Lecture 3 & 4 of 7

The Mechanics of Breathing

Dr Denis Loiselle

Objectives

At the end of this topic you should be able to:

1 Describe the events that cause inspiration and expiration.
2 Describe the functions of the muscles of respiration.
3 Explain the relationships among the pressures responsible for moving air into and out of the lungs.
4 Define the lung volumes and capacities.
5 Define compliance, explain how pulmonary compliance affects the movement of air into and out of the lungs and discuss factors which influence lung compliance.
6 Define airway resistance and explain how this affects the movement of air into and out of the lungs and discuss factors which influence airway resistance.
7. Briefly outline the basis of pathological states which affect pulmonary ventilation such as pneumothorax, emphysema, and asthma.

Introduction

For air to move into and out of the lungs there must be a pressure difference between the atmosphere and the alveoli. This pressure gradient is generated by cyclic changes in the volume of the thoracic cavity which contains the heart and lungs which are the result of contraction and relaxation of respiratory muscles. A number of factors other than pressure difference determine the rate at which air moves into and out of the lungs, and the extent to which the lungs can be inflated. These include the stiffness of the lungs and the resistance to air flow through the pulmonary airways.

This topic deals with the mechanics of ventilation. The physical processes involved are familiar to us all and can be understood on the basis of experience and common sense.

Topics

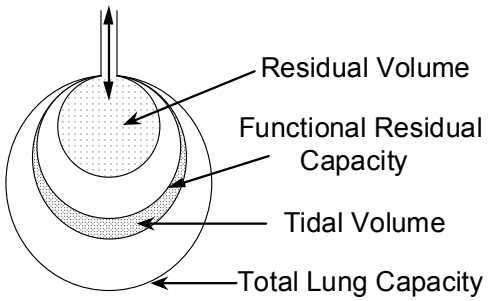
1 Gas pressure and Boyle's Law, (Tortora & Grabowski p.790).
2 The respiratory pump; muscle of respiration and their roles, (p.790 - 792).
3 Pressure-volume relations during respiration, (p.792 and lecture notes).
4 Lung volumes and capacities, (p.795-796).
5 Factor affecting ventilation: Pulmonary compliance, surface tension, surfactant, (p793 and lecture notes).
6 Factor affecting ventilation: Airway resistance, principal sites of airway resistance, effect of lung volume (p793 - 794 and lecture notes).

Resources

This topic is well-covered in Tortora & Grabowski. Use the topic list above to guide your reading. Additional diagrams and some brief additional notes are provided on the following pages. In preparing these, reference has been made to "Essentials of Physiology" Eds Sperelakis, N, & Banks, RO. Little Brown and Company, USA, 1996.

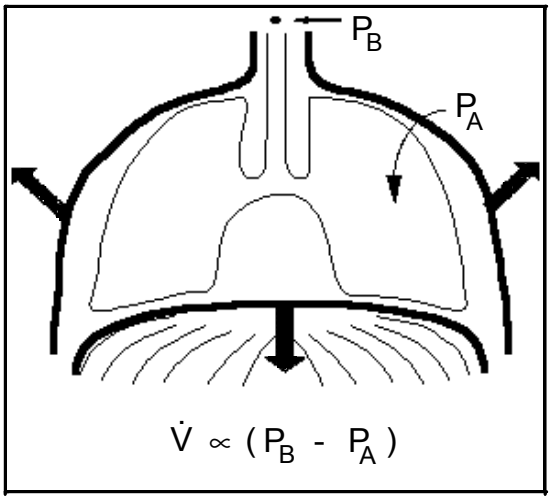
Lung Volumes

In mammals, breathing is 'tidal'. A single tidal volume can range in size from Residual Volume to Total Lung Capacity. The amount of air in the lungs at the end of a normal (relaxed) expiration is known as the Functional Residual Capacity.



Mechanics of Breathing

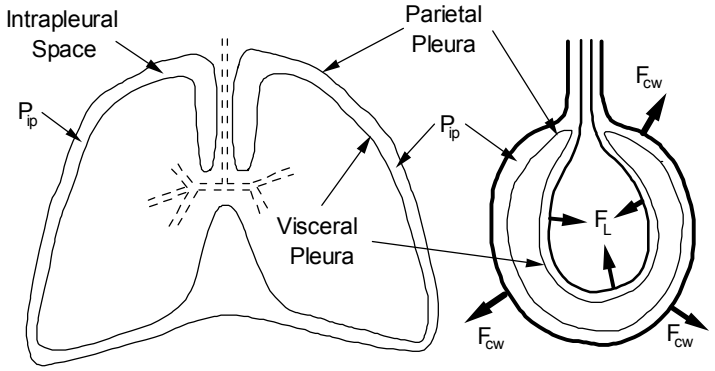
Air is a fluid. In order for it to move, there must exist a pressure-gradient. Air enters the lungs only if alveolar pressure (P_A) is less than atomspheric (barometric: P_B). Alveolar pressure becomes sub-atmospheric when thoracic volume increases. This is achieved by descent of the diaphragm and elevation of the rib-cage.



Balance of Forces

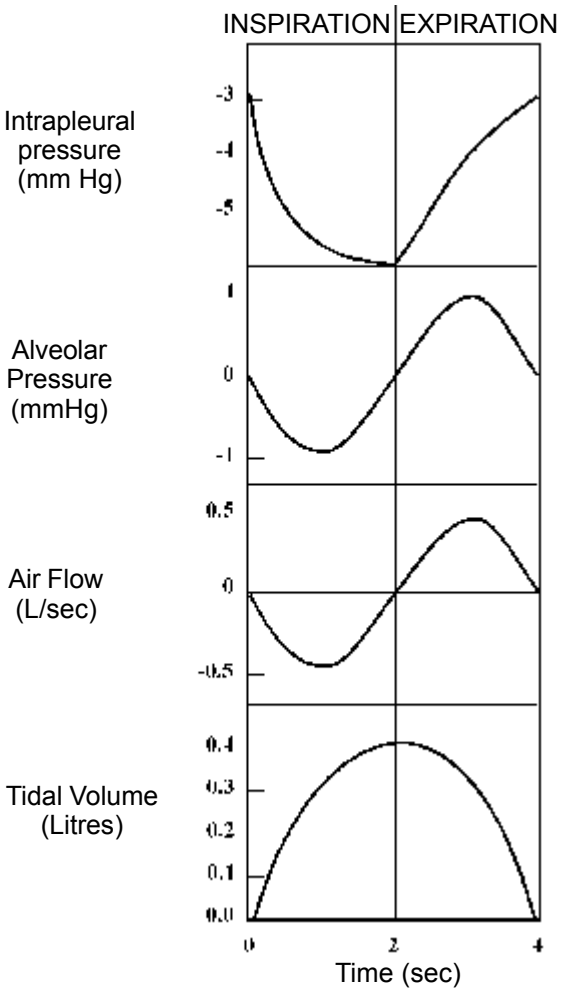
The lungs are highly elastic and tend to collapse to zero volume. This tends to separate the visceral and parietal pleura which reduces intra-pleural pressure (P_{ip}) below atmospheric while simultaneously pulling the rib-cage inwards. A balance of forces (between the collapsing lungs and the recoiling rib-cage) is achieved at Functional Residual Capacity.

A *pneumothorax* destroys this balance of forces.



Pressure-volume relations during respiration

The figure below illustrates the changes in pressure, air flow and volume that take place during a normal quiet breath. All pressures are given relative to atmospheric pressure (ie, the pressure at the nose and mouth are zero). Immediately before inspiration, alveolar pressure is equal to atmospheric pressure. There is no air flow, because there is no driving pressure from the atmosphere to the lungs. (Intrapleural pressure is about 4 mm Hg below atmospheric pressure.) Inspiration starts when contraction of the inspiratory muscles (primarily the diaphragm) enlarges the thoracic cavity. As thoracic volume increases, the intrapleural pressure becomes more subatmospheric and the lungs expand. The increase in lung volume causes alveolar pressure to decrease and air moves into the lungs. Air flow ceases when alveolar pressure returns to atmospheric pressure. When inspiration terminates, the diaphragm relaxes, intrapleural pressure rises and the lungs recoil. The gases in the alveoli are compressed which elevates alveolar pressure above atmospheric pressure driving air from the lungs to the atmosphere.



The negative values for air flow during inspiration in the figure indicates that air is flowing from atmosphere into the lungs, while the positive values indicate that air flows in the opposite direction during expiration. The total volume of air moving into (and out of) the lungs in a single breath is the tidal volume $V_{T.}$

Pressure, air flow and volume changes in one breathing cycle.
(Modified from: Comroe, J.H. Physiology of Respiration 2nd Edition, Year Book Medical Publishers, 1972:458)

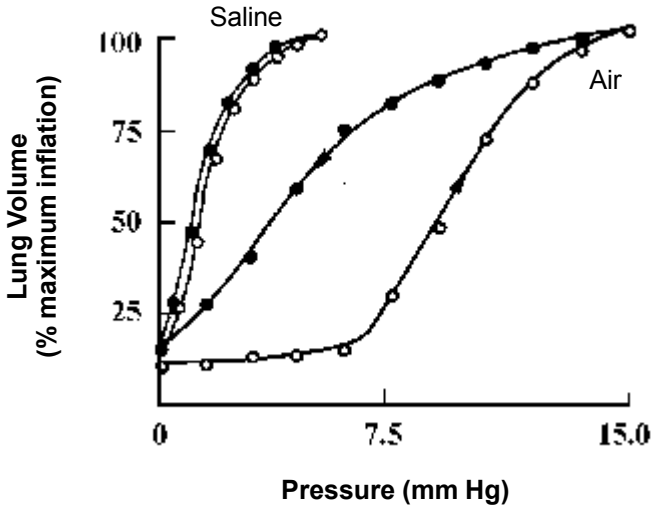
Compliance

Pulmonary compliance is a measure of the distensibility of the lungs and the chest wall and is determined from the pressure required to produce a small change in volume. Greatly increased compliance (loss of elastic fibres) characterises *emphysema*.

Pressure-volume relationship of Lungs

The figure below illustrates the pressure-volume relationship for the isolated lung. At low lung volume the lungs are very incompliant. This is because most alveoli have collapsed so that relatively large pressure is required to overcome surface tension forces in order to reopen them. Once open, the lungs distend relatively easily until they are near fully inflated. The deflation curve differs from the inflation curve and this hysteresis is primarily the result of surface tension.

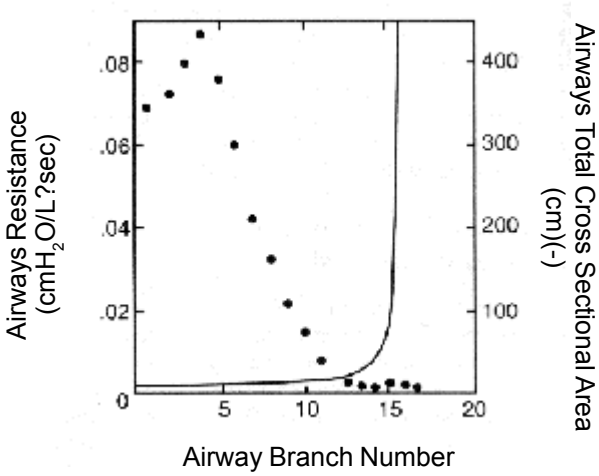
Note that much less effort is required to inflate the lungs when they are filled with saline rather than air and hysteresis is much less evident in the pressure-volume relationship.



Comparison of pressure-volume curves of air-filled and saline-filled lungs. *Open circles*, inflation; *closed circles*, deflation. The saline-filled lung has a higher compliance and also much less hysteresis than the air-filled lung. *(Modified from: West, JB, ed. Best & Taylor's Physiological Basis of Medical Practice 12th Edition, Williams & Wilkins, 1990: 564)*

Airway Resistance

The flow of air into and out of the lungs depends on the pressure difference between atmosphere and alveoli and the resistance to flow through the airways. The adjacent figure shows the resistance to air flow at different sites in the tracheo-bronchial tree. This is compared with the total cross-sectional area of the airways at each of those sites. The mouth and nose contribute significant resistance to air-flow, but resistance is greatest in the medium-sized tertiary (segmental) bronchi. Resistance decreases as total cross-sectional area increases in the smaller respiratory airways.

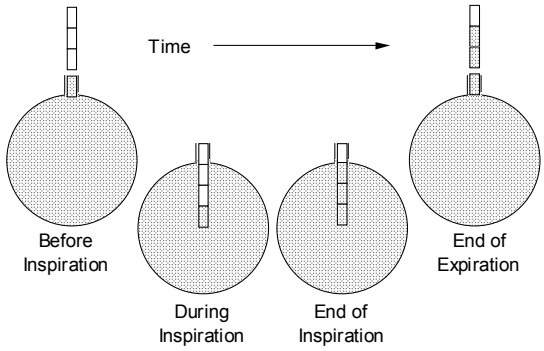


Airway resistance (solid circles) and total cross-sectional area (solid line) *(From: "Essentials of Physiology" Eds Sperelakis, N, & Banks, RO. Little Brown and Company, USA, 1996: 366)*

Asthma is a chronic condition characterised by sporadic bronchconstriction that increases airway resistance.

Dead-Space

Anatomic dead-space (V_D) is the volume of the conducting airways. No exchange of respiratory gases occurs in this volume. Dead-space volume is an obligatory consequence of tidal ventilation. Its presence necessarily dilutes each tidal inspiration with alveolar air remaining from the previous expiration. At rest, V_D (about 150 mL in a healthy adult) comprises about one-third of V_T (about 500 mL).



Lecture 5 of 7

Exchange of Oxygen and Carbon Dioxide

Dr Denis Loiselle

Objectives

At the end of this lecture you should be able to:

1 Describe the fundamental properties of gases .
2 Explain how gases diffuse from regions of higher partial pressure to regions of lower partial pressure.
3 Describe the exchange of oxygen and carbon dioxide from atmosphere to cell.
4 Distinguish minute ventilation from alveolar ventilation.
5 Explain the relationships among alveolar ventilation, oxygen consumption and carbon dioxide production and the partial pressures of oxygen and carbon dioxide.

Introduction

The key processes of respiration are the exchange of oxygen and carbon dioxide between air and blood on the one hand and the exchange of these gases with cells on the other hand. Oxygen and carbon dioxide move from the pulmonary alveoli to the blood by passive diffusion. The behaviour of these gases at the air-blood interface is described by basic gas laws, in particular Dalton's law and Henry's law. In cellular respiration, oxygen is consumed and carbon dioxide produced and at this level also, the exchange of oxygen and carbon dioxide between cells and blood occurs by passive diffusion. The levels of oxygen and carbon dioxide in arterial blood are determined by the balance between air flow to the alveoli and the rate at which oxygen is consumed and carbon dioxide is produced in the tissues. This lecture deals with the scientific basis of these fundamental processes of respiratory gas exchange.

Topics

1 Gas Laws: Dalton's Law and Henry's Law, (Tortora & Grabowski p.796-797 and lecture notes).
2 Distribution of oxygen and carbon dioxide partial pressures from the lungs to the cells (p.797 - 799 and lecture notes).
3 Factors affecting diffusive gas exchange, (p.798 and lecture notes).
4 Minute Volume, Dead space and Alveolar Ventilation (p795-796).
5 Alveolar ventilation, Carbon Dioxide, and Oxygen (lecture notes).

Resources

This topic is well-covered in Tortora & Grabowski. Use the topic list above to guide your reading. Additional diagrams have been taken from "Essentials of Physiology" Eds Sperelakis, N, & Banks, RO. Little Brown and Company, USA, 1996.

Gas Laws

The Universal Gas Law $P = nRT/V$

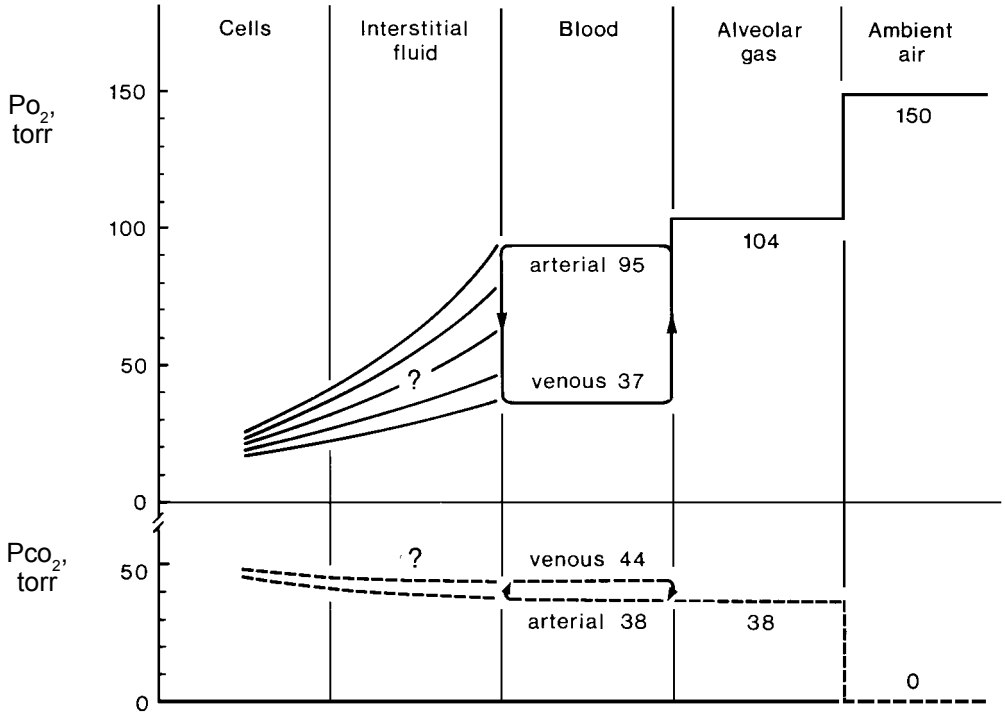
Dalton's Law $P_{total} = \sum_i P_i$

The partial pressure of a dissolved gas is that externally applied pressure required to prevent it coming out of solution.

Henry's Law $C = \sigma P$

The concentration C of a dissolved gas varies directly with its partial pressure. The constant of proportionality (σ) is called solubility. The solubility of a gas depends on the solvent (O_2 is more soluble in oil than in water) and (inversely) on the temperature. Carbon dioxide is about 24 times more soluble in blood than is oxygen.

Distribution of Oxygen and Carbon Dioxide Partial Pressures from Lungs to Cells



Partial pressures of O_2 and CO_2, Po_2 and Pco_2, in ambient air and in the various compartments of the gas exchange system of a man at rest and at sea level. The partial pressures of O_2 and CO_2 in the interstitial fluid and inside the cells are not well known.

[Fig 7-2, From: Dejours P, Principles of Comparative Respiratory Physiology (P 92), North-Holland Publishing Co, Amsterdam, 1975]

Gas exchange by diffusion

Oxygen and carbon dioxide move between the alveoli and pulmonary capillary blood and from systemic capillary blood to the cells by the process of **diffusion** which is described by **Fick's Law**. The volume of gas transported across a membrane such as the alveolar-pulmonary capillary interface per unit time is **directly related** to the:

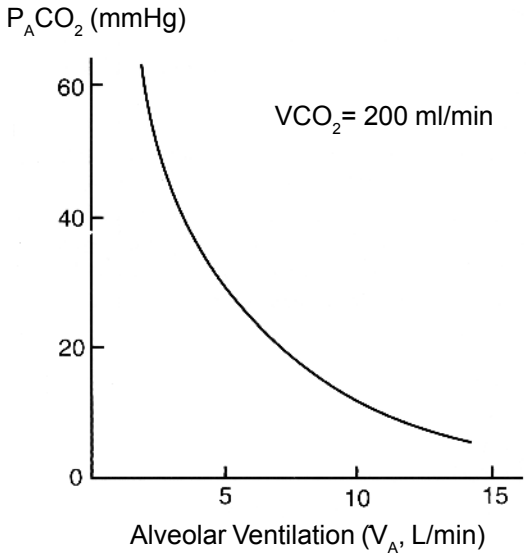
- driving pressure or difference in partial pressure of the gas across the membrane
- area of the membrane
- solubility of the gas

and is **inversely related** to the:

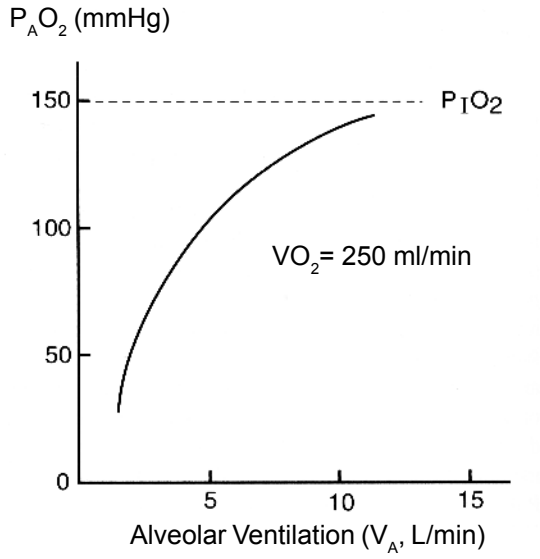
- the length of the diffusion pathway (thickness of the membrane)
- square root of the molecular weight of the gas

Alveolar Ventilation

Alveolar ventilation replenishes O_2, which has been removed from the blood by the tissues, and excretes from the alveoli CO_2 that has been added to the blood by the tissues. Alveolar ventilation is normally regulated so that O_2 intake at the lungs matches O_2 consumption by the tissues and elimination of CO_2 is similarly matched to CO_2 production. This maintains essentially constant partial pressures of O_2 and CO_2 in arterial blood. It follows that any change of alveolar ventilation relative to metabolism will alter the levels of O_2 and CO_2 in arterial blood – as indicated in the following Figures.



Alveolar CO_2 tension(P_ACO_2) plotted as a function of alveolar ventilation (V_A) at a constant production of Vco_2. As V_A increases, P_Aco_2 declines. (Modified from: Cherniack, N. S., Altose, M.D. and Kelsen, S.G.
The respiratory system, In: Berne, R.H. and Levy, M.N., eds., *Physiology.* St. Louis: MOsby, 1983, P.685.)



Alveolar O_2 tension(P_AO_2) plotted as a function of V_A at a constant O_2 production (Vo_2). As V_A increases, P_Ao_2 rises, approaching the level of inspired O_2. (Modified from: Cherniack, N. S., Altose, M.D. and Kelsen, S.G.
The respiratory system, In: Berne, R.H. and Levy, M.N., eds., *Physiology.* St. Louis: MOsby, 1983, P.686.)

[Fig 32-1 & 32-2, From: "Essentials of Physiology" Eds Sperelakis, N, & Banks, RO. Little Brown and Company, USA, 1996: 372]

Lecture 6 of 7

Transport of Oxygen and Carbon Dioxide in Blood

Dr Denis Loiselle

Objectives

At the end of this lecture you should be able to:

1 Explain how oxygen and carbon-dioxiode are transported in the blood.
2 Define oxygen content and oxyhaemoglobin saturation.
3 Explain the shape of the oxyhaemoglobin dissociation curve and discuss the various factors which affect the affinity of haemoglobin for oxygen.
4 Discuss the physiological significance of the oxyhaemoglobin dissociation curve.
5. Describe the carbon-dioxide dissociation curve and outline the mechanisms responsible for carbon-dioxide transport in blood.

Introduction

Oxygen does not dissolve readily in water. If oxygen dissolved in plasma were the only way that blood could transport this gas, cardiac output would need to be more than 80 litres per minute in order to meet metabolic requirements at rest. The majority of the oxygen transported by blood is bound to haemoglobin in red blood cells. The relationship between the binding of oxygen to haemoglobin and oxygen partial pressure (the oxyhaemoglobin dissociation curve) favours loading of oxygen to blood in the lungs and unloading of oxygen in metabolising tissues. Most carbon-dioxide is transported in blood plasma as bicarbonate ions.

Topics

1 Haemoglobin, oxygen content and oxyhaemoglobin saturation, (Tortora & Grabowski p.799 and lecture notes).
2 The oxyhaemoglobin dissociation curve and factors affecting the affinity of haemoglobin for oxygen: acidity; partial pressure of carbon-dioxide, temperature, 2,3-diphosphoglycerate (2,3-DGP), (p.800 - 802).
3 Effects of anaemia and carbon monoxide on oxygen transport, (p.802 and lecture notes).
4 Carbon-dioxide transport, (p.802-803).
5 The carbon-dioxide dissociation curve, (lecture notes).
6 A summary of gas exchange and transport in lungs and tissues (p803 - 804 and lecture notes).

Resources

This topic is covered extremely well in Tortora & Grabowski, but some additional information is provided in the notes which follow. Use the topic list above to guide your reading.

Oxygen Content and Oxyhaemoglobin Saturation

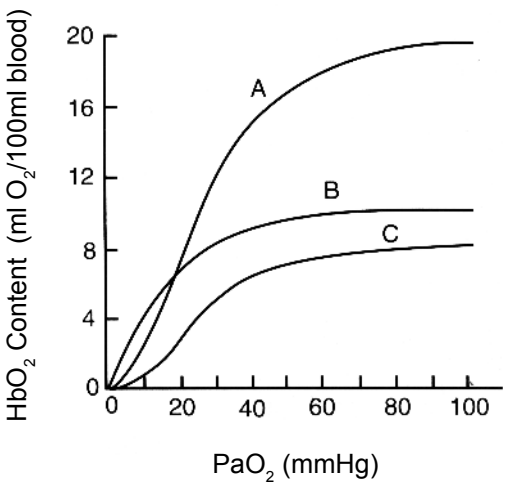
The **oxygen content** of blood is the total amount of O_2 carried. The oxygen content of blood is the sum of the O_2 combined with haemoglobin and the O_2 dissolved in plasma. Whole blood in healthy adults contains about 150 g of haemoglobin per litre of blood. One gram of haemoglobin can bind 1.34 mL of O_2 and therefore up to 200 mL of O_2 can be bound to haemoglobin per litre of blood.

The **percent saturation of haemoglobin** is the amount of O_2 actually bound to haemoglobin relative to the maximum amount which can be bound (normally 200 mL per L of blood), expressed as a percentage. Under normal circumstances arterial blood is around 98% saturated. Per litre of blood, about 197 mL of O_2 are bound to haemoglobin while a further 3 mL are dissolved in the plasma.

Effects of Anaemia and Carbon Monoxide on Oxygen Transport

The effects of anaemia and carbon-monoxide poisoning are illustrated in the figure below.

Effects of anemia (C) and carbon monoxide poisoning (B) on the oxyhemoglobin (HbO_2) content (the volume of O_2 bound to hemoglobin). (A) the normal curve. Note that both anemia and carbon monoxide poisoning reduce the HbO_2 content but for different reasons (see text). (Modified from: Cherniack, N. S., Altose, M.D. and Kelsen, S.G. The respiratory system, In: Berne, R.H. and Levy, M.N., eds., *Physiology.* St. Louis: MOsby, 1983, P.691.)



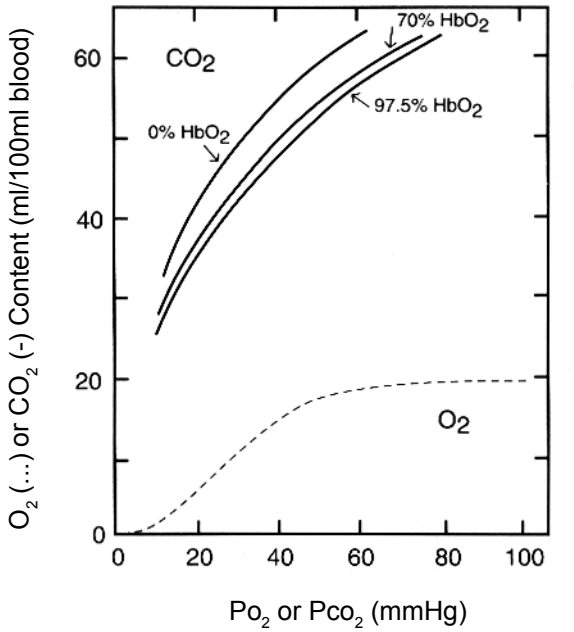
[Fig. 32-7 From: "Essentials of Physiology" Eds Sperelakis, N, & Banks, RO. Little Brown and Company, USA, 1996: 377]

It should be noted that these curves do not give *percentage oxyhaemoglobin saturation* but, instead, relate the *amount* of O_2 bound to haemoglobin. Curve A presents data from a normal adult subject, while curves B and C illustrate the effects of carbon-monoxide poisoning and anaemia, respectively. For C, haemoglobin is reduced to 6 mL per litre of blood, which is less than half the normal level. As a result, the total amount of oxyghaemoglobin is substantially reduced - despite the fact that haemoglobin remains about 98% saturated.

With carbon-monoxide poisoning, on the other hand, binding of oxygen to haemoglobin is blocked by carbon-monoxide which has a much higher affinity for haemoglobin than does oxygen. This causes a substantial reduction in oxyhaemoglobin saturation.

The Carbon Dioxide Dissociation Curve

In the Figure below CO_2 and O_2 *content* are plotted as functions of the partial pressures of CO_2 and O_2 respectively. The CO_2 dissociation curve is much more linear than the oxyhaemoglobin dissociation curve. Moreover, CO_2 content is increased with O_2 desaturation of haemoglobin and decreases with O_2 desaturation of haemoglobin.



CO_2 (solid lines) and O_2 (dashed line) plotted as a function of partial pressures of CO_2 (Pco_2) or O_2 (Po_2), respectivly. CO_2 content is increased with desaturation of hemoglobin and decreased with increasing saturation of hemoglobin. In the physiologic range, the CO_2 content curve is essentially linear, as compared with the oxyhemoglobin dissociation curve.

[Fig. 32-8. From: "Essentials of Physiology" Eds Sperelakis, N, & Banks, RO. Little Brown and Company, USA, 1996: 378]

A Summary of Gas Exchange and Transport in Lungs and Tissues

Lungs

$$Hb + O_2 \rightleftharpoons HbO_2$$

Tissues

$$HbO_2 \rightleftharpoons Hb + O_2$$

$$O_2 + \begin{matrix}\text{carbohydrates}\\ \text{fats}\end{matrix} \longrightarrow CO_2 + H_2O$$

$$CO_2 + Hb \rightleftharpoons HbCO_2$$

Lungs

$$HbCO_2 \rightleftharpoons Hb + CO_2$$

Overall

$$HbCO_2 + O_2 \underset{\text{Tissues}}{\overset{\text{Lungs}}{\rightleftharpoons}} HbO_2 + CO_2$$

Lecture 7 of 7

Control of Ventilation

Dr Denis Loiselle

Objectives

At the end of this lecture you should be able to:

1 Give an overview of the control of breathing. What is sensed? What is regulated?
2 Explain the role of the muscles of ventilation in regulating the depth of ventilation.
3 Describe the role of receptors in the thorax in the control of ventilation.
4 Explain the role of chemical feedback in the control of ventilation.
5 Compare the different respiratory reponses to reduced arterial oxygen levels and raised arterial carbon dioxide levels.

Introduction

The primary function of the respiratory system is to maintain appropriate partial pressures of oxygen and carbon-dioxide in the blood. The partial pressures of oxygen and carbon-dioxide in arterial blood are determined by the balance between air flow to the alveoli and the rate at which oxygen is consumed and carbon-dioxide is produced in the tissues. Ventilation is controlled by neurons in the central nervous system (CNS) which regulate the depth and frequency of respiratory activity. Information is continuously fed back to the respiratory control centres in the CNS from regions in the circulation that are sensitive to arterial PO_2 and PCO_2. Hydrogen ion concentration in the extracellular fluid that bathes the brainstem also modifies respiratory drive. Finally, further information is relayed to the respiratory control centres from receptors in the lungs, thoracic wall and respiratory muscles. This system provides precise control of respiratory function for a range of different activities that can impose widely varying metabolic demands.

Topics

1 Ventilatory responses to reduce P_IO_2 and increase P_ICO_2 (lecture notes).
2 Components of the respiratory control system (lecture notes).
3 Feedback from the airways and lung parenchyma, (p.807-808 and lecture notes).
4 Feedback from peripheral and central chemoreceptors, (p.806-807 and lecture notes).
5 Exercise and the respiratory system (p809).

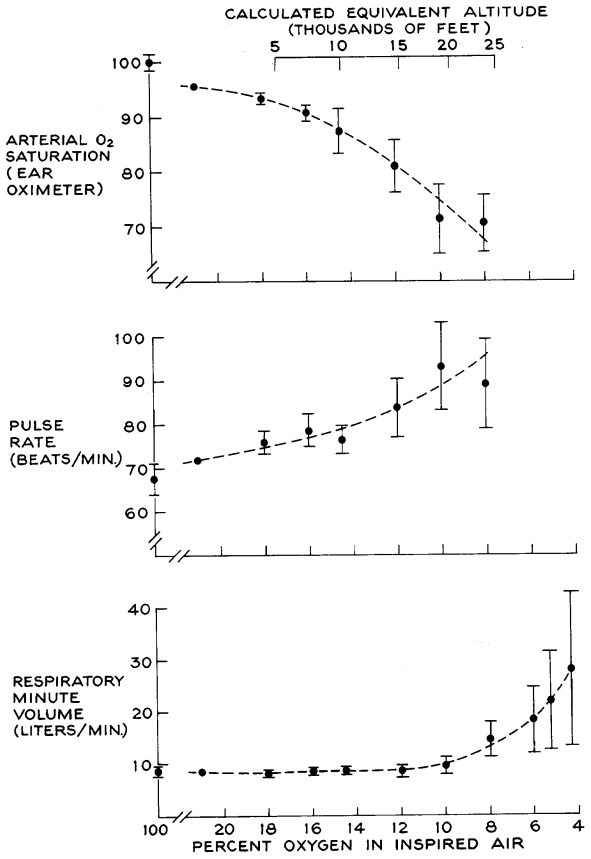
Resources

This topic is covered in Tortora & Grabowski. Additional diagrams have been included from: “Essentials of Physiology”, Eds Sperelakis, N & Banks, RO. Little Brown and Company, USA, 1996. Use the topic list above to guide your reading.

Response to altered INSPIRATORY partial pressures of oxygen (P_IO_2) and carbon-dioxide (P_ICO_2)

Response to brief anoxia. Healthy men breathed gas mixtures low or high in O_2 for 8 min. Measurements are average values over the last 3 min. Cross lines represent one standard deviation from the mean. Note the wide variation in individual responses to inhalation of the same gas mixtures; this is an index of the wide range of sensitivity of chemoreceptor response to anoxia in man. The men who increased their ventilation most in response to low O_2 had the highest arterial O_2 saturation. Some men show no respiratory stimulation even when breathing 10% O_2.

[From Comroe, *Physiology of Respiration*, Year Book Medical Publishers, Inc, Chicago, 1968; p.40.]



Response to CO_2, O_2 and pH.

[ibid; p.6o]

Respiratory Centres in the Central Nervous System

Unlike the heart beat, which is generated by an intrinsic pacemaker, breathing relies on neural input to the muscles of ventilation. Respiratory rhythm originates in the brainstem. The basic respiratory rhythm is generated by two groups of neurons in the medulla oblongata. These *medullary centres* are: the Dorsal Respiratory Group (DRG, neurons of which are active primarily during inspiration) and the Ventral Respiratory Group (VRG, some neurons of which are active during inspiration, others during expiration and some during the transition).

The rhythmic drive which originates in the brainstem is transmitted to **motoneurons** in the brainstem (cranial motoneurons) and spinal cord which, in turn, drive the muscles involved in breathing (diaphragm, intercostals and upper airway muscles).

Feedback from the airways and lung parenchyma

Slowly adapting stretch receptors located in walls of the bronchi and bronchioles send signals back via myelinated fibres in the vagus nerve to brainstem respiratory centres. Activation of these receptors by lung inflation terminates inspiration.

Irritant Sensors in the airways send signals via myelinated and unmyelinated (C-fibres) in the vagus nerves and respond to:

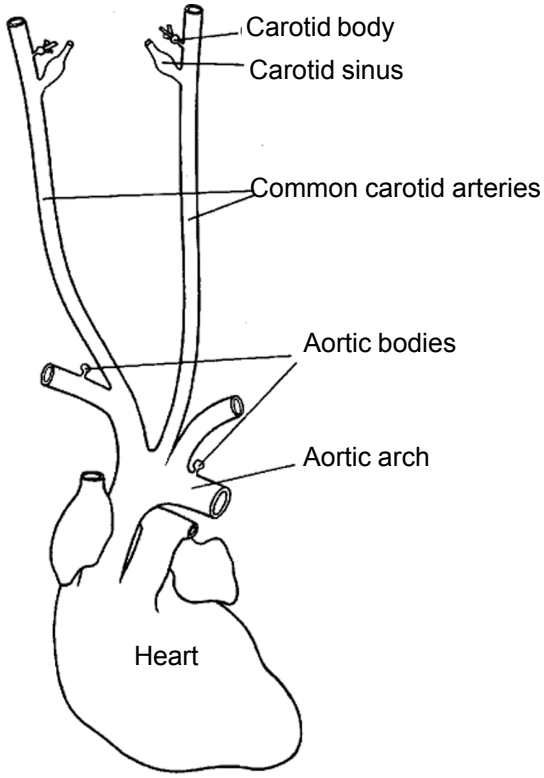
- noxious mechanical and chemical stimuli (smoke, smog, pollen, "food going down the wrong pipe", etc),
- histamine and prostaglandins produced in responses to allergies and inflammation, and
- lung hyperinflation.

Activation of these receptors can lead to reflex constriction of bronchioles (smooth muscle), coughing, rapid shallow breathing, and increased mucous secretion.

Feedback from peripheral and central chemoreceptors

Peripheral sensors in the carotid bodies and aortic bodies detect arterial PO_2, PCO_2 and pH - informing the central respiratory control centre if more ventilation is required in order to maintain blood gases at appropriate levels.

The carotid bodies are located at the bifurcation of the common carotid arteries. They are highly vascularized, having a very high blood flow rate relative to their metabolic needs, and are well suited to "measure" the O_2 and CO_2 levels in the blood. They respond to decreases in P_aO_2 or increases in P_aCO_2.



Location of carotid and aortic bodies
[From Patton et al., Textbook of Physiology, Volume 2, 1989]

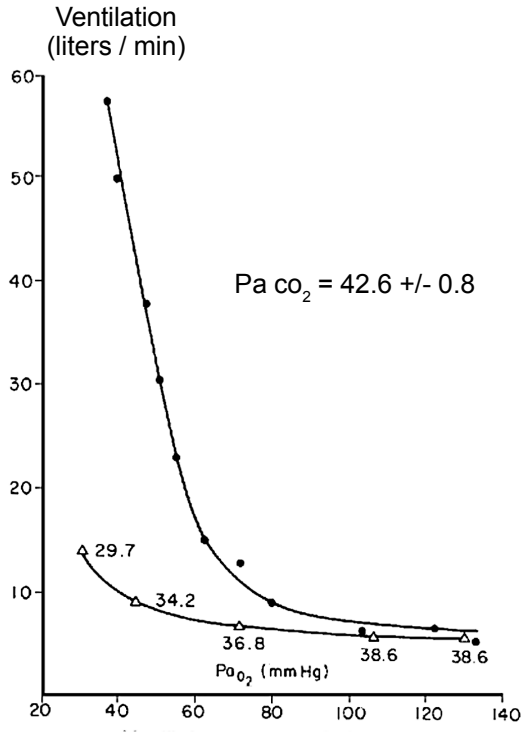
Afferents from the carotid bodies travel in the **carotid sinus nerve** (along with afferents from the carotid sinus baroreceptors) which joins the **glossopharygeal** (**IXth cranial) nerve** as it enters the medulla.

The **aortic bodies** are found in the aortic arch and subclavian arteries. Their afferents travel in the **vagus nerve**.

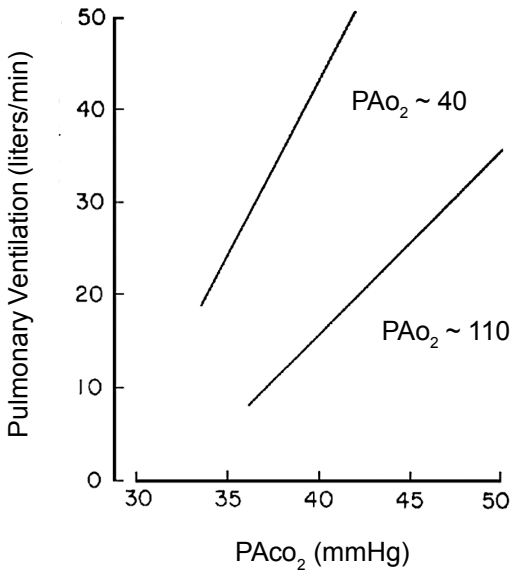
Central chemoreceptors located on the ventral surface of medulla are sensitive to the pH of the cerebrospinal fluid.

Revealing the intrinsic sensitivity to P_aO_2 and P_aCO_2

The intrinsic sensitivity of ventilation to O_2 and CO_2 can be revealed by measuring the ventillatory response to changing each, in turn, while artificially holding the other constant. The Figure below shows the results of performing this experiment on a single subject.



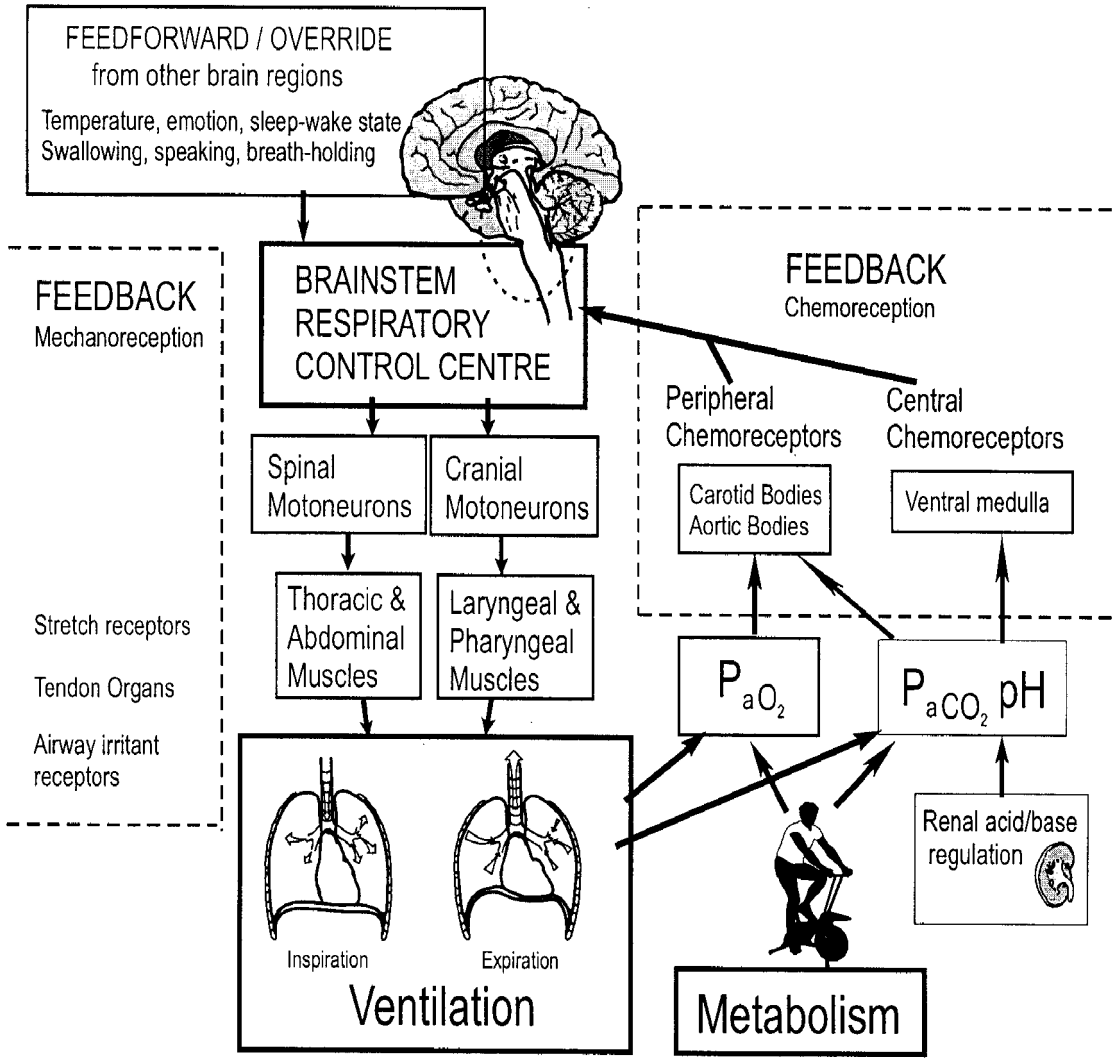
Ventilatory response to hypoxia in one human sbject. The upper curve shows the ventilatory response when alveolar Pco_2 was kept constant at 42.6 mm Hg by adding CO_2 to inspired gas mixture. The lower curve shows the ventilatory response when alveolar Pco_2 was allowed to fall with hyperventilation. The numbers beside the lower curve refer to the measured alveolar Pco2 at each point on the curve.



A human subjects ventilatory response to hypercapnia at two levels of alveolar Po_2. Note that the response is linear at each Po_2 level and the hypoxia increases its slope. (Based on the data of Nielson and Smith, Acta Physiol, Scand 24:293-313, 1952.)

[From Patton *et al*., *Textbook of Physiology*, Volume 2, 1989.]

Components of the Respiratory Control System



CONTROL OF VENTILATION

(From Dempsey, I.A. & Pack, A.I.: *Regulation of Breathing*, New York, 1995, Marcel Dekker).