ P _I O ₂	↓	↓	↓	↓	normal	yes
R-L Shunt	↓	normal	↓	normal	↑	no [see caveat * on page 3]
Diffusion defect	↓	normal	↓	normal	↑ during exercise	yes
VA/Q inequality	↓	normal	↓	normal	↑	yes
Tissue hypoxia						
Anemic hypoxia	normal	normal	↓	normal	normal	no
CO poisoning	normal	normal	↓	normal	normal	possibly
Stagnant hypoxia	normal	normal	↓	normal	normal	no
Histotoxic hypoxia	normal	normal	↑	normal	normal	no