Respiratory system

15. 11. 2011

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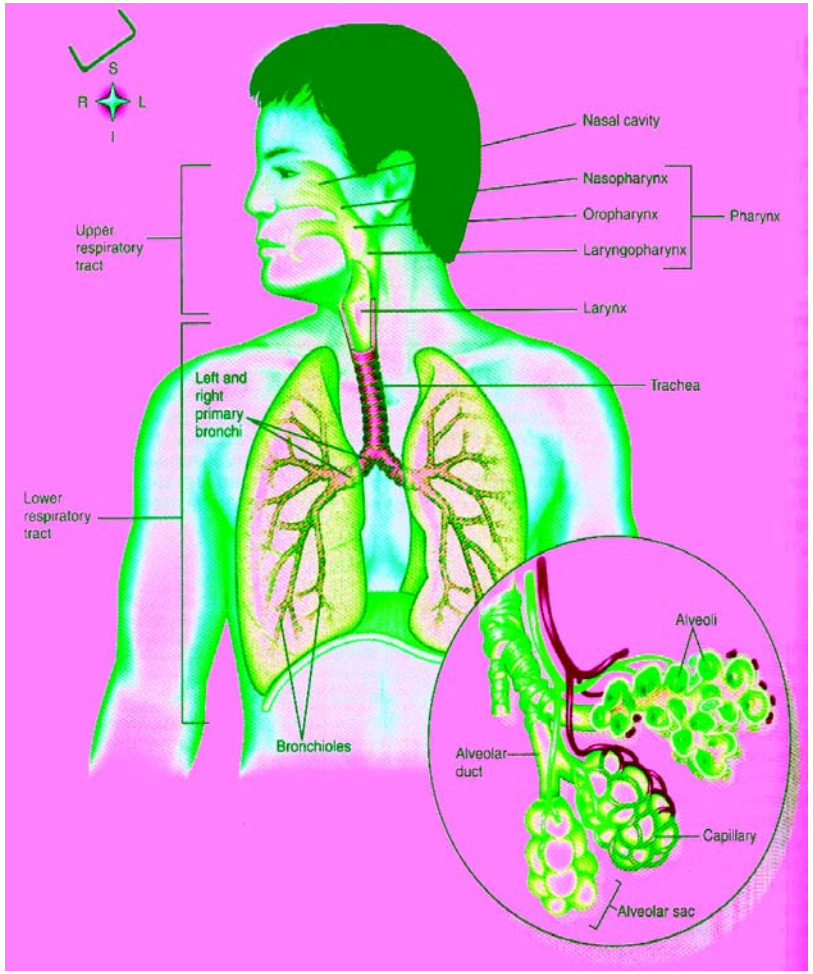


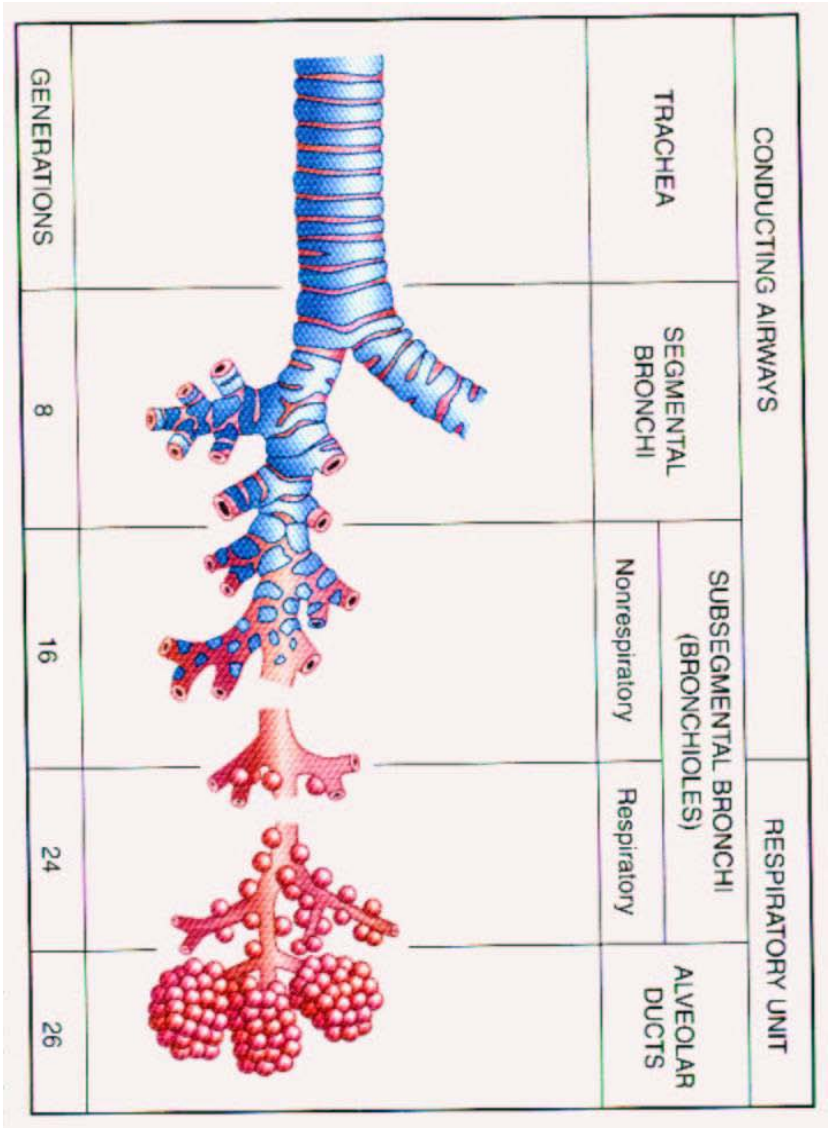
- The main role of the respiratory system is *to work closely with the heart and blood to extract oxygen* from the external environment and *dispose of waste gases, principally carbon dioxide*.

- This requires the lungs to function as an efficient bellows, expelling used air, bringing fresh air in and mixing it efficiently with the air remaining in the lungs.

- The lungs have to provide *a large surface area* for gas exchange and the alveoli walls have to present *minimal resistance to gas diffusion*. This means the lungs have to present a large area to the environment and this *can be damaged* by dusts, gases and infective agents.

- Host defence is therefore a key priority for the lung and is achieved by a combination of structural and immunological defences.

The trachea, bronchi and bronchioles



- The *trachea* is 10-12 cm in length. It lies slightly to the right of the midline and divides at the carina into right and left main bronchi.
- The *carina* lies under the junction of the manubrium sternum and the second right costal cartilage.
- The *right main bronchus* is more vertical than the *left* and, hence, inhaled material is more likely to pass into it. The right main bronchus divides into the *upper lobe bronchus and the intermediate bronchus,* which further subdivides into the *middle and lower lobe bronchi.*
- On the left the main bronchus divides into *upper and lower lobe bronchi only.* Each lobar bronchus further divides into segmental and subsegmental bronchi. There are about *25 divisions* in all between the trachea and the alveoli.

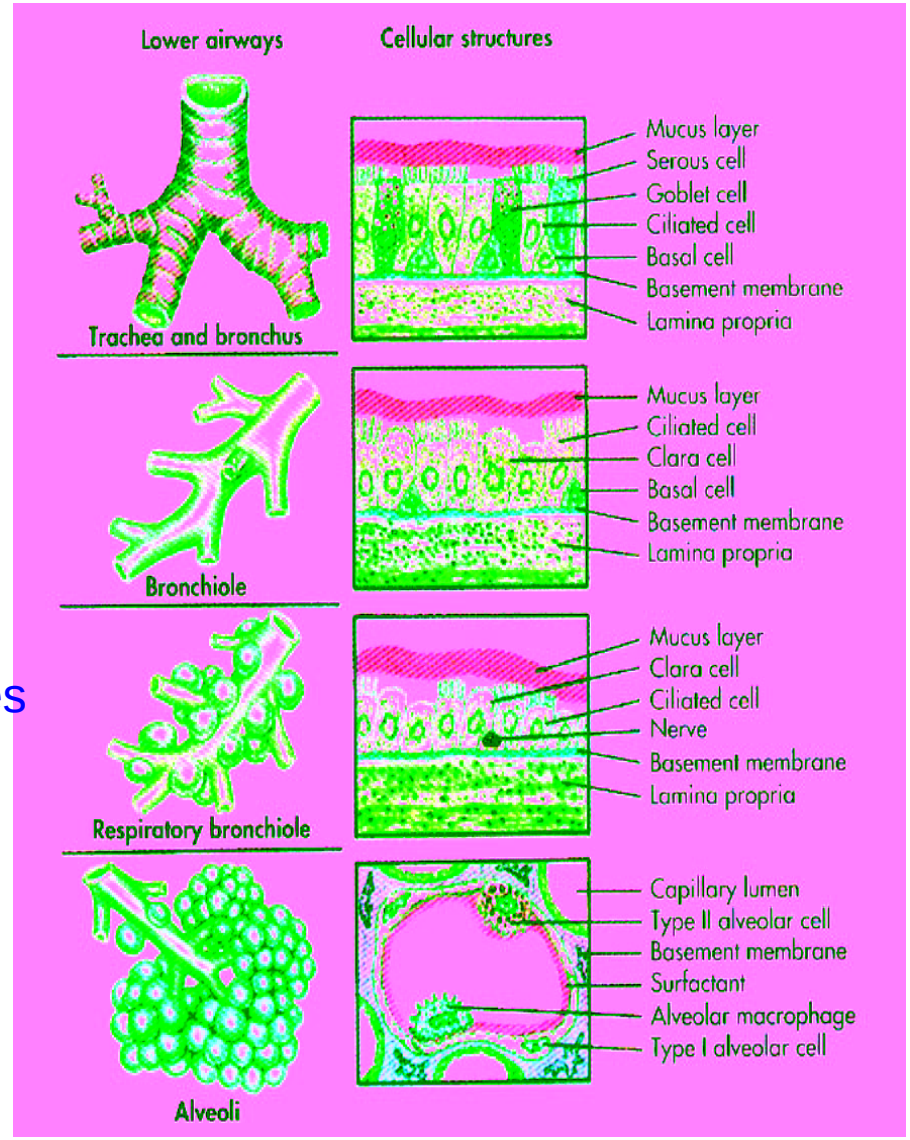
Structure

Of the first seven divisions, the bronchi have:

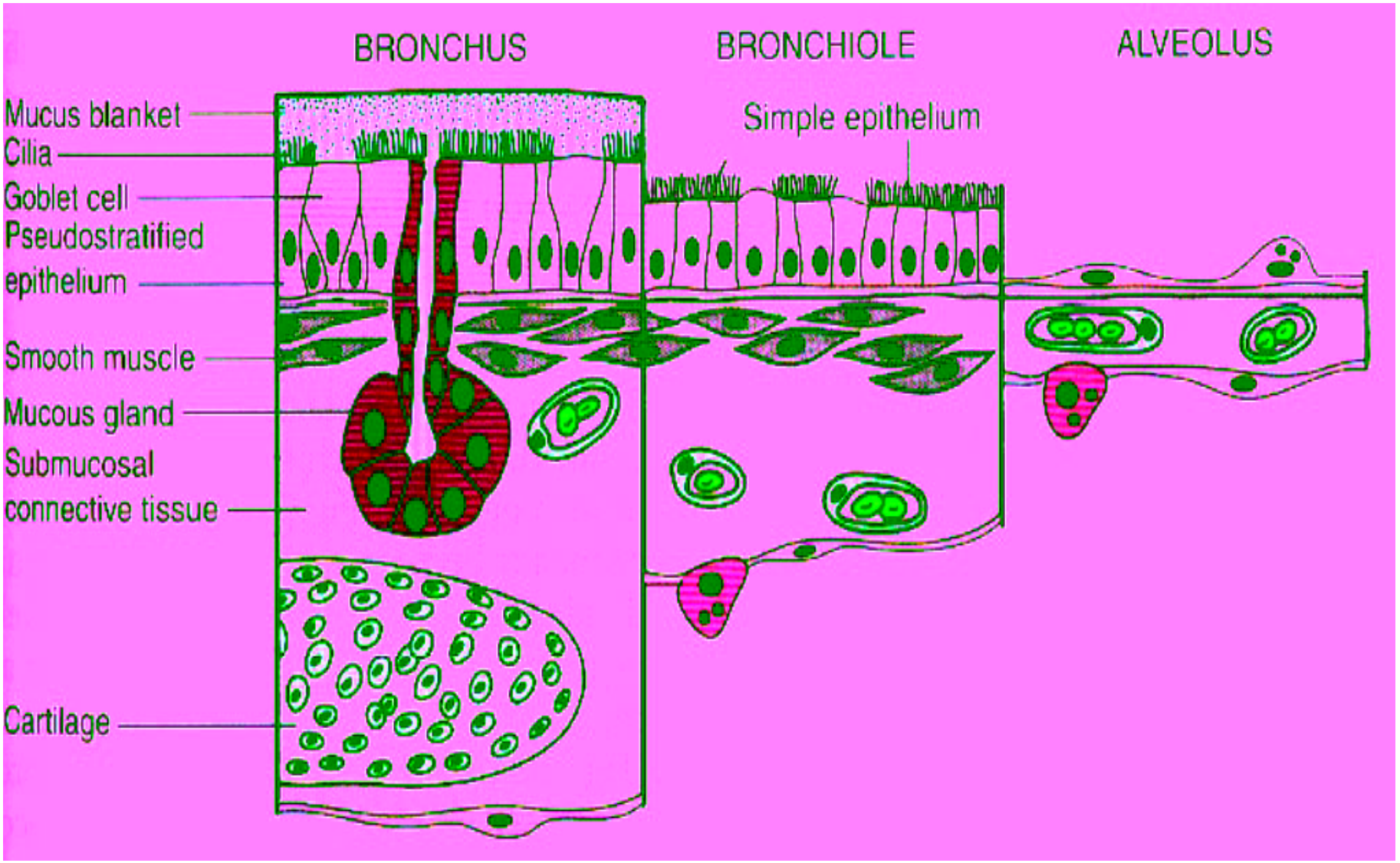
- walls consisting of cartilage and smooth muscle
- epithelial lining with cilia and goblet cells
- submucosal mucus-secreting glands
- endocrine cells - Kulchitsky or APUD (amine precursor and uptake decarboxylation) containing 5-hydroxytryptamine

In the next 16-18 divisions the bronchioles have:

- no cartilage and a muscular layer that progressively becomes thinner
- a single layer of ciliated cells but very few goblet cells
- granulated Clara cells that produce a surfactant-like substance.



Structure of the wall: bronchus, bronchiolus a alveolus

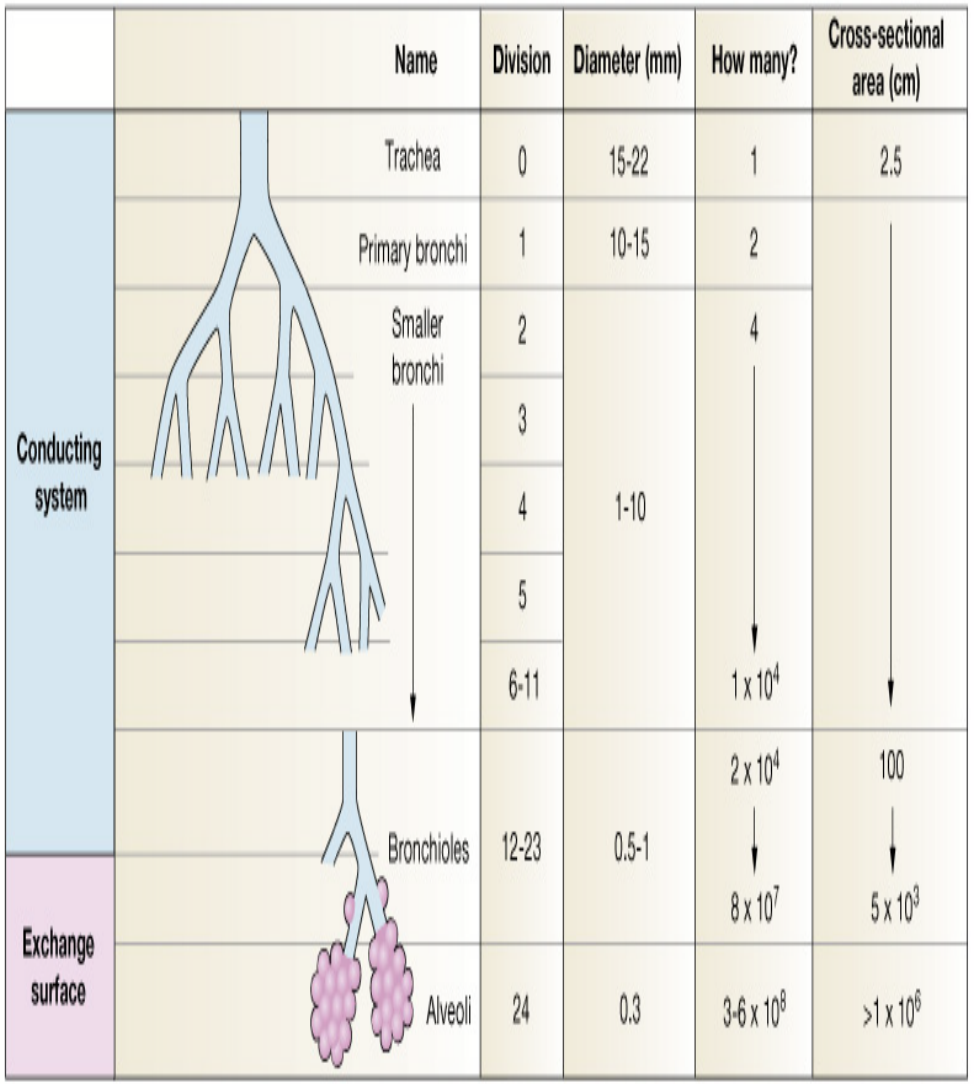


- Anatomical **dead space**
  - nose (mouth), larynx
  - trachea, bronchi & bronchioles

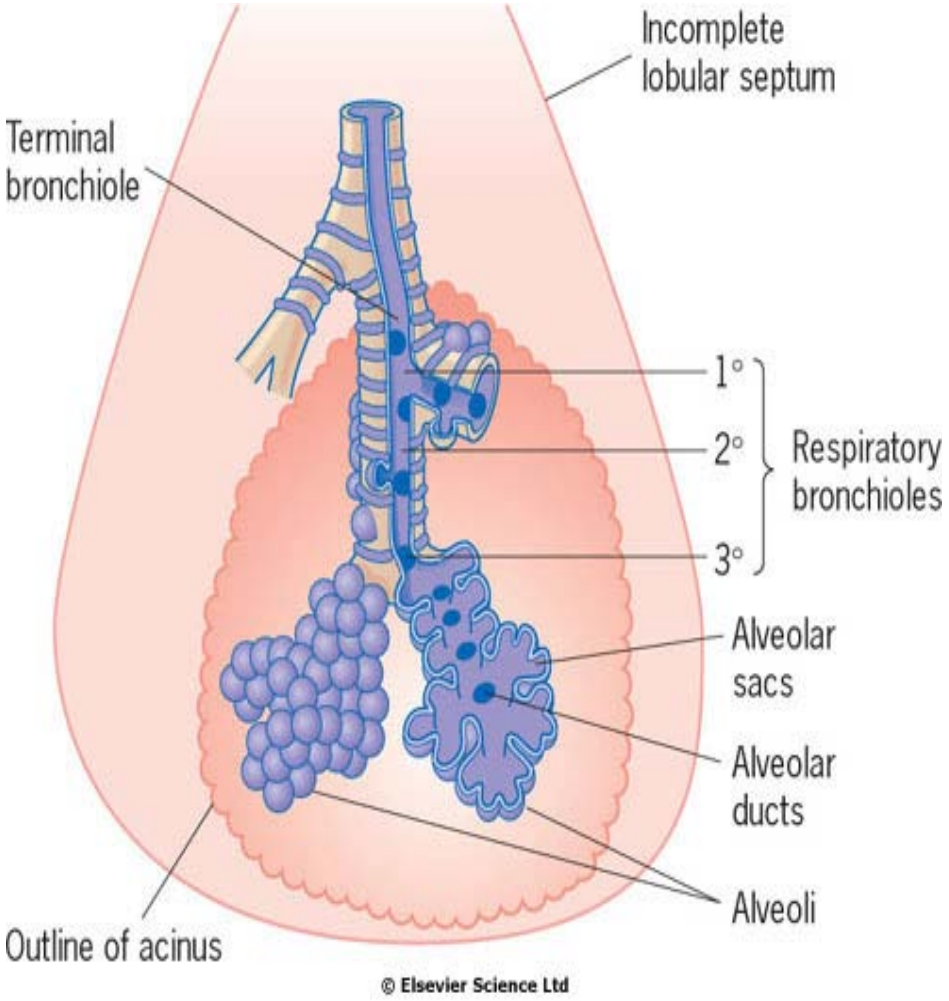
  - Filtration & warming
  - gas exchange is not present, only gas transport

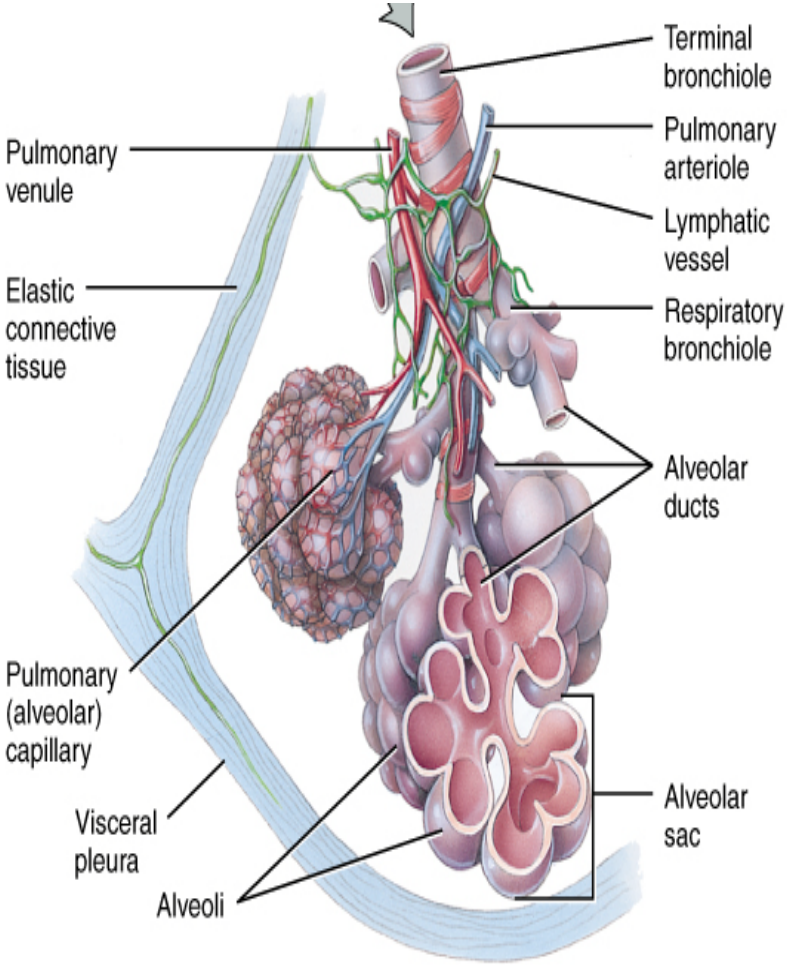
- **respiratory space**
  - respiratory bronchioles, alveolar sacs and alveoli

  - **gas exchange**



- Respiratory bronchioles, alveolar ducts, alveoli - **acinus**.





Alveoli

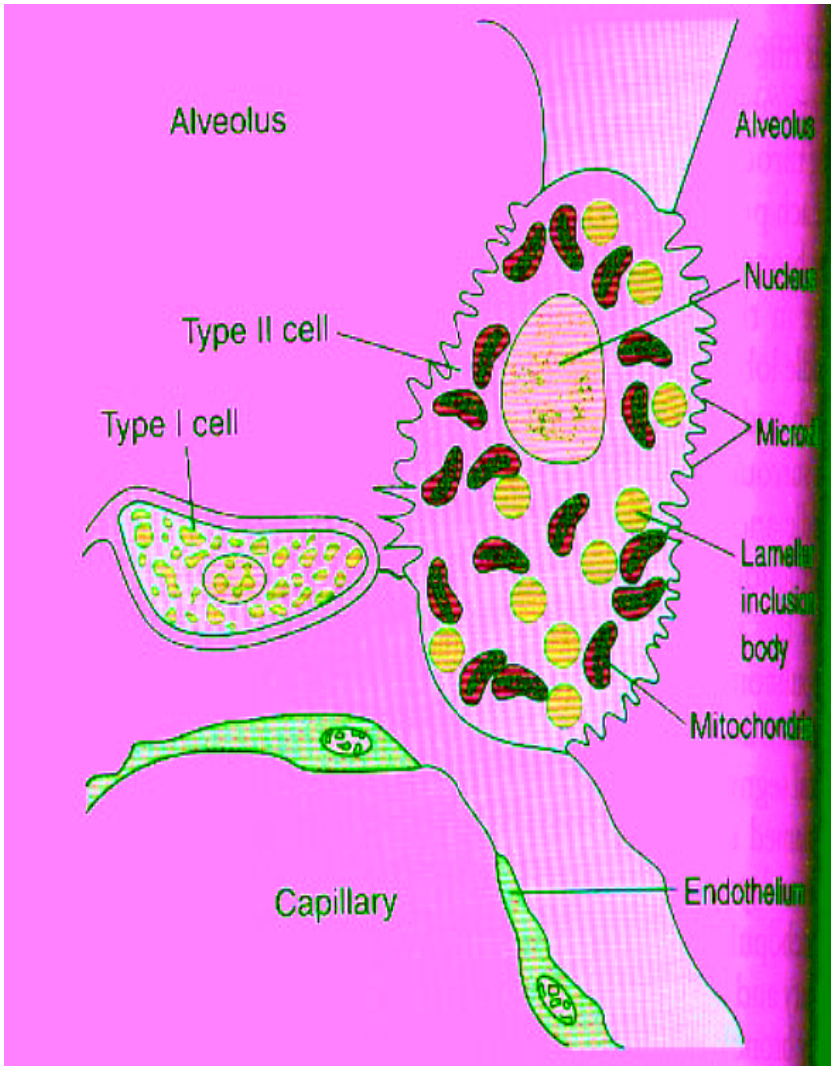
• There are approximately 300 million alveoli in each lung. Their total surface area is 40-80 m2.

• The epithelial lining consists largely of *type I pneumocytes*. These cells have an extremely attenuated cytoplasm, and thus provide only a thin barrier to gas exchange. They are derived from type II pneumocytes. *Type I cells* are connected to each other by tight junctions that limit the fluid movements in and out of the alveoli.

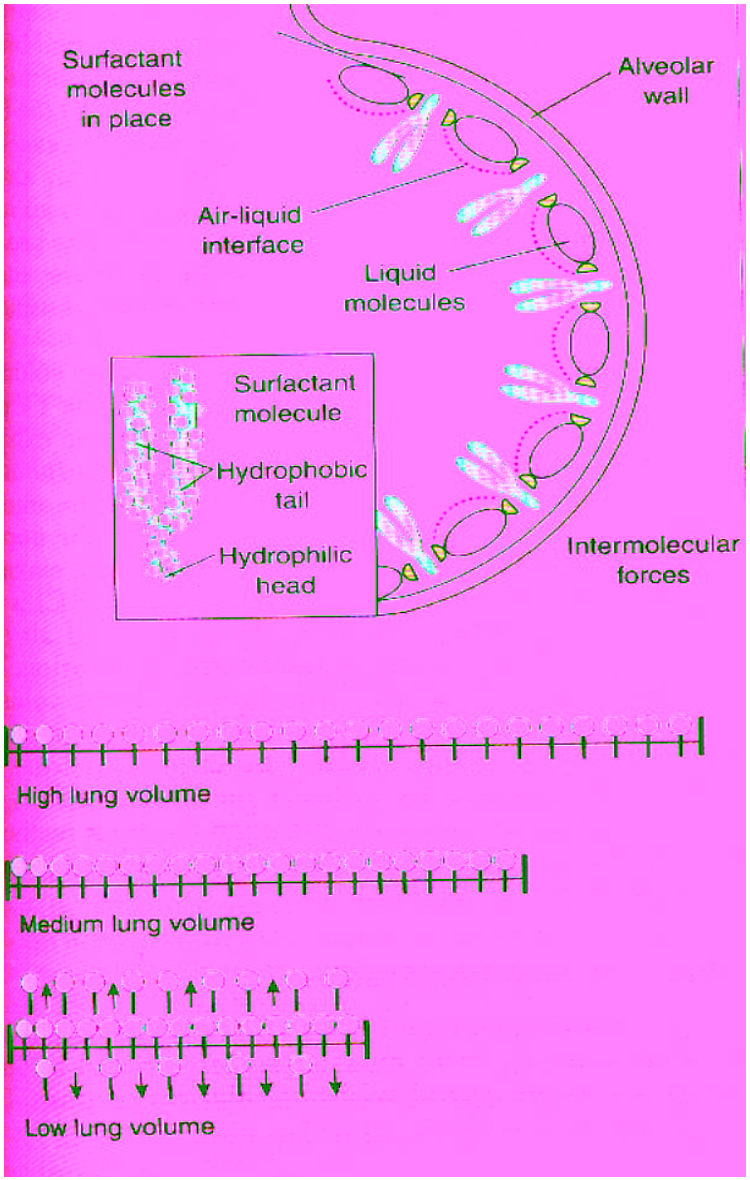
• *Type II pneumocytes* are slightly more numerous than type I cells but cover less of the epithelial lining. They are found generally in the borders of the alveolus and contain distinctive lamellar vacuoles, which are the *source of surfactant*.

• *Macrophages* are also present in the alveoli and are involved in the defence mechanisms of the lung.

•The *pores of Kohn* are holes in the alveolar wall allowing communication between alveoli of adjoining lobules.



Surfactant – alveolar stability



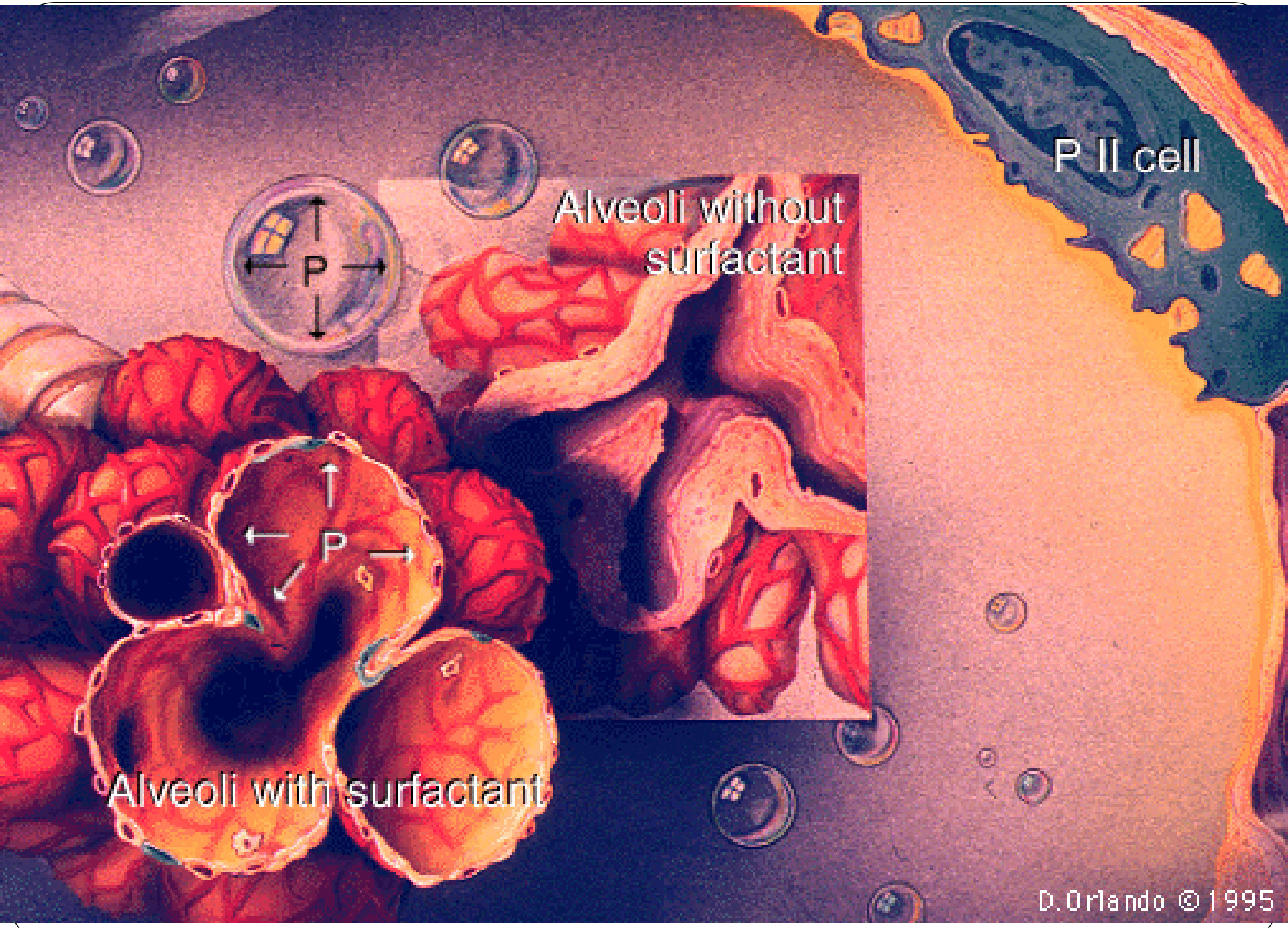
During quiet breathing, small areas of the lung undergo *collapse,* but it is possible to re-expand these rapidly by a deep breath; hence the importance of slight or deep breaths as a feature of normal breathing. Failure of such a mechanism - which can occur, for example, in patients with fractured ribs - gives rise to patchy basal lung collapse.

Surfactant levels may be reduced in a number of diseases that cause damage to the lung (e.g. pneumonia).

Lack of surfactant plays a central role in the *respiratory distress syndrome of the new-born*.

Severe reduction in perfusion of the lung causes impairment of surfactant activity and may well account for the characteristic areas of collapse associated with pulmonary embolism.

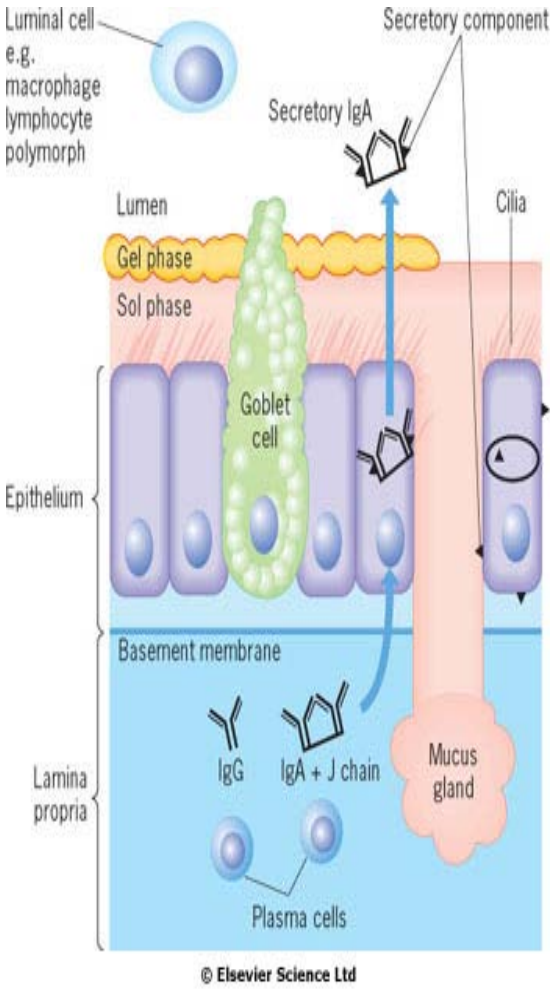
Adult respiratory distress syndrome (ARDS)


P
Alveoli without surfactant
P II cell
P
Alveoli with surfactant
D.Orlando ©1995

Defence mechanisms of the respiratory tract

- Pulmonary disease often results from a failure of the many defence mechanisms that usually protect the lung in a healthy individual.

- These can be divided into physical and physiological mechanisms and humoral and cellular mechanisms.



Physical and physiological mechanisms

Humidification

- This prevents dehydration of the epithelium.

Particle removal

- Over 90% of particles greater than 10 µm diameter are removed in the nostril or nasopharynx. This includes most pollen grains which are typically >20 microns in diameter.
- Particles between 5-10 microns become impacted in the carina.
- Particles smaller than 1 micron tend to remain airborne,
- The particles capable of reaching the deep lung are confined to the 1-5 micron range.

Particle expulsion

- ***This is effected by coughing, sneezing or gagging.***

Respiratory tract secretions

- The mucus of the respiratory tract is a gelatinous substance consisting chiefly of acid and neutral polysaccharides.

- The mucus consists of a 5 mm thick gel that is relatively impermeable to water. This floats on a liquid or sol layer that is present around the cilia of the epithelial cells. The gel layer is secreted from goblet cells and mucous glands as distinct globules that coalesce increasingly in the central airways to form a more or less *continuous mucus blanket*.

- Under normal conditions the tips of the cilia are in contact with the under surface of the gel phase and coordinate their movement to push the mucus blanket upwards. Whilst it may only take 30-60 minutes for mucus to be cleared from the large bronchi, there may be a delay of several days before clearance is achieved from respiratory bronchioles.

Respiratory tract secretions

One of the major long-term effects of cigarette smoking is a reduction in mucociliary transport. This contributes to *recurrent infection* and in the larger airways it *prolongs contact with carcinogens*.

Air pollutants, local and general anaesthetics and bacterial and viral infections also reduce mucociliary clearance.

Congenital defects in mucociliary transport occur. In the '*immotile cilia*' syndrome there is an absence of the dynein arms in the cilia themselves, and in *cystic fibrosis* an abnormal mucus composition is associated with ciliary dyskinesia. Both diseases are characterized by recurrent infections and eventually with the development of bronchiectasis.

Humoral and cellular mechanisms

- ***Non-specific soluble factors***

- *α-Antitrypsin* (α-antiprotease is present in lung secretions derived from plasma. It inhibits chymotrypsin and trypsin and neutralizes proteases and elastase.
- *Lysozyme* is an enzyme found in granulocytes that has bactericidal properties.
- *Lactoferrin* is synthesized from epithelial cells and neutrophil granulocytes and has bactericidal properties.
- *Interferon* is produced by most cells in response to viral infection. It is a potent modulator of lymphocyte function. It renders other cells resistant to infection by any other virus.
- *Complement* is present in secretions and is derived by diffusion from plasma. In association with antibodies, it plays an important cytotoxic role.
- *Surfactant protein A* (SPA) is one of four species of surfactant proteins which opsonizes bacteria/particles, enhancing phagocytosis by macrophages.
- *Defensins* are bactericidal peptides present in the azurophil granules of neutrophils.

Humoral and cellular mechanisms

Pulmonary alveolar macrophages

- These are derived from precursors in the bone marrow and migrate to the lungs via the bloodstream.
- They phagocytose particles, including bacteria, and are removed by the mucociliary escalator, lymphatics and bloodstream. They are the dominant cell in the airways at the level of the alveoli and comprise 90% of all cells obtained by bronchoalveolar lavage.
- Alveolar macrophages work principally as scavengers and are not particularly good at presenting antigens to the immune system.

Dendritic cells

- form a network throughout the airways and are thought to be the key antigen-presenting cell in the airway.

Humoral and cellular mechanisms

Lymphoid tissue

- The lung contains large numbers of lymphocytes which are scattered throughout the airways. Sensitized lymphocytes contribute to local immunity through differentiation into **IgA-secreting plasma cells**. IgG and IgE are found in low concentrations in airway secretions from a combination of local and systemic production.

- In addition to these resident cells, the lung has the usual range of acute inflammatory responses and can mobilize neutrophils promptly in response to injury or infection and play a major part in inflammatory conditions such as asthma.

The ciliated epithelium

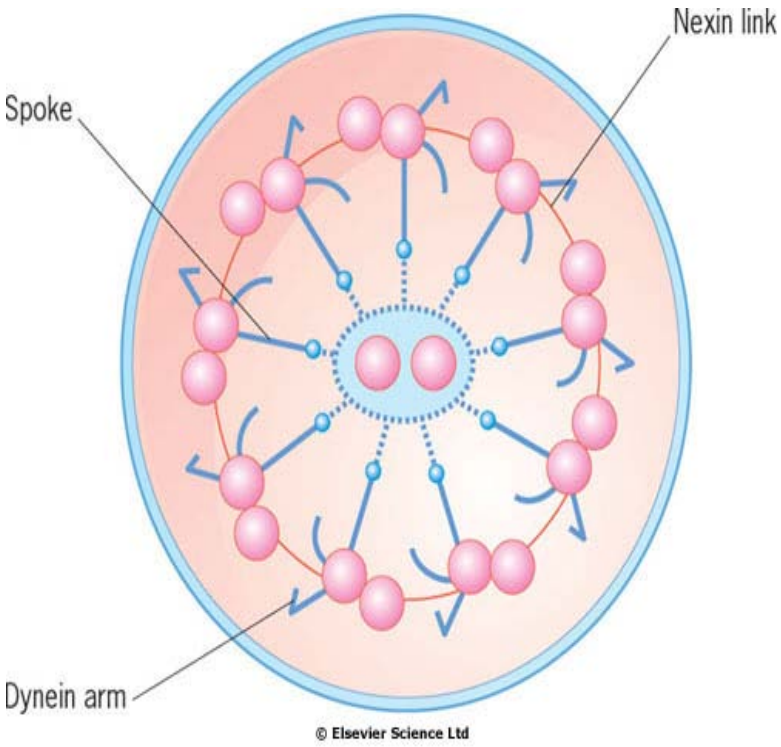
- is an important defence mechanism.

• Each cell contains approximately 200 *cilia* beating at 1000 beats per minute in organized waves of contraction.

• Each cilium consists of nine peripheral pairs and two inner longitudinal fibrils in a cytoplasmic matrix. *Nexin* links join the peripheral pairs. *Dynein arms* consisting of ATPase protein project towards the adjacent pairs.

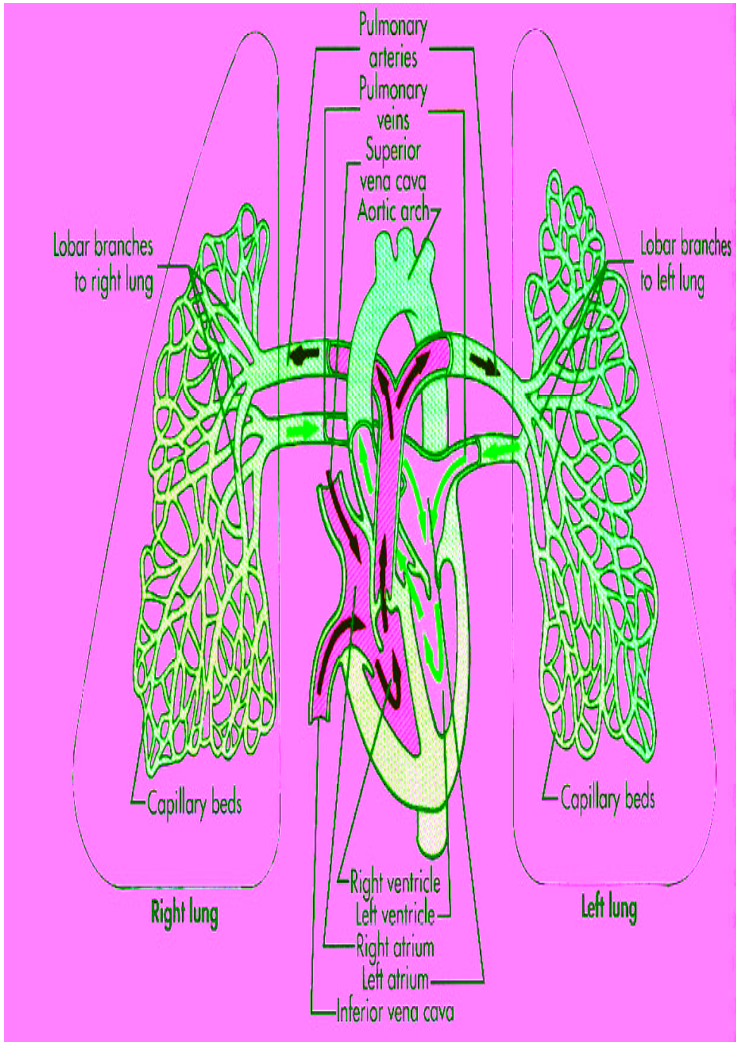
• Bending of the cilia results from a sliding movement between adjacent fibrils powered by an ATP-dependent shearing force developed by the dynein arms. Absence of dynein arms leads to immotile cilia.

• *Mucus*, which contains macrophages, cell debris, inhaled particles and bacteria, is moved by the cilia towards the larynx at about 1.5 cm/min (the 'mucociliary escalator,).



Pulmonary vasculature and lymphatics

- The lung has a dual blood supply.
- It receives deoxygenated blood from the right ventricle via the pulmonary artery and also has a systemic supply throughout the bronchial circulation.
- The pulmonary artery divides to accompany the bronchi. The arterioles accompanying the respiratory bronchioles are thin-walled and contain little smooth muscle. The pulmonary venules drain laterally to the periphery of the lobules, pass centrally in the interlobular and intersegmental septa, and eventually join to form the four main pulmonary veins.
- The bronchial circulation arises from the descending aorta. These bronchial arteries supply tissues down to the level of the respiratory bronchiole.
- The bronchial veins drain into the pulmonary vein, forming part of the physiological shunt observed in normal individuals.
- Lymphatic channels lie in the potential interstitial space between the alveolar cells and the capillary endothelium of the pulmonary arterioles. The tracheobronchial lymph nodes are arranged in five main groups: paratracheal, superior tracheobronchial, subcarinal, bronchopulmonary and pulmonary. In practical terms these form a continuous network of nodes from the lung substance up to the trachea.



Breathing

Lung ventilation can be considered in two main tasks:

- the mechanical process of inspiration and expiration
- the control of respiration to a level appropriate for the metabolic needs.

Breathing as mechanical process

- *Inspiration* is an active process and results from the descent of the diaphragm and movement of the ribs upwards and outwards under the influence of the intercostal muscles. In resting healthy individuals, *contraction of the diaphragm* is responsible for most inspiration.

- *Respiratory muscles* are similar to other skeletal muscles but are less prone to fatigue. However, weakness may play a part in respiratory failure resulting from neurological and muscle disorders and possibly with severe chronic airflow limitation.

- *Expiration* follows passively as a result of gradual lessening of contraction of the intercostal muscles, allowing the lungs to collapse under the influence of their own elastic forces.

- ***Inspiration against increased resistance*** may require the use of the *accessory muscles* of ventilation, such as the sternomastoid and scalene muscles.
- ***Forced expiration*** is also accomplished with the aid of accessory muscles, chiefly those of the abdominal wall, which help to push up the diaphragm.

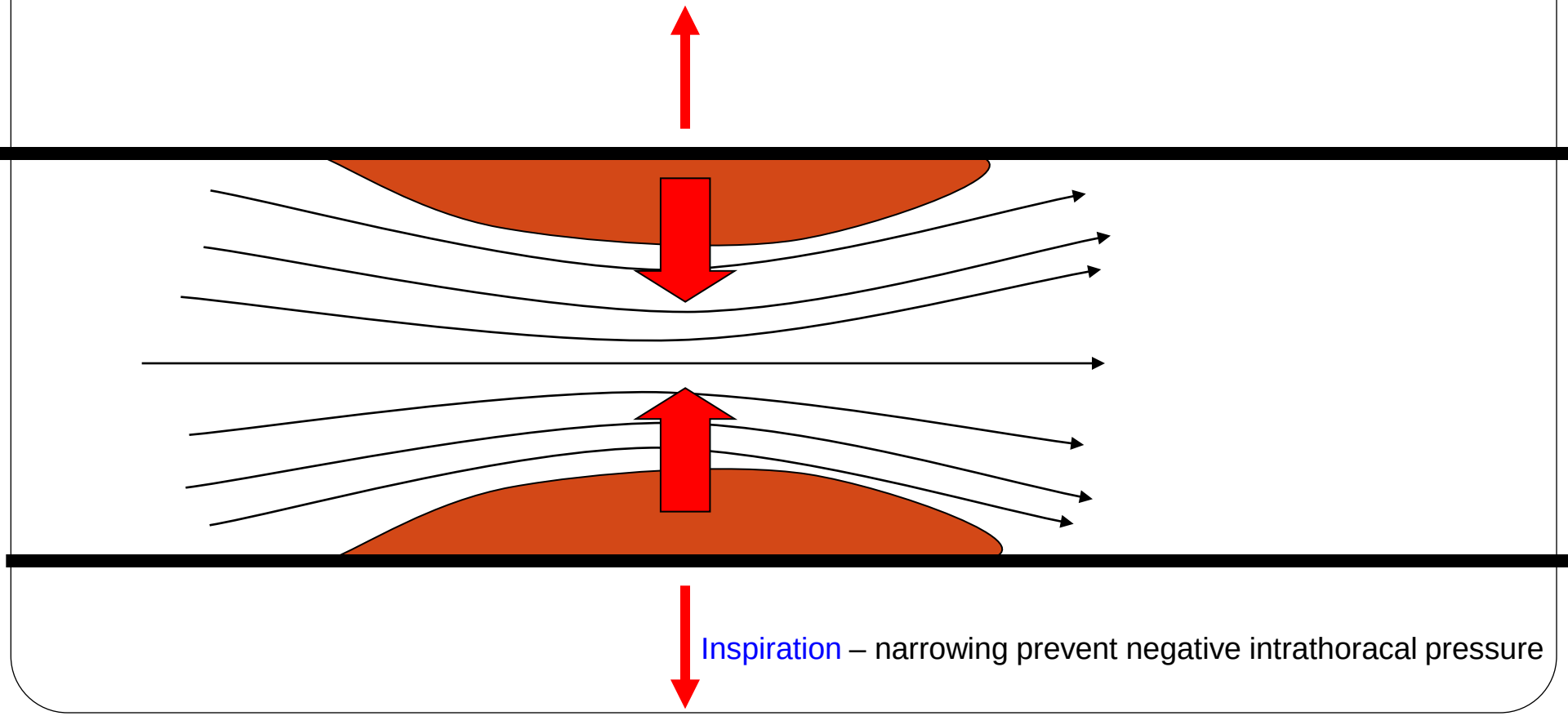
Breathing as mechanical process

- The lungs have an inherent *elastic* property that causes them to tend to collapse away from the thoracic wall, generating a *negative pressure within the pleural space*. The strength of this retractive force relates to the volume of the lung; for example, at higher lung volumes the lung is stretched more, and a greater negative intrapleural pressure is generated.

- ***Lung compliance*** is a measure of the relationship between this retractive force and lung volume. It is defined as **the *change in lung volume brought about by unit change in transpulmonary (intrapleural) pressure*** and is measured in litres per kilopascal (L/kPa). At the end of a quiet expiration, the retractive force exerted by the lungs is balanced by the tendency of the thoracic wall to spring outwards. At this point, respiratory muscles are resting and the volume of the lung is known as the ***functional residual capacity*** (FRC).

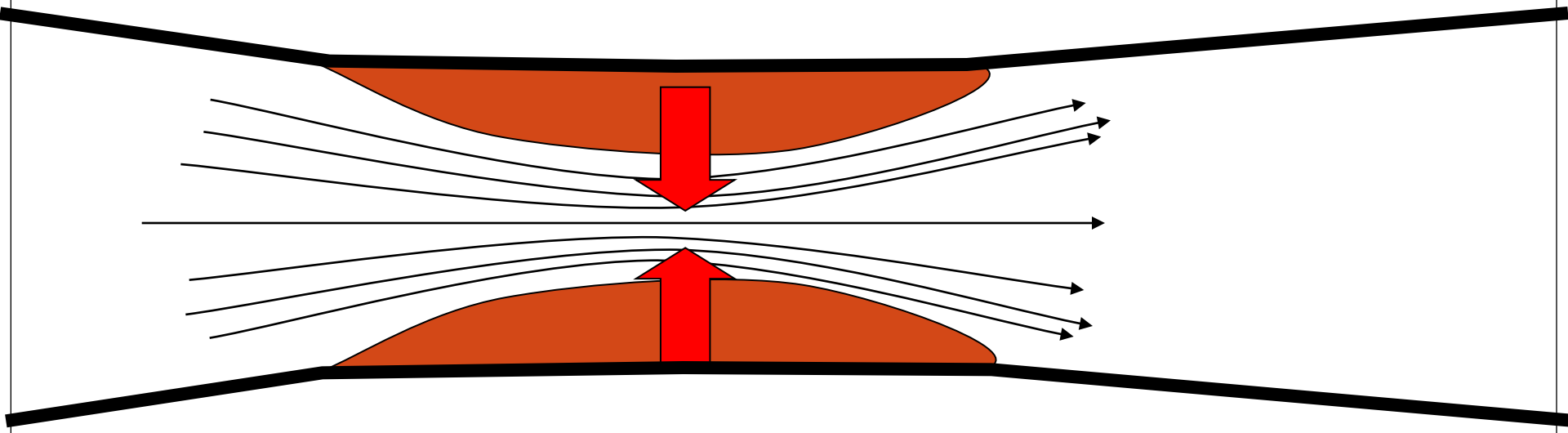
- Diseases that affect the movement of the thoracic cage and diaphragm can have a profound effect on ventilation. These include diseases of the thoracic spine such as ***ankylosing spondylitis*** *and* ***kyphoscoliosis***, ***neuropathies*** *(e.g. the Guillain-Barré syndrome),* ***injury to the phrenic nerves***, *and* ***myasthenia gravis***.

Constricted bronchiolus (bronchoconstriction, mucus…)



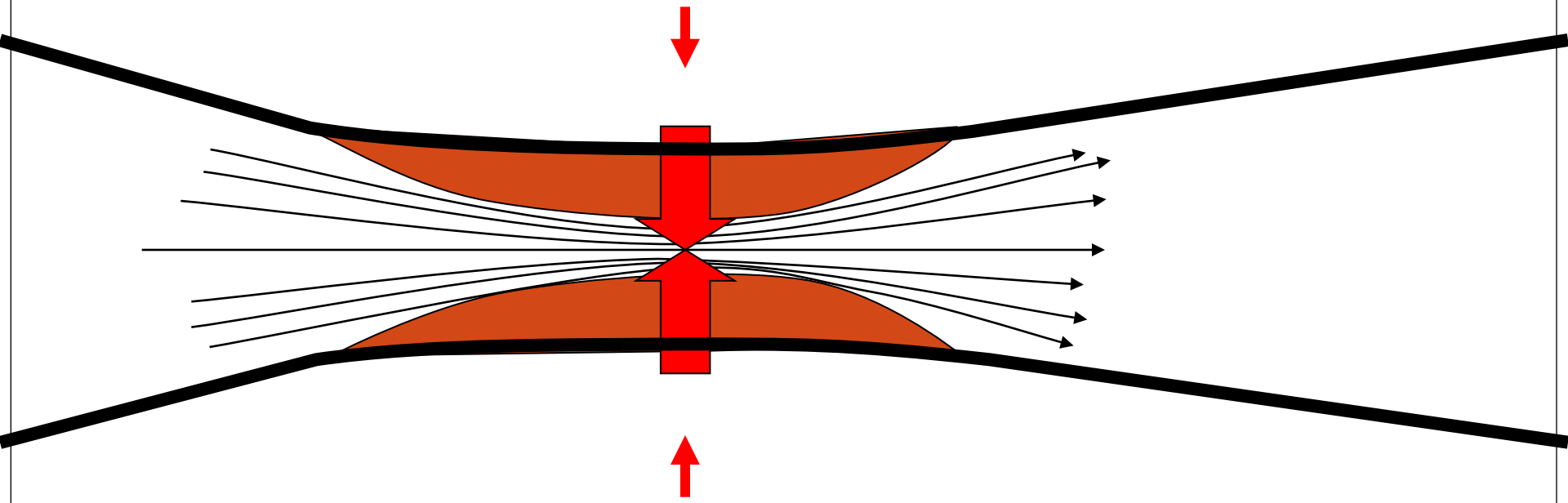
Inspiration – narrowing prevent negative intrathoracal pressure

Constricted bronchiolus (bronchoconstriction, mucus…)

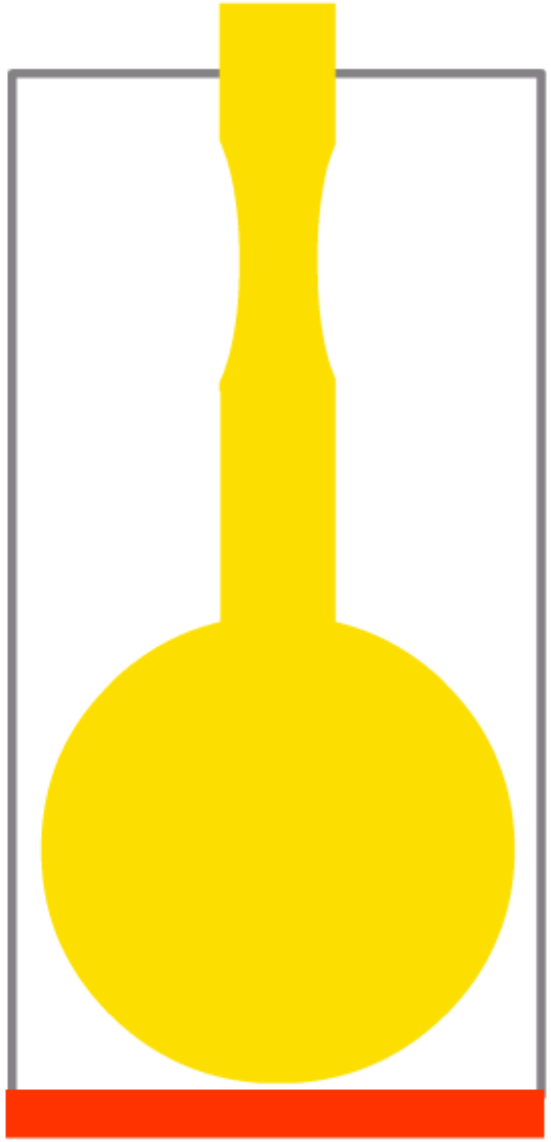


Expiration – constriction of bronchioles during expiration

Constricted bronchiolus (bronchoconstriction, mucus…)



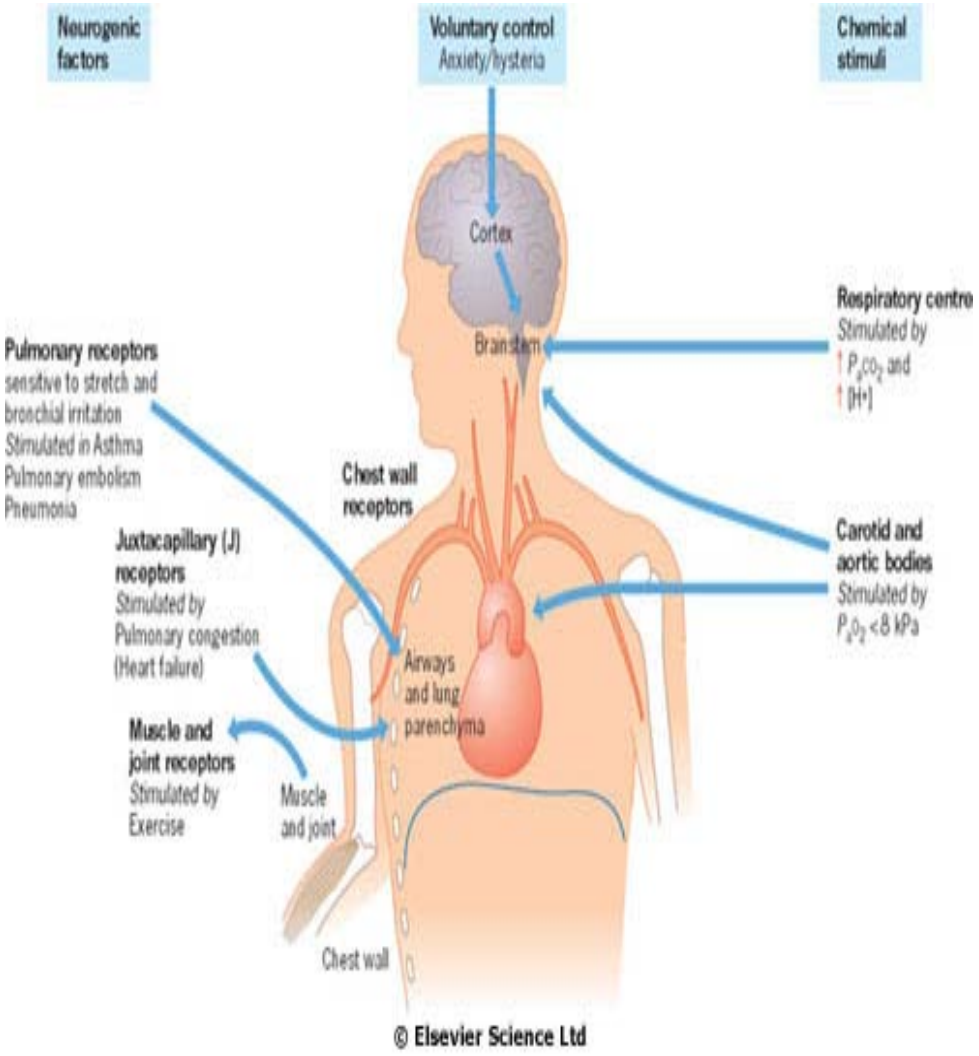
Forced expiration leads to worsening obstruction



Bronchial obstruction leads to worsening expiration

The control of respiration

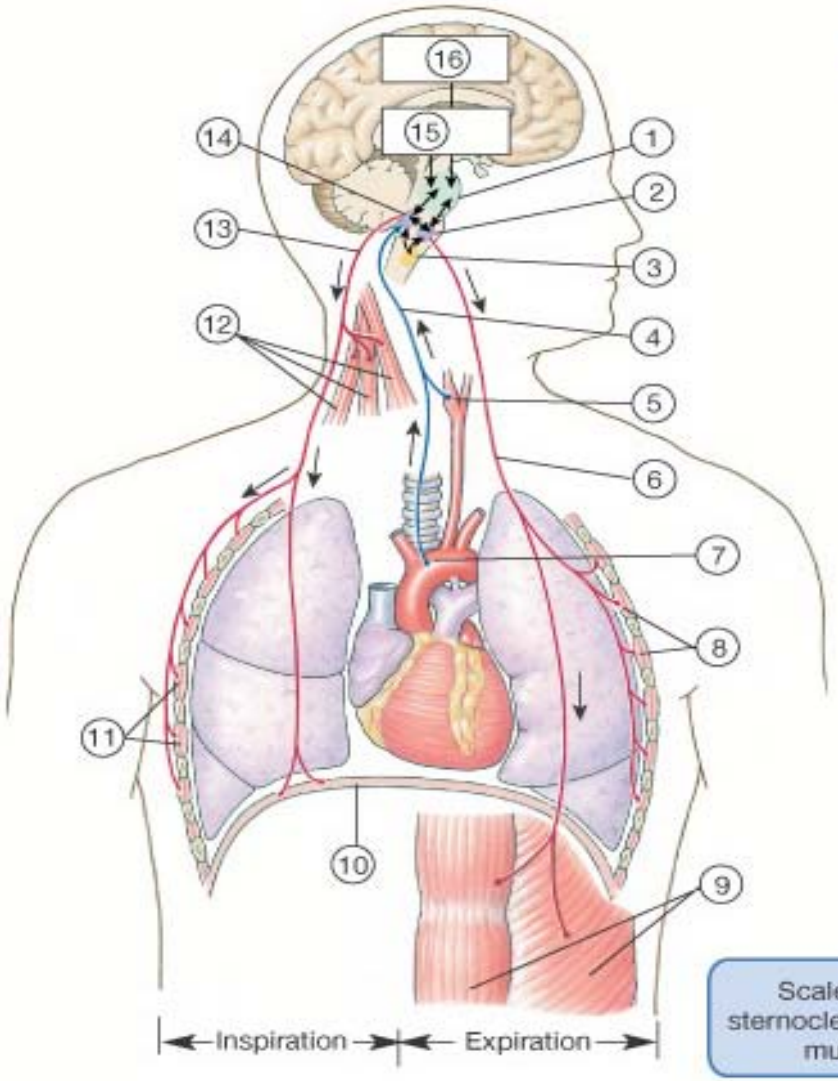
- Coordinated respiratory movements result from rhythmical discharges arising in interconnected neurones in the reticular substance of the brainstem, known as the *respiratory centre*. Motor discharges from the respiratory centre travel via the phrenic and intercostal nerves to the respiratory musculature. The pressures of oxygen and carbon dioxide in arterial blood are closely controlled. In a typical normal adult at rest:
- The pulmonary blood flow of 5 L/min carries 11 mmol/min (250 mL/min) of oxygen from the lungs to the tissues.
- Ventilation at about 6 L/min carries 9 mmol/min (200 mL/min) of carbon dioxide out of the body.
- **The normal pressure of oxygen in arterial blood (PaO_2) is between 11 and 13 kPa (83 - 98 mmHg).**
- **The normal pressure of carbon dioxide in arterial blood ($PaCO_2$) is 4.8-6.0 kPa (36-45 mmHg).**



The control of respiration

Ventilation is controlled by a combination of neurogenic and chemical factors.

- *Breathlessness* on physical exertion is normal and not considered a symptom unless the level of exertion is very light, such as when walking slowly. Although breathlessness is a very common symptom, the sensory and neural mechanisms underlying it remain obscure. The sensation of breathlessness is derived from at least three sources:
- *Changes in lung volume.* These are sensed by receptors in thoracic wall muscles signalling changes in their length.
- *The tension developed by contracting muscles.* This can be sensed by Golgi tendon organs. The tension developed in normal muscle can be differentiated from that developed in muscles weakened by fatigue or disease.
- *Central perception of the sense of effort.*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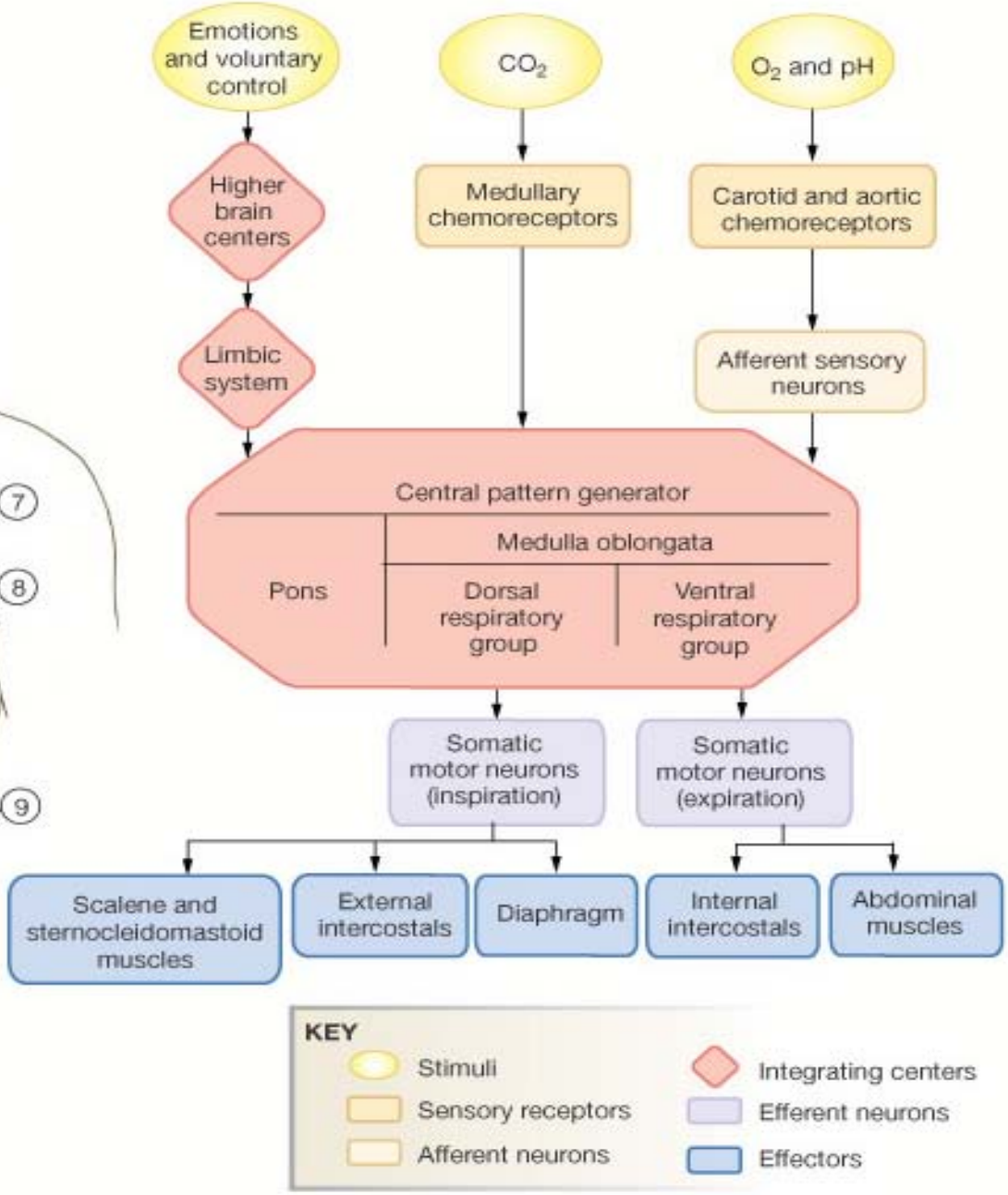
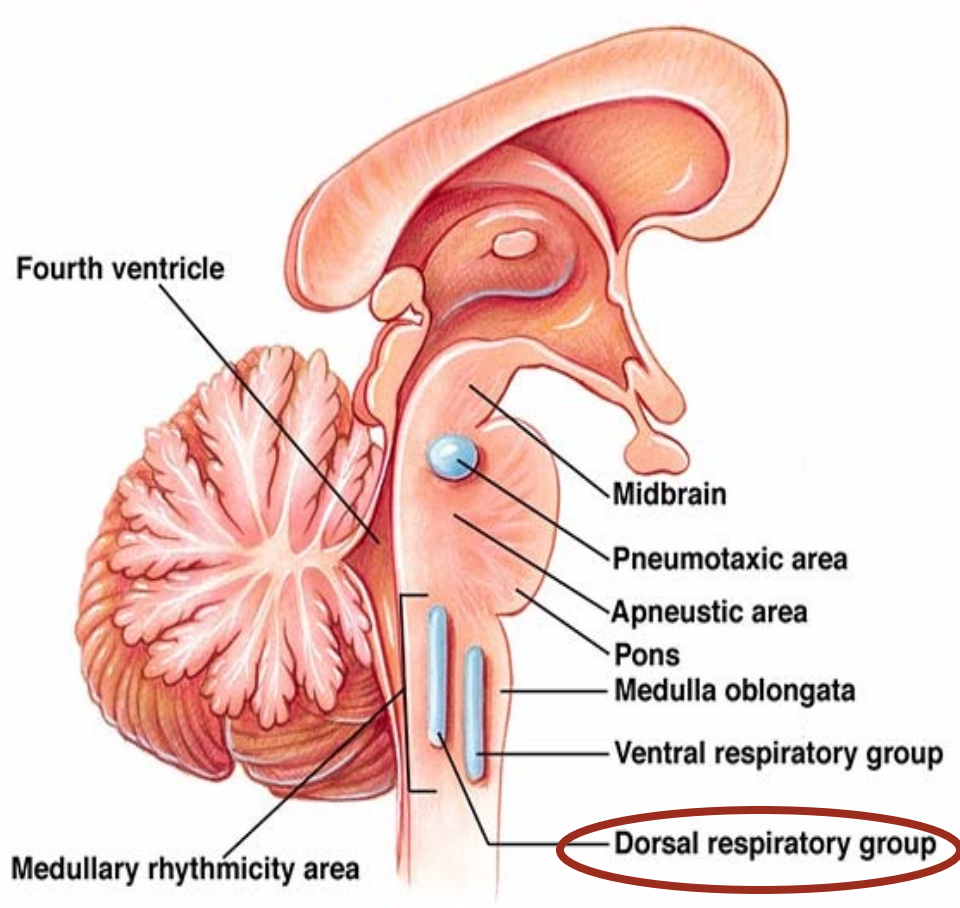
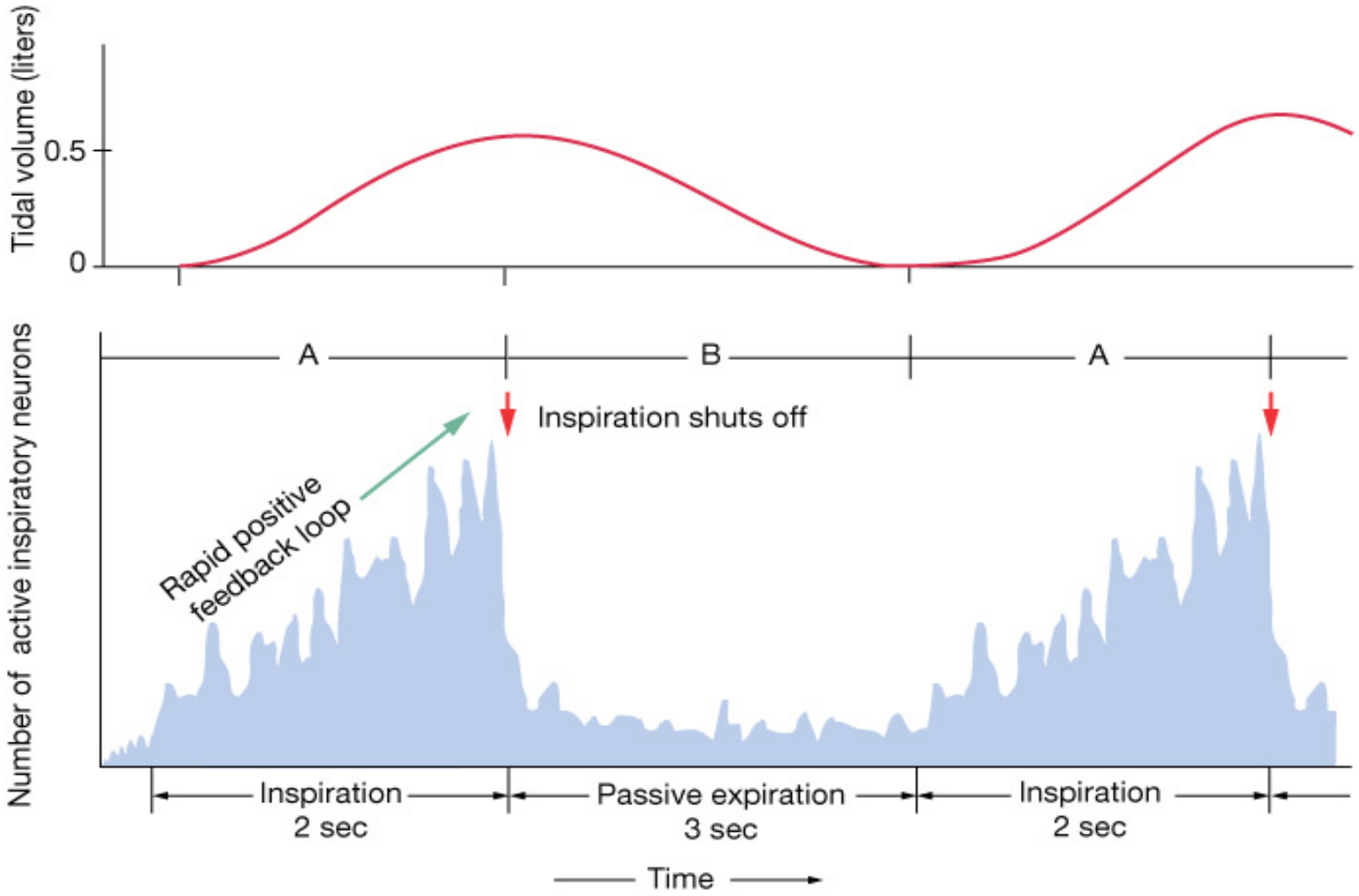
Inspiration
Expiration


Emotions and voluntary control
CO_2
O_2 and pH
Higher brain centers
Medullary chemoreceptors
Carotid and aortic chemoreceptors
Limbic system
Afferent sensory neurons
Central pattern generator
Medulla oblongata
Pons
Dorsal respiratory group
Ventral respiratory group
Somatic motor neurons (inspiration)
Somatic motor neurons (expiration)
Scalene and sternocleidomastoid muscles
External intercostals
Diaphragm
Internal intercostals
Abdominal muscles
KEY
Stimuli
Sensory receptors
Afferent neurons
Integrating centers
Efferent neurons
Effectors

Dorsal Respiratory Group (DRG) — quiet inspiration

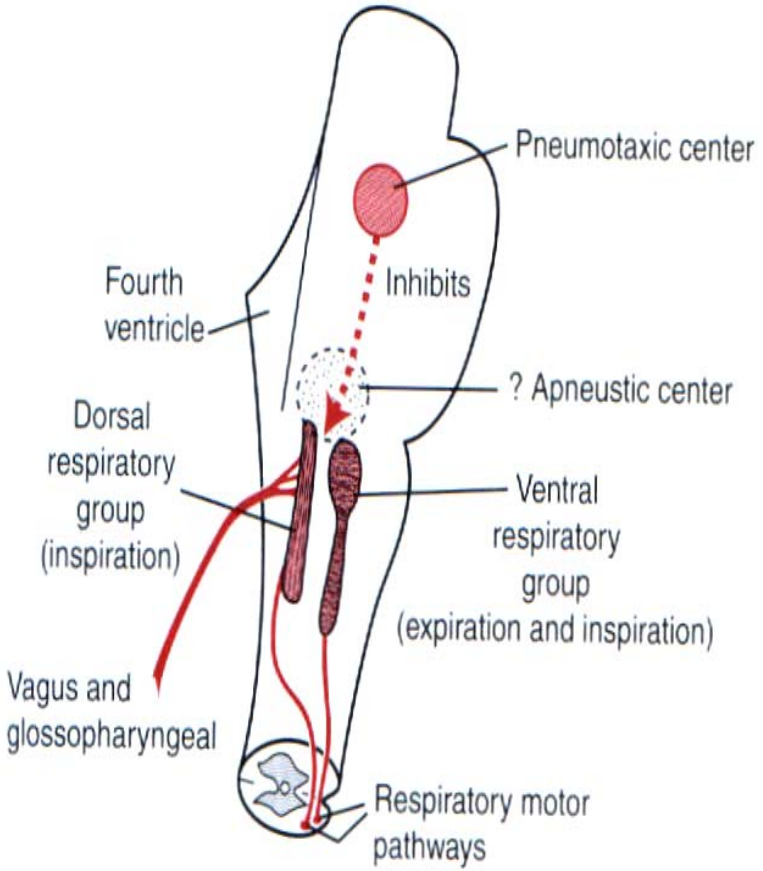
Ventral Respiratory Group (VRG) — effort inspiration and forced expiration

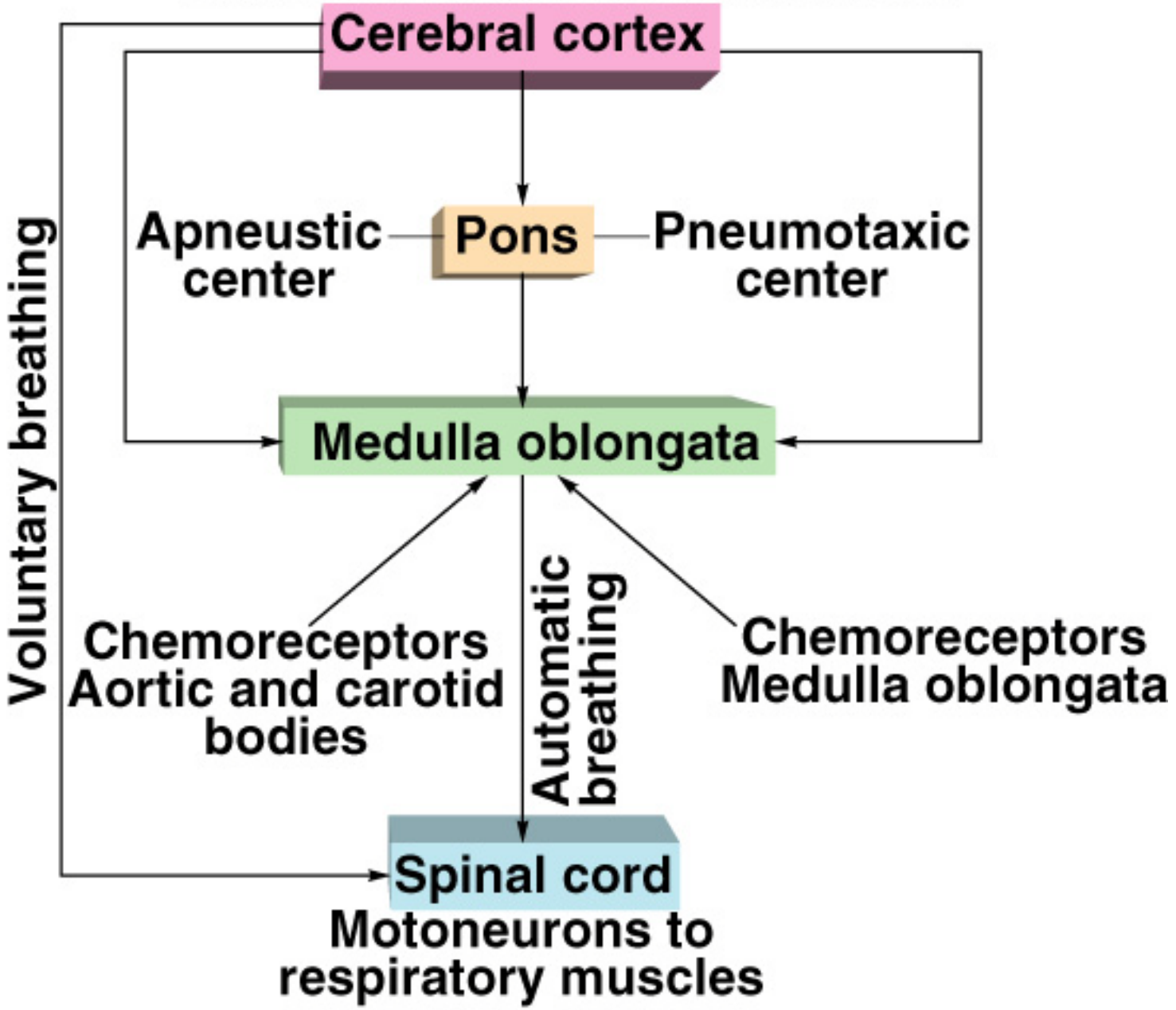




During inspiration, the acitvity of inspiratory neurons increases steadily, apparently through a positive feedback mechanism. At the end of inspiration, the activity shuts off abruptly and expiration takes place through recoil of elastic lung tissue.

- ***Apneustic centre***:
  - *Supported inspiration by the activity of inspiration neurons*
- ***Pneumotaxic centre***:
  - *Antagonise apneustic centre.*
  - *Inhibition of inspiration.*



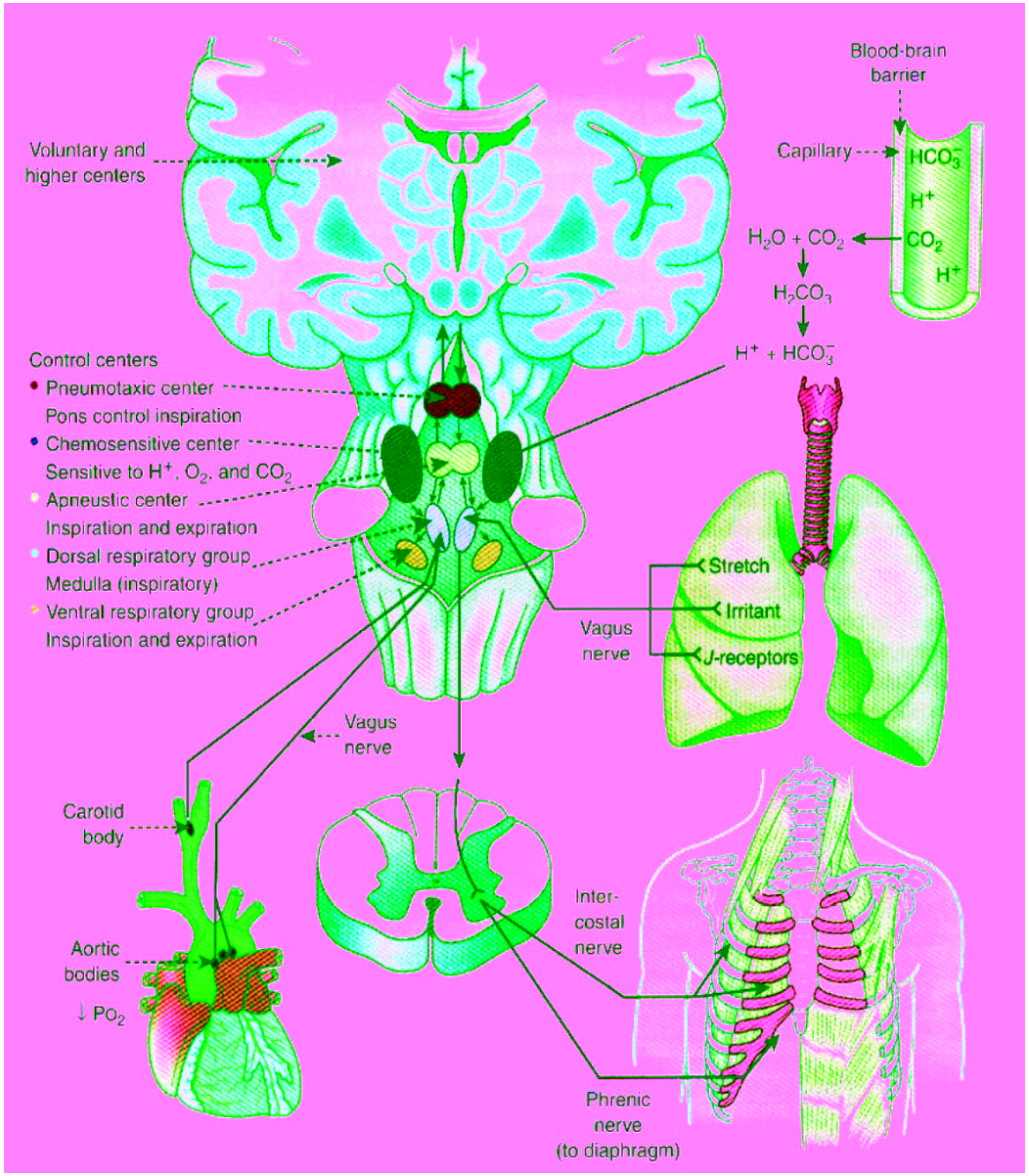


Respiratory control

Respiratory centre is formed by several groups of neurons:

- The basic automatic rhytm of respiration is due to **activity of DRG** (inspiration neurons) – efferent impulses go to diaphragma and inspiration intercostal muscles.
- DRG also obtain afferent stimuli from the peripheral chemoreceptors and several pulmonary receptors.
- **VRG** contains both inspiration and expiration neurons. They are inactive due to normal ventilation, increased ventilation leads to their activation.
- **Pneumotaxic** and **apneustic** centres can modulate depth of ventilation and its quickness

Ventilation can be modulate by cortex, limbic systém and hypothalamus (emotions and diseases).

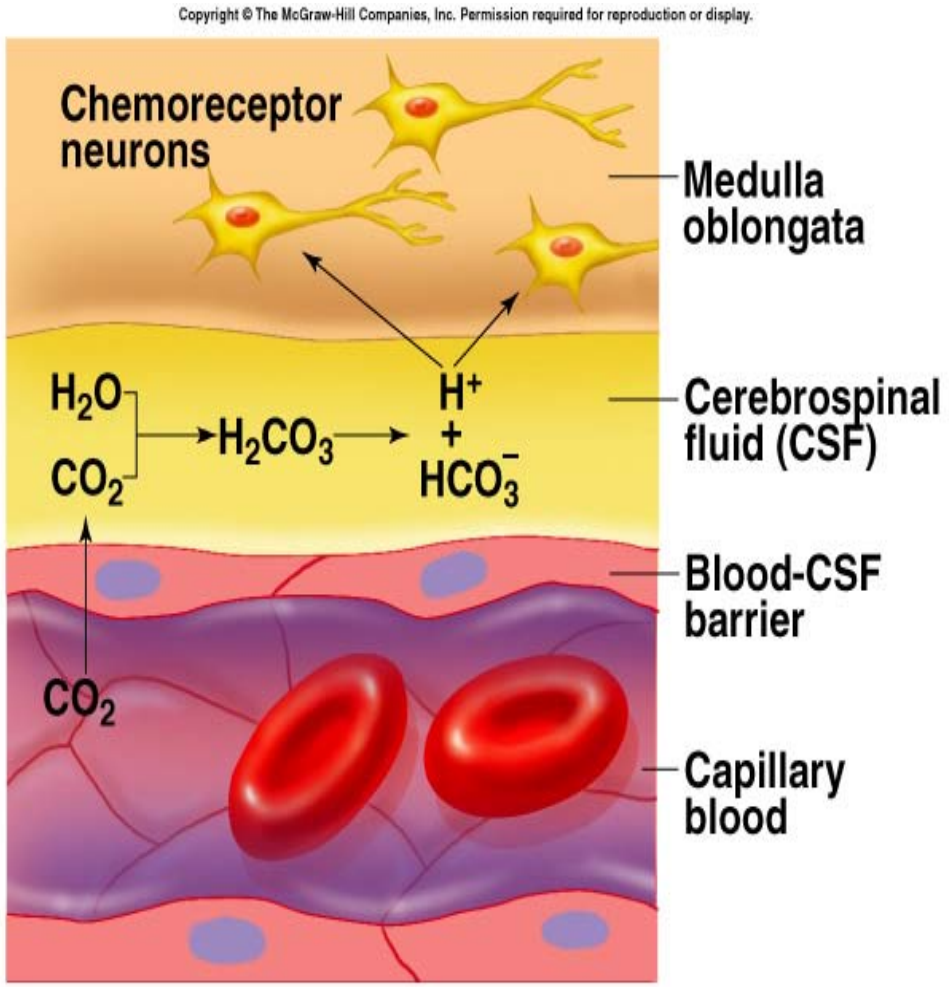


Chemoreceptors

- 2 groups of chemoreceptors (changes of blood P_{CO_2}, P_{O_2}, and pH).

- **Central:**
  - *Medulla oblongata*

- **Peripheral:**
  - *Glomus caroticum and aorta*.

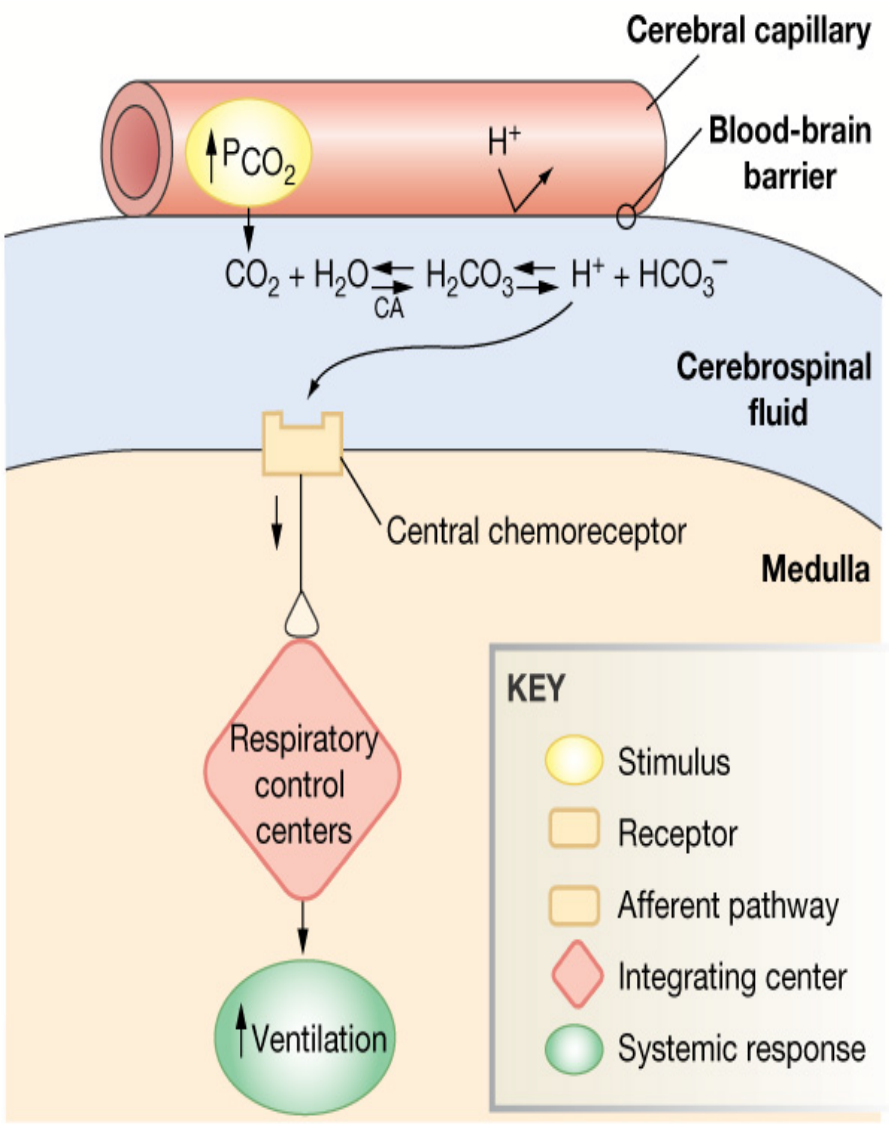


Central chemoreceptors

Sensitive to changes of arterial P_{CO_2}

- *H^+ cannot go through hematoencephalic barrier*
- *CO_2 can go through this barrier and form H_2CO_3.*
  - *Decrease pH of the CSF.*

Directly stimulate central chemoreceptors.



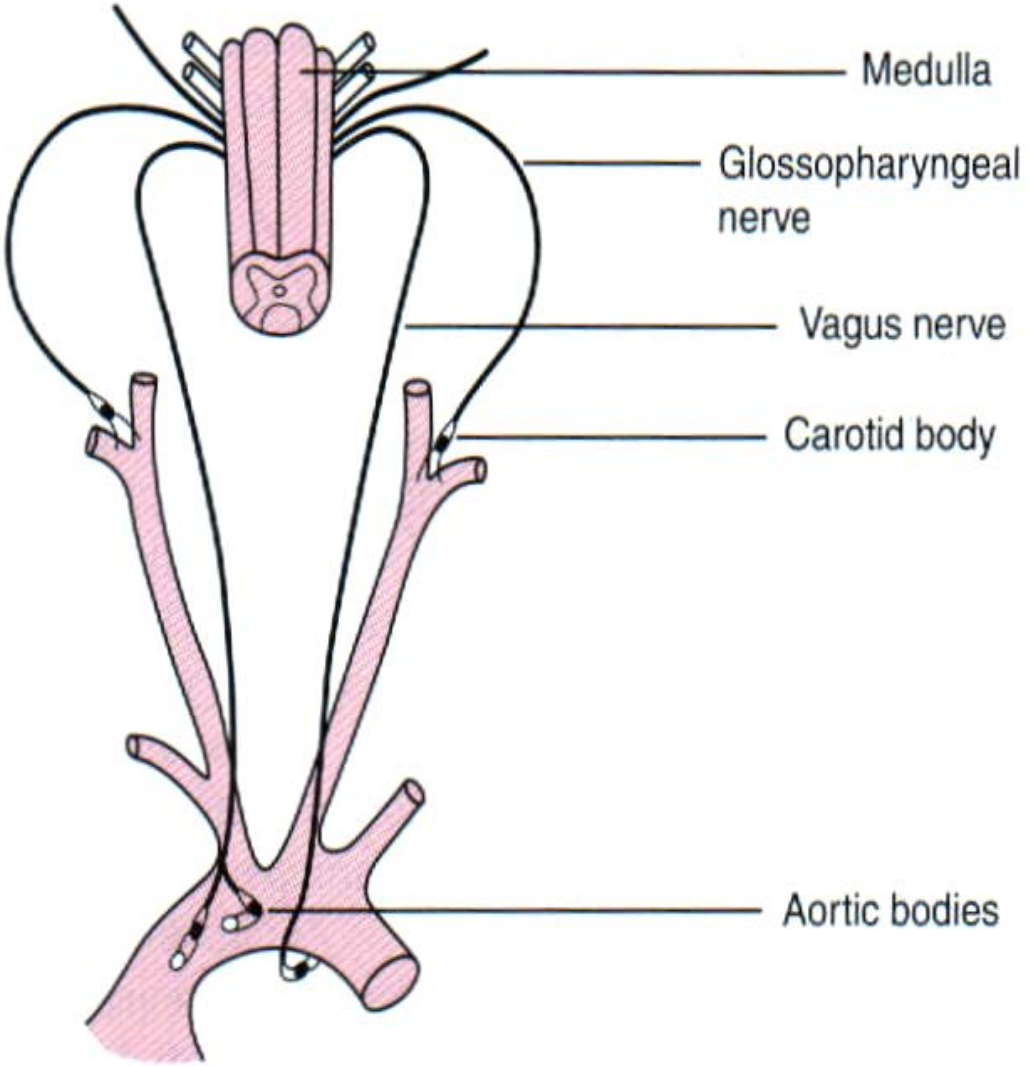
Chemical and neurogenic factors in the control of ventilation.

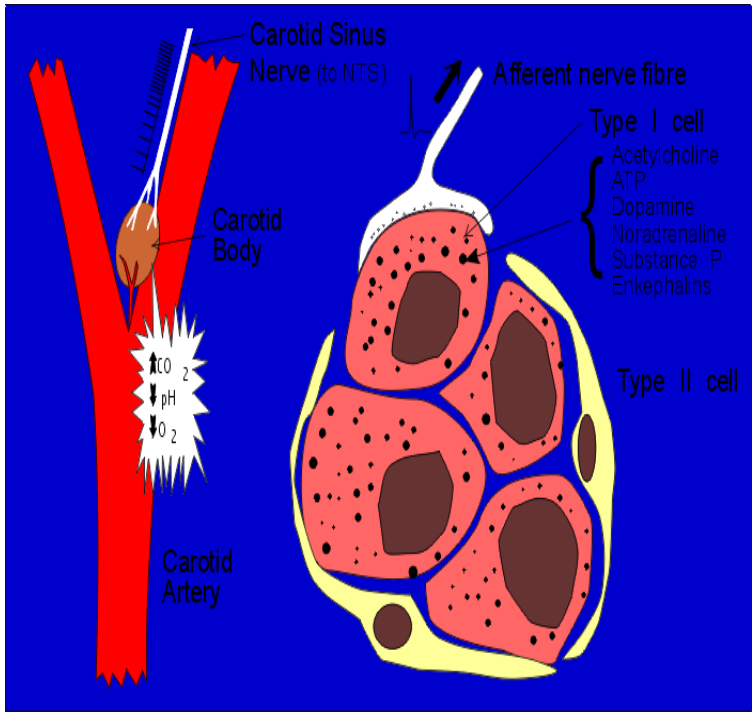
The strongest stimulant to ventilation is a rise in *P*aco2 which increases [H+] in CSF. Sensitivity to this may be lost in COPD. In these patients hypoxaemia is the chief stimulus to respiratory drive; oxygen treatment may therefore reduce respiratory drive and lead to a further rise in *P*aco2.

An increase in [H+] due to metabolic acidosis as in diabetic ketoacidosis will increase ventilation with a fall in *P*aco2 causing deep sighing (Kussmaul) respiration.

Oxygen senzors (where are?)

Glomus caroticus and aortic bodies





Oxygen senzors (how work?)

- Sensitive to change of arterial P_{0_2}

Decrease 0_2 close K+ channels

↓

depolarization

↓

↑intracellular concentration of Ca^{2+}

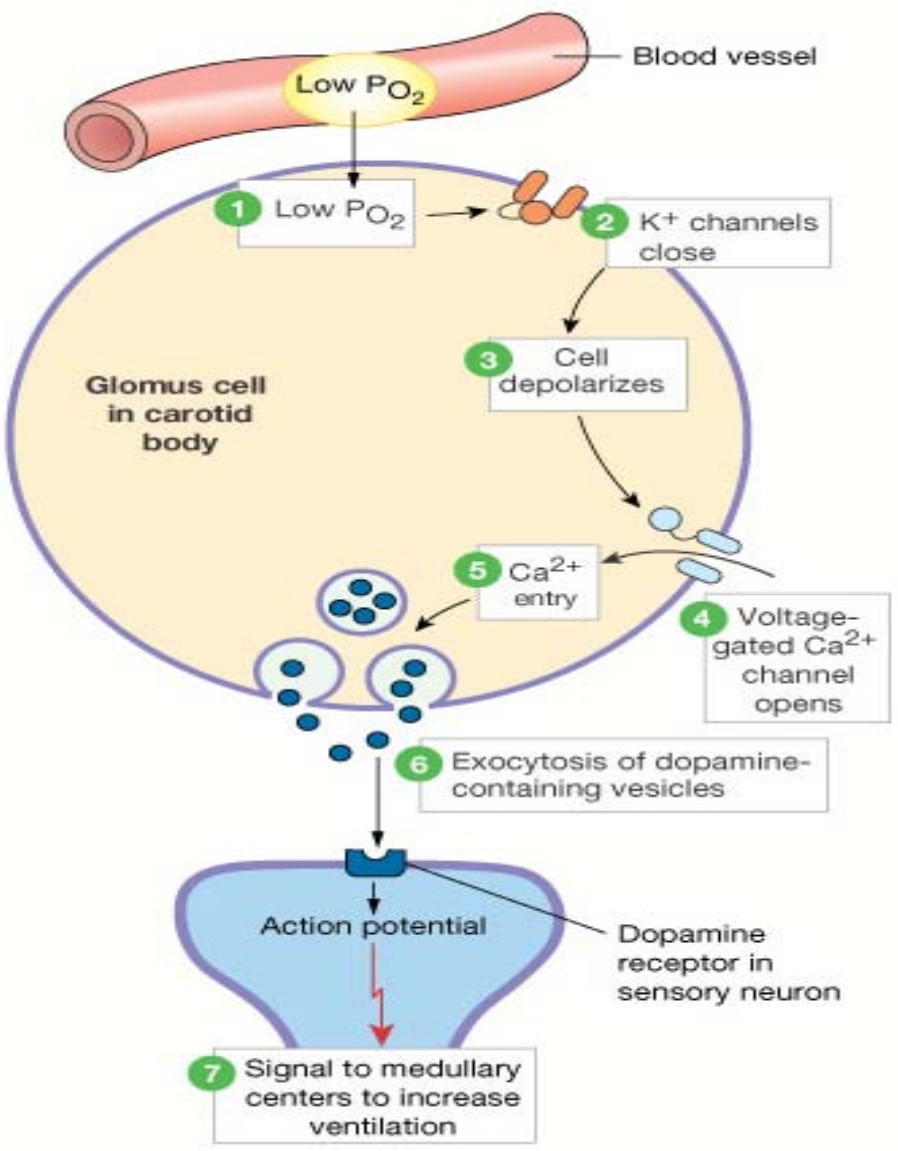
↓

excitation

↓

respiration centre

- When hypoxemia is not accompanied with hypercapnia, activation of this sensors is when PaO_2<7,3 kPa (55 mm Hg)



Control of ventilation

- From the trachea to the periphery, the airways become smaller in size (although greater in number). The cross-sectional area available for airflow increases as the total number of airways increases. The flow of air is greatest in the trachea and slows progressively towards the periphery (as the velocity of airflow depends on the ratio of flow to cross-sectional area). In the terminal airways, gas flow occurs solely by diffusion.

- The resistance to airflow is very low (0.1-0.2 kPa/L in a normal tracheobronchial tree), steadily increasing from the small to the large airways. Airways expand as lung volume is increased, and at full inspiration (total lung capacity, TLC) they are 30-40% larger in calibre than at full expiration (residual volume, RV).

- In chronic obstructive pulmonary disease (COPD) the small airways are narrowed and this can be partially compensated by breathing at a larger lung volume.

Control of airway tone

- This is under the control of the ***autonomic nervous system***. Bronchomotor tone is maintained by vagal efferent nerves. Many adrenoceptors on the surface of bronchial muscles respond to circulating catecholamines; sympathetic nerves do not directly innervate them.

- Airway tone shows a ***circadian rhythm***, which is greatest at 04.00 and lowest in the mid-afternoon. Tone can be increased briefly by inhaled stimuli acting on epithelial nerve endings, which trigger reflex bronchoconstriction via the vagus. These stimuli include cigarette smoke, inert dust and cold air; airway responsiveness to these increases following respiratory tract infections even in healthy subjects.

  In **asthma**, the airways are very irritable and as the circadian rhythm remains the same, asthmatic symptoms are usually worst in the early morning.

Airflow

- Movement of air through the airways results from a *difference between the pressure in the alveoli and the atmospheric pressure*; a positive alveolar pressure occurs in expiration and a negative pressure occurs in inspiration.

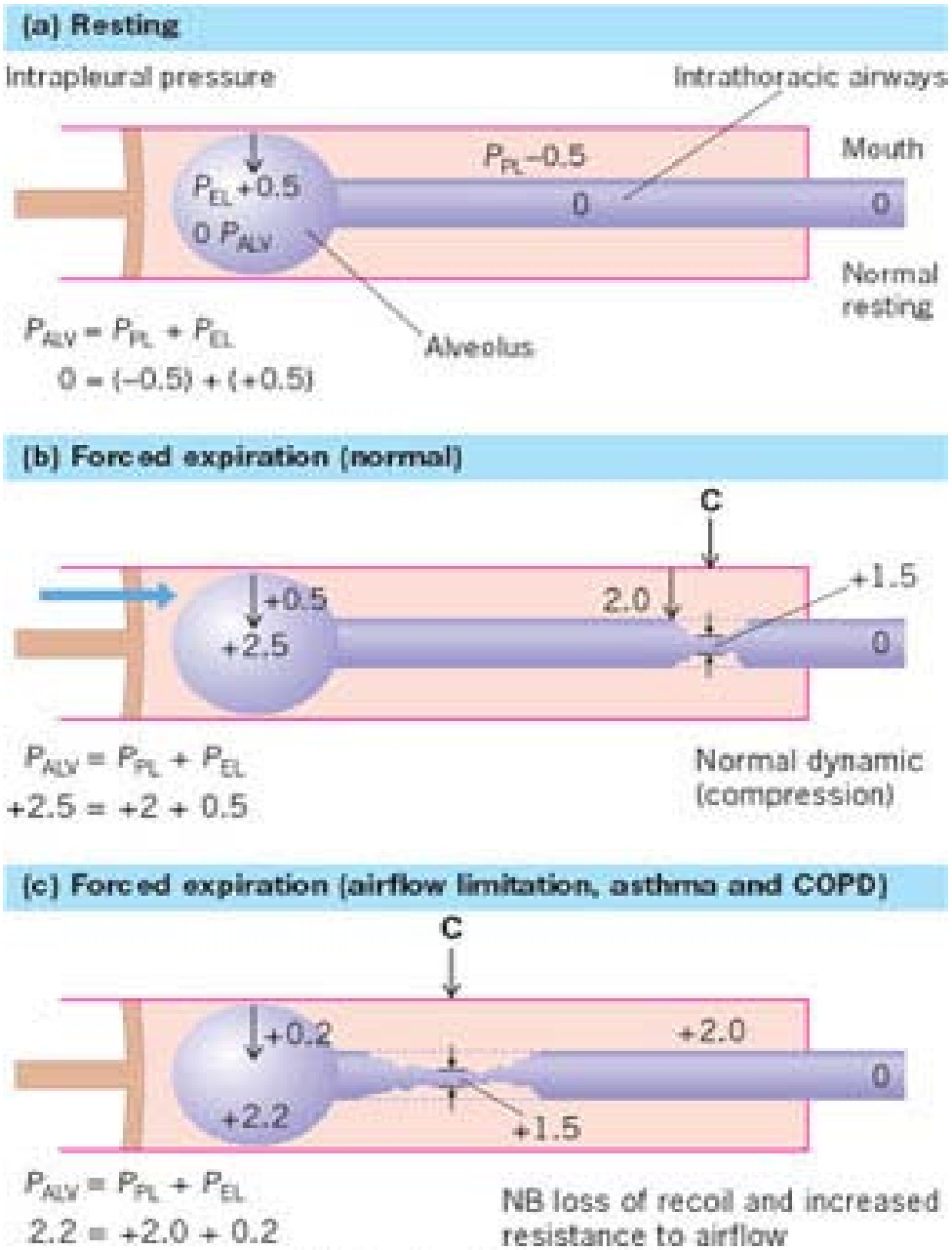
- During quiet breathing the sub-atmospheric pleural pressure throughout the breathing cycle slightly distends the airways. With vigorous expiratory efforts (e.g. cough), although the central airways are compressed by positive pleural pressures exceeding 10 kPa, the airways do not close completely because the driving pressure for expiratory flow (alveolar pressure) is also increased.

- ***Alveolar pressure PALV is equal to the elastic recoil pressure (PEL) of the lung plus the pleural pressure (PPL).***

Airflow

- When there is no airflow (i.e. during a pause in breathing) the tendency of the lungs to collapse (the positive recoil pressure) is exactly balanced by an equivalent negative pleural pressure. As air flows from the alveoli towards the mouth there is a gradual loss of pressure owing to flow resistance.

- In forced expiration, the driving pressure raises both the alveolar pressure and the intrapleural pressure. Between the alveolus and the mouth, a point will occur (C) where the airway pressure will equal the intrapleural pressure, and airway compression will occur. However, this compression of the airway is temporary, as the transient occlusion of the airway results in an increase in pressure behind it (i.e. upstream) and this raises the intra-airway pressure so that the airways open and flow is restored. The airways thus tend to vibrate at this point of *'dynamic compression*'.



Diagrams showing ventilatory forces

- **(a)** During resting at functional residual capacity.
- **(b)** During forced expiration in normal subjects.
- **(c)** During forced expiration in a patient with COPD.
- The respiratory system is represented as a piston with a single alveolus and the collapsible part of the airways within the piston. C, compression point; *P*ALV, alveolar pressure; *P*EL, elastic recoil pressure; *P*PL, pleural pressure.

Airflow

- The elastic recoil pressure of the lungs decreases with decreasing lung volume and the 'collapse point' moves upstream (i.e. towards the smaller airways).

- Where there is **pathological loss of recoil pressure** (as in chronic obstructive pulmonary disease, COPD), the 'collapse point' starts even further upstream and these patients are often seen to 'purse their lips' in order to increase airway pressure so that their peripheral airways do not collapse. The expiratory airflow limitation is the pathophysiology that underlies chronic airflow limitation. The measurement of the forced expiratory volume in 1 second (FEV1) is a useful clinical index of this phenomenon. On inspiration, the intrapleural pressure is always less than the intraluminal pressure within the intrathoracic airways, so there is no limitation to airflow with increasing effort. Inspiratory flow is limited only by the power of the inspiratory muscles.

Flow-volume loops

- The relationship between maximal flow rates on expiration and inspiration is demonstrated by the maximal flow-volume (MFV) loops.

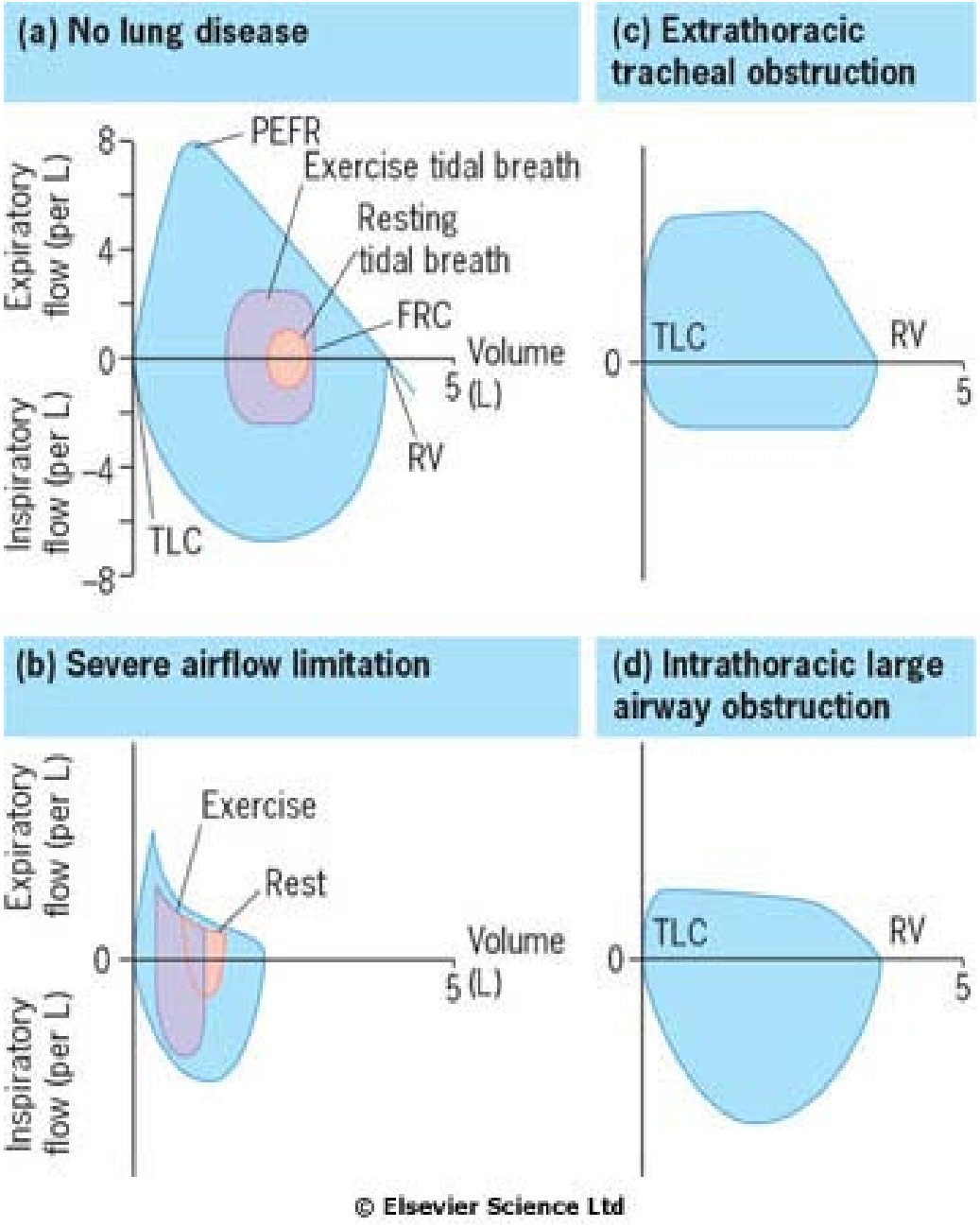
- In subjects with healthy lungs the clinical importance of flow limitation will not be apparent, since maximal flow rates are rarely achieved even during vigorous exercise.

- In patients with severe COPD, limitation of expiratory flow occurs even during tidal breathing at rest.To increase ventilation these patients have to breathe at higher lung volumes and also allow more time for expiration by increasing flow rates during inspiration, where there is relatively less flow limitation. Thus patients with severe airflow limitation have a prolonged expiratory phase to their respiration.

Flow-volume loops

- The measure of the volume that can be forced in from RV in 1 second (FIV1) will always be greater than that which can be forced out from TLC in 1 second (FEV1). Thus, the ratio of FEV1 to FIV1 is below 1.

- The only exception to this occurs when there is significant obstruction to the airways outside the thorax, such as with a tumour mass in the upper part of the trachea. Under these circumstances expiratory airway narrowing is prevented by the tracheal resistance (a situation similar to pursing the lips) and expiratory airflow becomes more effort-dependent. During forced inspiration this same resistance causes such negative intraluminal pressure that the trachea is compressed by the surrounding atmospheric pressure. Inspiratory flow thus becomes less effort-dependent, and the ratio of FEV1 to FIV1 becomes greater than 1. This phenomenon, and the characteristic flow-volume loop, is used to diagnose extrathoracic airways obstruction. When obstruction occurs in large airways within the thorax (lower end of trachea and main bronchi), expiratory flow is impaired more than inspiratory flow but a characteristic plateau to expiratory flow is seen.



Maximal flow-volume loops, showing the relationship between maximal flow rates on expiration and inspiration (to the previous picture)

- **(a)** In a normal subject.

- **(b)** In a patient with severe airflow limitation. Flow-volume loops during tidal breathing at rest (starting from the functional residual capacity (FRC)) and during exercise are also shown. The highest flow rates are achieved when forced expiration begins at total lung capacity (TLC) and represent the peak expiratory flow rate (PEFR). As air is blown out of the lung, so the flow rate decreases until no more air can be forced out, a point known as the residual volume (RV). Because inspiratory airflow is only dependent on effort, the shape of the maximal inspiratory flow-volume loop is quite different, and inspiratory flow remains at a high rate throughout the manoeuvre.

- **(c)** Extrathoracic tracheal obstruction with a proportionally greater reduction of maximal inspiratory (as opposed to expiratory) flow rate.

- **(d)** Intrathoracic large airway obstruction; the expiratory plateau is more pronounced and inspiratory flow rate is less reduced than in (c). In severe airflow limitation the ventilatory demands of exercise cannot be met, greatly reducing effort tolerance.

Ventilation-perfusion

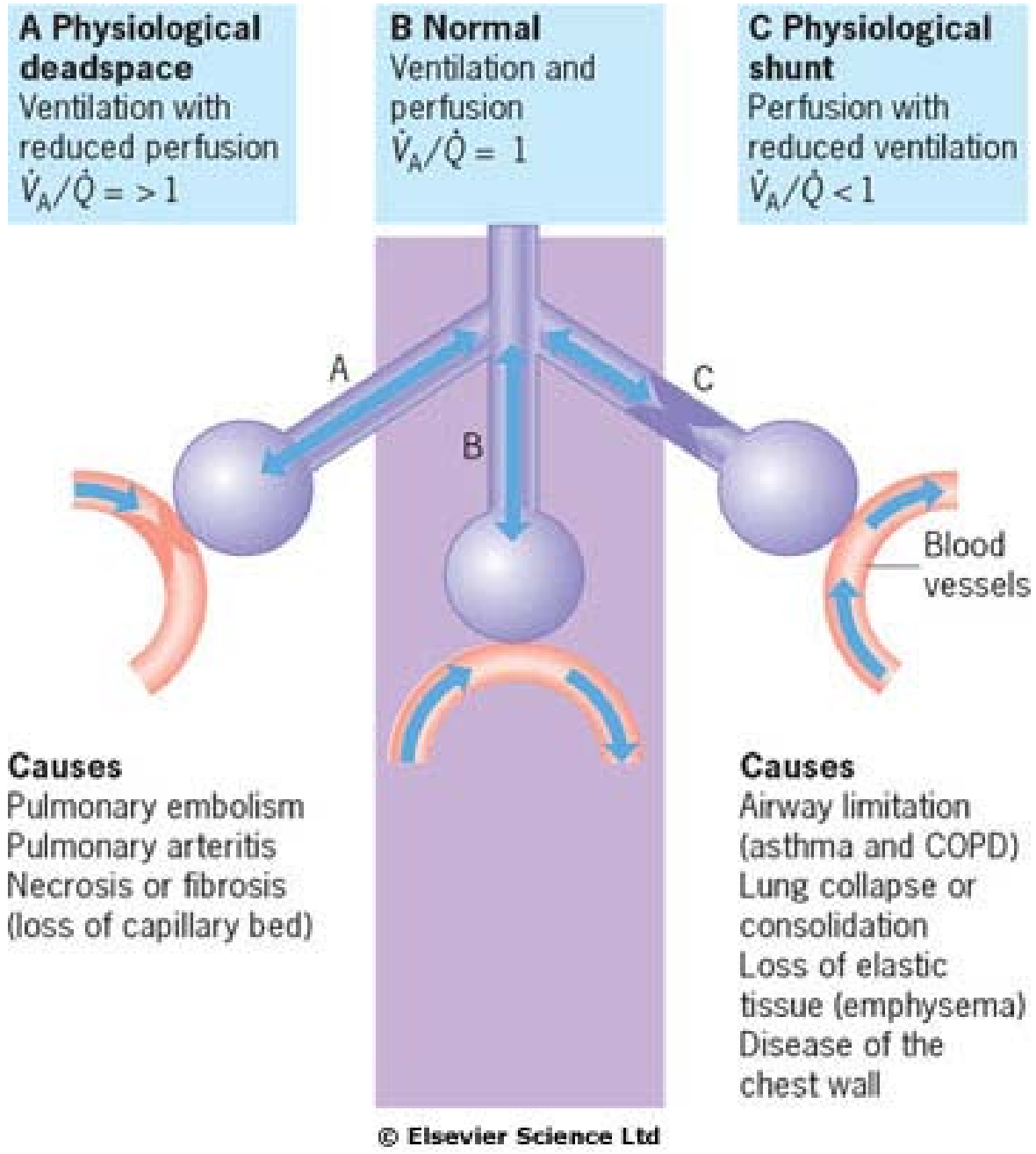
- For efficient gas exchange it is important that there is a match between ventilation of the alveoli ([Vdot]A) and their perfusion ([Qdot]).

- There is a wide variation in the [Vdot]A/[Qdot] ratio throughout both normal and diseased lung. In the normal lung the extreme relationships between alveolar ventilation and perfusion are:

  - ventilation with reduced perfusion (physiological deadspace)

  - perfusion with reduced ventilation (physiological shunting)

  - In normal lungs there is a tendency for ventilation not to be matched by perfusion towards the apices, with the reverse occurring at the bases.



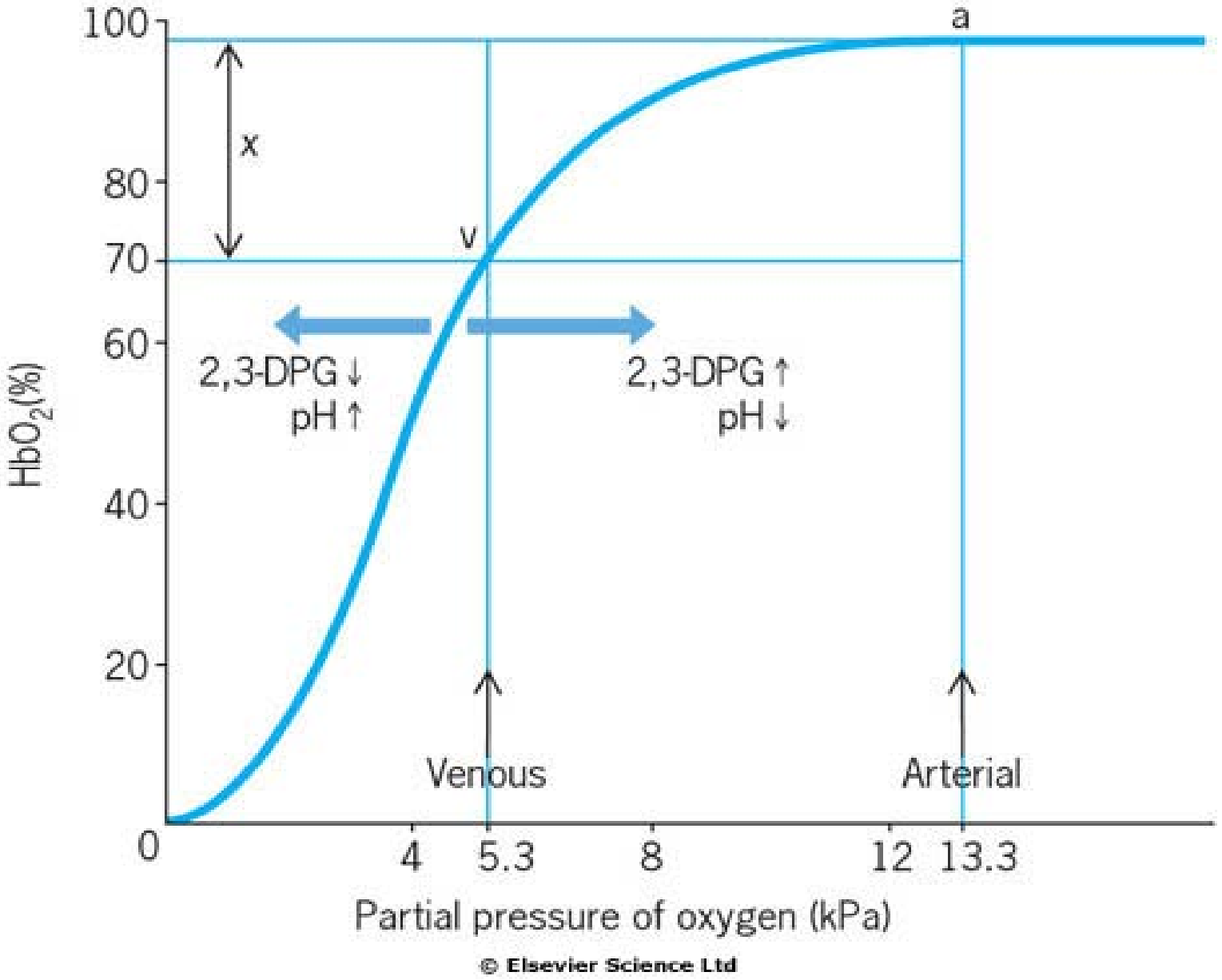
Ventilation- perfusion

- An increased physiological shunt results in *arterial hypoxaemia*. The effects of an increased physiological deadspace can usually be overcome by a compensatory increase in the ventilation of normally perfused alveoli. In advanced disease this compensation cannot occur, leading to increased alveolar and arterial *P*co2, together with hypoxaemia which cannot be compensated by increasing ventilation.

- Hypoxaemia occurs more readily than hypercapnia because of the different ways in which oxygen and carbon dioxide are carried in the blood.

- Carbon dioxide can be considered to be in simple solution in the plasma, the volume carried being proportional to the partial pressure.

- Oxygen is carried in chemical combination with haemoglobin in the red blood cells, and the relationship between the volume carried and the partial pressure is not linear.



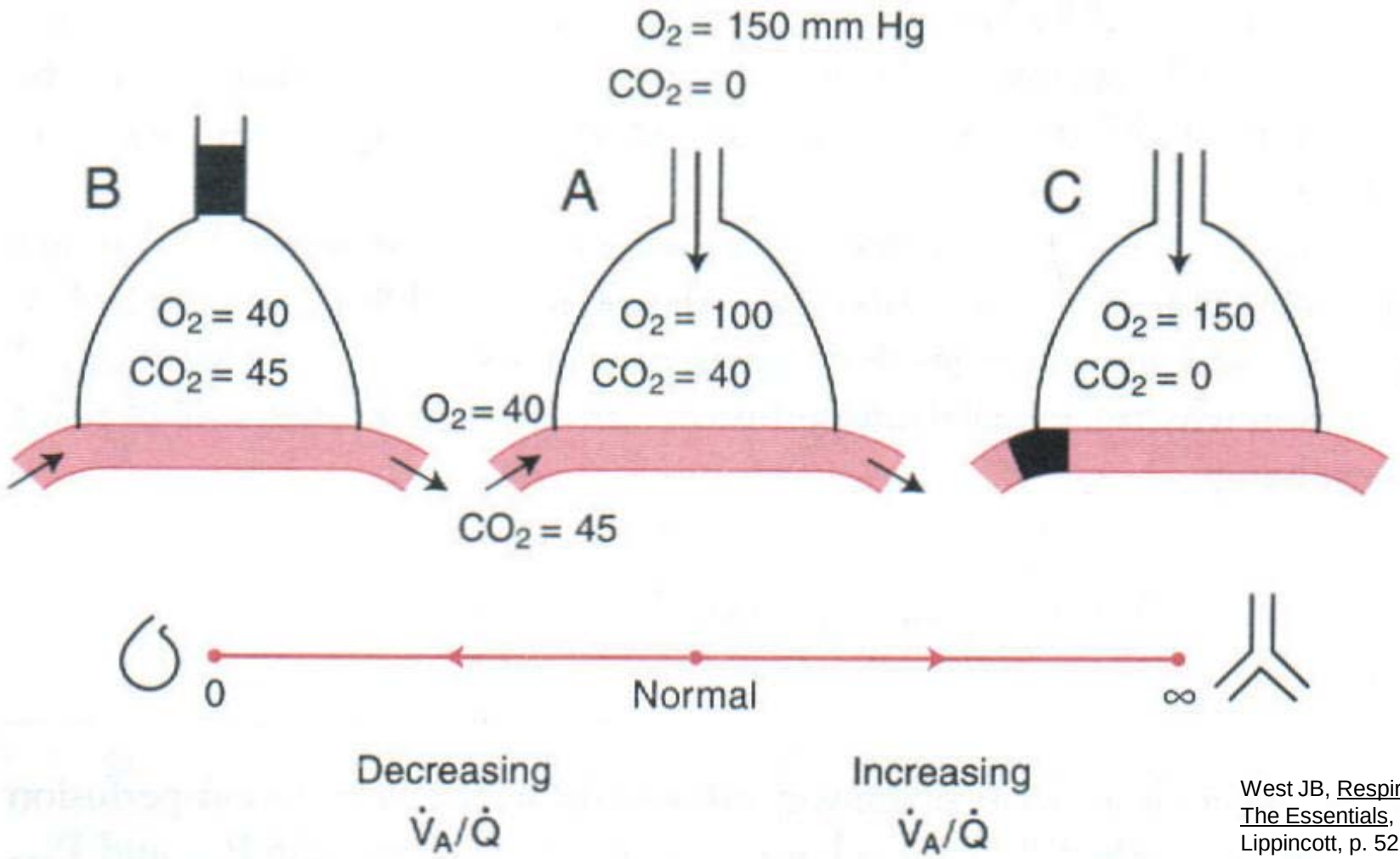
Ventilation-perfusion

- Alveolar hyperventilation reduces the alveolar *P*co2 and diffusion leads to a proportional fall in the carbon dioxide content of the blood.

- However, as the haemoglobin is already saturated with oxygen, there is no significant increase in the blood oxygen content as a result of increasing the alveolar *P*o2 through hyperventilation. The hypoxaemia of even a small amount of physiological shunting cannot therefore be compensated for by hyperventilation. The *P*ao2 and *P*aco2 of some individuals who have mild disease of the lung causing slight [Vdot]A/[Qdot] mismatch may still be normal.

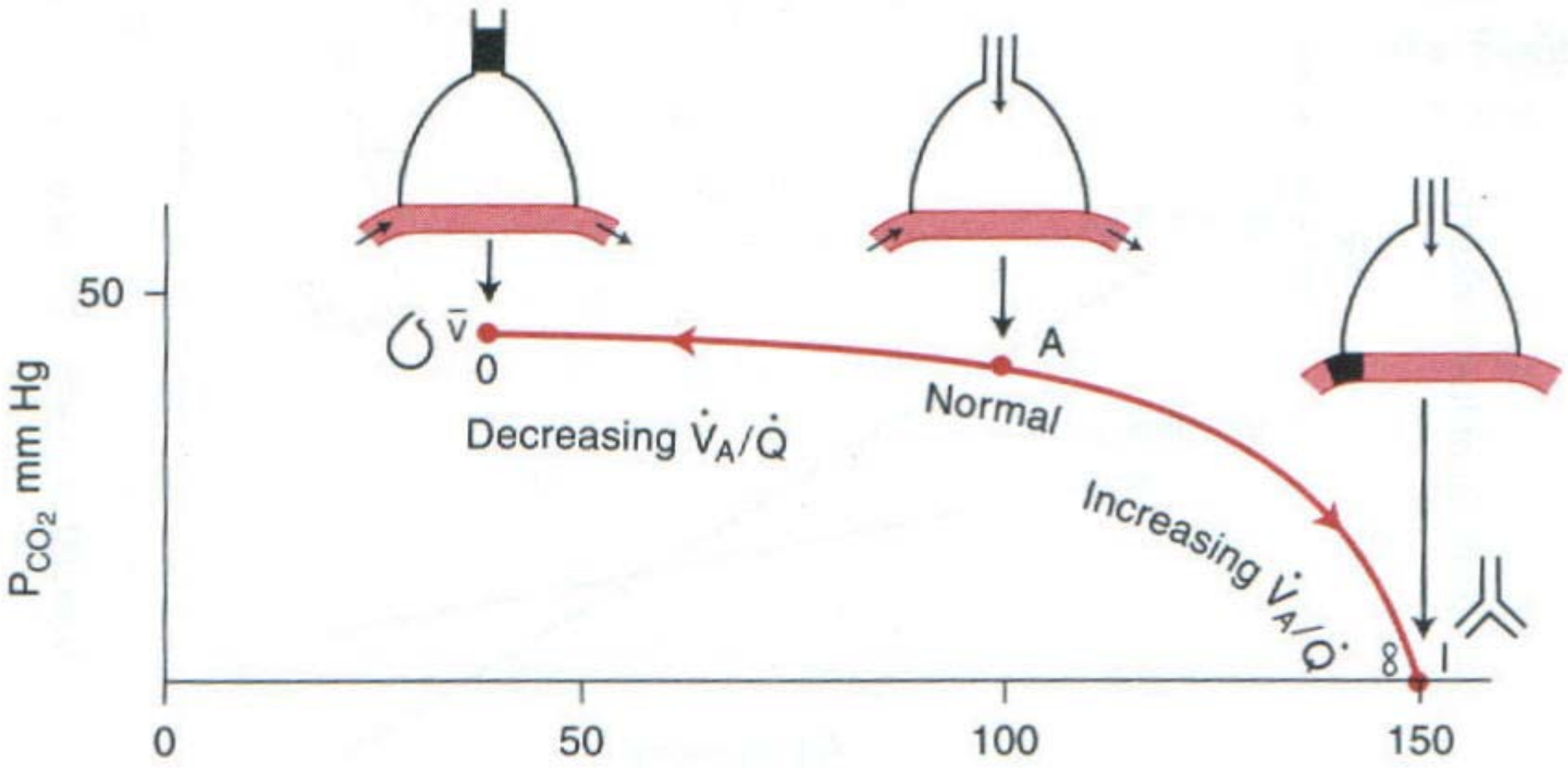
- Increasing the requirements for gas exchange by exercise will widen the [Vdot]A/[Qdot] mismatch and the *P*ao2 will fall. [Vdot]A/[Qdot] mismatch is by far the most common cause of arterial hypoxaemia.

Effect of Altering Ventilation Perfusion Ratio



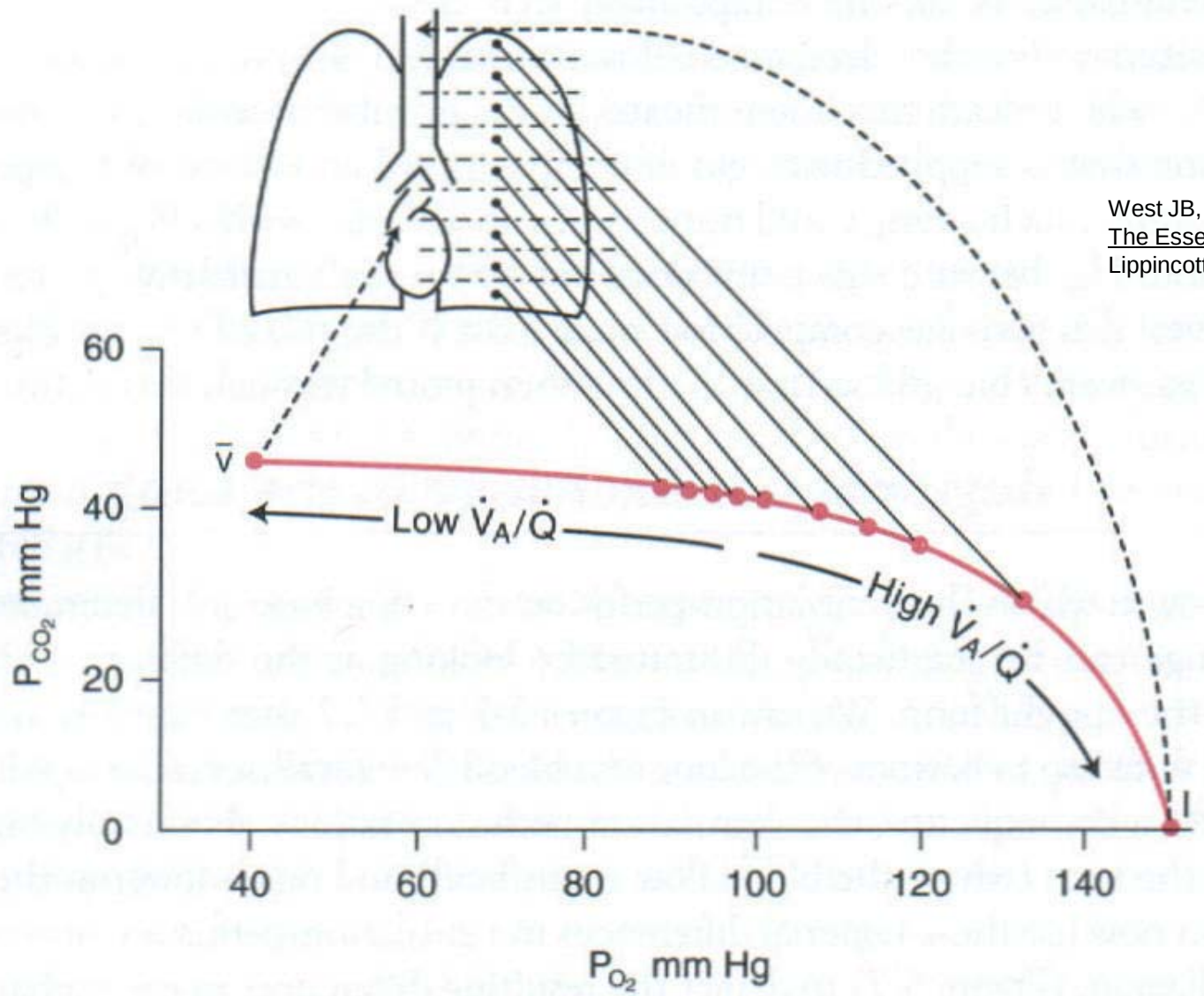
West JB, Respiratory Physiology, The Essentials, 6th ed. 2000, Lippincott, p. 52.

P_{CO2} vs. P_{O2} as Ventilation Perfusion Changes



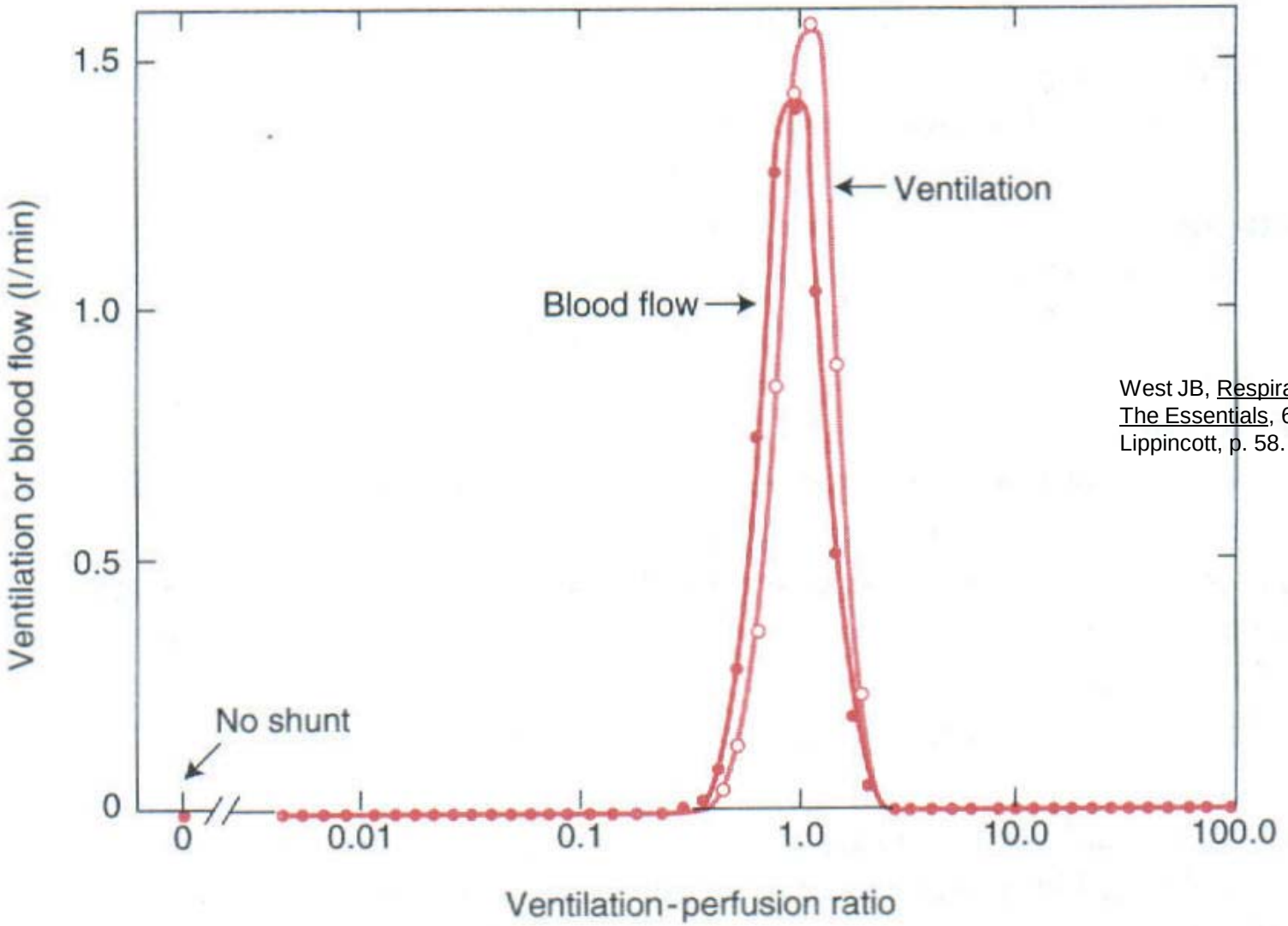
West JB, Respiratory Physiology, The Essentials, 6th ed. 2000, Lippincott, p. 53.

Result of Ventilation Perfusion Inequality



West JB, Respiratory Physiology, The Essentials, 6th ed. 2000, Lippincott, p. 54.

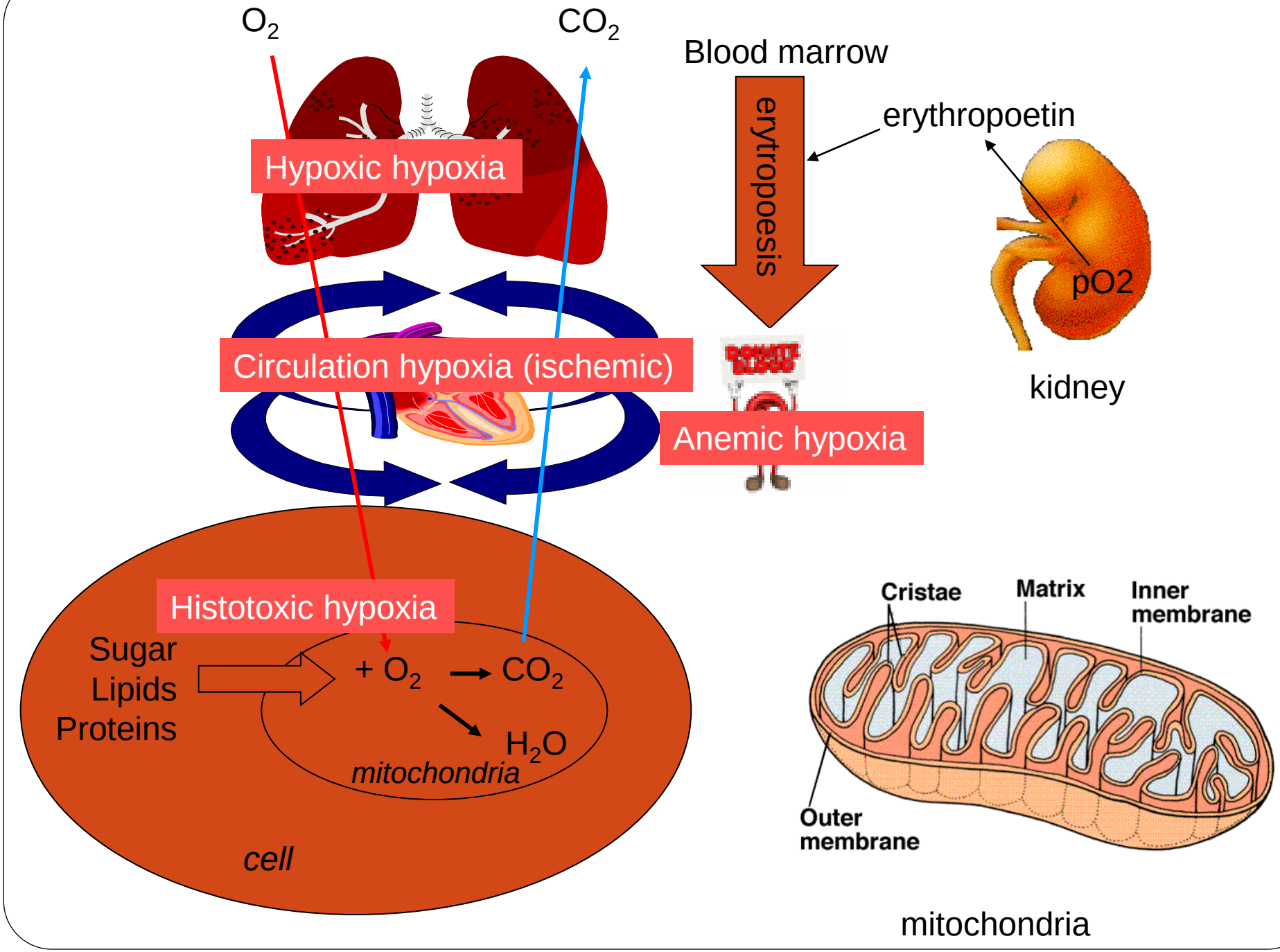
Distribution of Ventilation and Perfusion—Normal Lungs



West JB, Respiratory Physiology, The Essentials, 6th ed. 2000, Lippincott, p. 58.

Hypoxia

- = deficiency of O_2 in the organism ($\downarrow paO_2$ <10kPa/75mm Hg)
- types:
  - (1) hypoxic hypoxia - $\downarrow$ arterial PO_2 – leads to **central cyanosis**
    - decreased partial pressure of oxygen in inspired air
    - Hypoventilation due to damage of respiration centre
    - Pulmonary diseases
  - (2) anemic hypoxia – normal aterial PO_2
    - Decreased hemoglobine
      - anemia, leukemias
    - Hemoglobin with low ability to bind oxygen with low ability to bind oxygen
      - carboxyhemoglogin (COHb)
      - methemoglogine
  - (3) circulation hypoxia = normal arterial PO_2 – leads to **peripheral cyanosis**
    - decrease of cardiac output
    - decrease of systemic blood pressure
    - local tissue ischemia
    - microcirculation defects
  - (4) histotoxic hypoxia – normal arterial PO_2, $\uparrow$ venous PO_2
    - Intoxication of kyanides, cobaltum,…)


O_2
CO_2
Hypoxic hypoxia
Circulation hypoxia (ischemic)
Blood marrow
erythropoesis
erythropoetin
pO2
kidney
Anemic hypoxia
Histotoxic hypoxia
Sugar
Lipids
Proteins
+ O_2
CO_2
H_2O
mitochondria
cell
Cristae
Matrix
Inner membrane
Outer membrane
mitochondria

Causes of Hypoxemia

1. Low inhaled PO2 (high altitude, low FiO2)—A-a gradient is normal
2. Hypoventilation—A-a gradient is normal
3. Diffusion impairment (fibrosis, emphysema)
4. Shunting of unoxygenated blood
5. Ventilation Perfusion mismatch

Intermittent hypoxia

- Intermittent hypoxia is an effective stimulus for evoking the respiratory, cardiovascular, and metabolic adaptations normally associated with continuous chronic hypoxia.

- These adaptations are thought by some to be beneficial in that they may provide protection against disease as well as improve exercise performance in athletes.

- The long-term consequences of chronic intermittent hypoxia may have detrimental effects, including hypertension, cerebral and coronary vascular problems, developmental and neurocognitive deficits, and neurodegeneration due to the cumulative effects of persistent bouts of hypoxia.

Chronic intermittent hypoxia

- significantly increases right ventricular heart mass, likely associated with pulmonary vascular remodeling and pulmonary hypertension

- There are also detrimental effects on normal development, especially in the fetus because intermittent hypoxia significantly decreases fetal growth.

- However, it is the association of hypertension, developmental defects, neuropathological and neurocognitive deficits, enhanced susceptibility to oxidative injury, and possibly increased myocardial and cerebral infarction in patients with **obstructive sleep apnea (OSA)** syndromes that has fostered an intense interestin examining the link between intermittent hypoxia and these adverse events.

- OSA is characterized by episodic obstructions of airflow during sleep, often more than 60 times per hour, with significant desaturations of hemoglobin to levels as low as 50%. These events are not only associated with hypoxemia but significant hypercapnia and frequent arousals leading to significant sleep fragmentation as well. Thus the specific role of intermittent hypoxia in producing the major clinical consequences of OSA has been difficult to sort out from clinical studies.

Chronic hypoxia

- induces proliferation of the vasculature due to angiogenesis but can also change the integrity of vessels, leading to changes in vascular permeability. A host of growth factors, including vascular endothelial growth factor (VEGF), interacting with integrins orchestrates the formation and maintenance of blood vessels. Hypoxia influences the dynamics of the processes inducing angiogenesis primarily through its ability to upregulate VEGF.

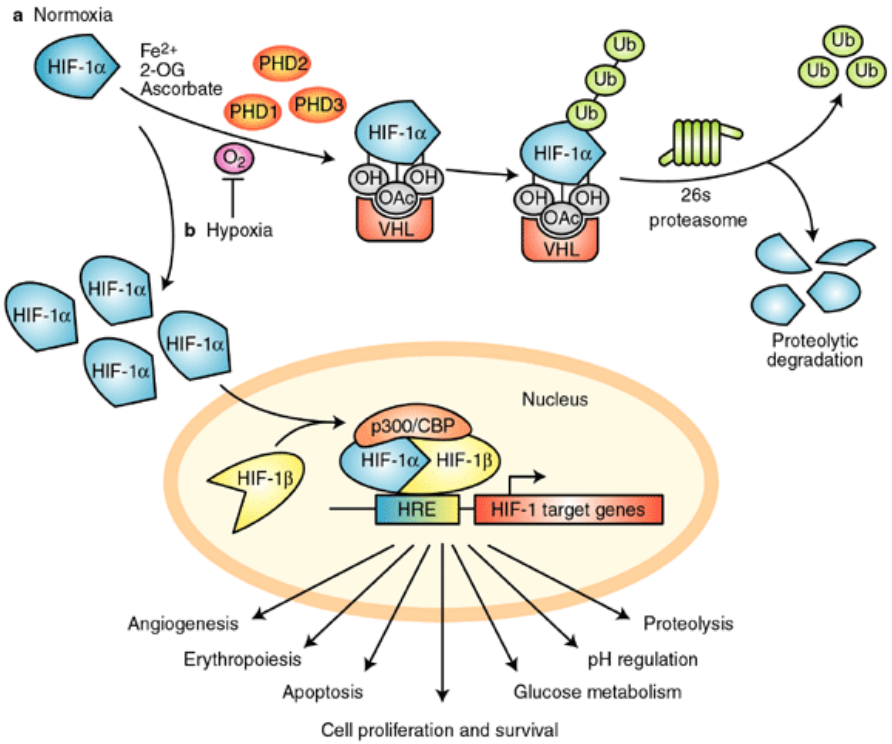
- is well known for its ability to increase capillary density as well as to cause acute mountain sickness by destabilizing vascular integrity, resulting in leakage of proteins and water through the blood-brain barrier, which leads to impaired brain function.

Hypoxia and gene transcription

• The ability of hypoxia to promote persistent adaptations is due in part to its ability to induce changes in gene transcription.

• The regulation of the expression of a wide variety of genes involved in hypoxic adaptations is largely due to activation of a hypoxia-sensitive transcription factor, hypoxia-inducible factor 1 (HIF-1).

• HIF-1 is a heterodimer of HIF-1 alpha and HIF-1 beta. Oxygen levels directly regulate the expression of the HIF-1 component in a dose-dependent manner, with a gradual increase from 20 to 5% O2 and a pronounced increase below 5% O2. Tissue PO2 is normally 20-40 Torr, suggesting that HIF-1 is exquisitely sensitive to changes in tissue oxygenation.



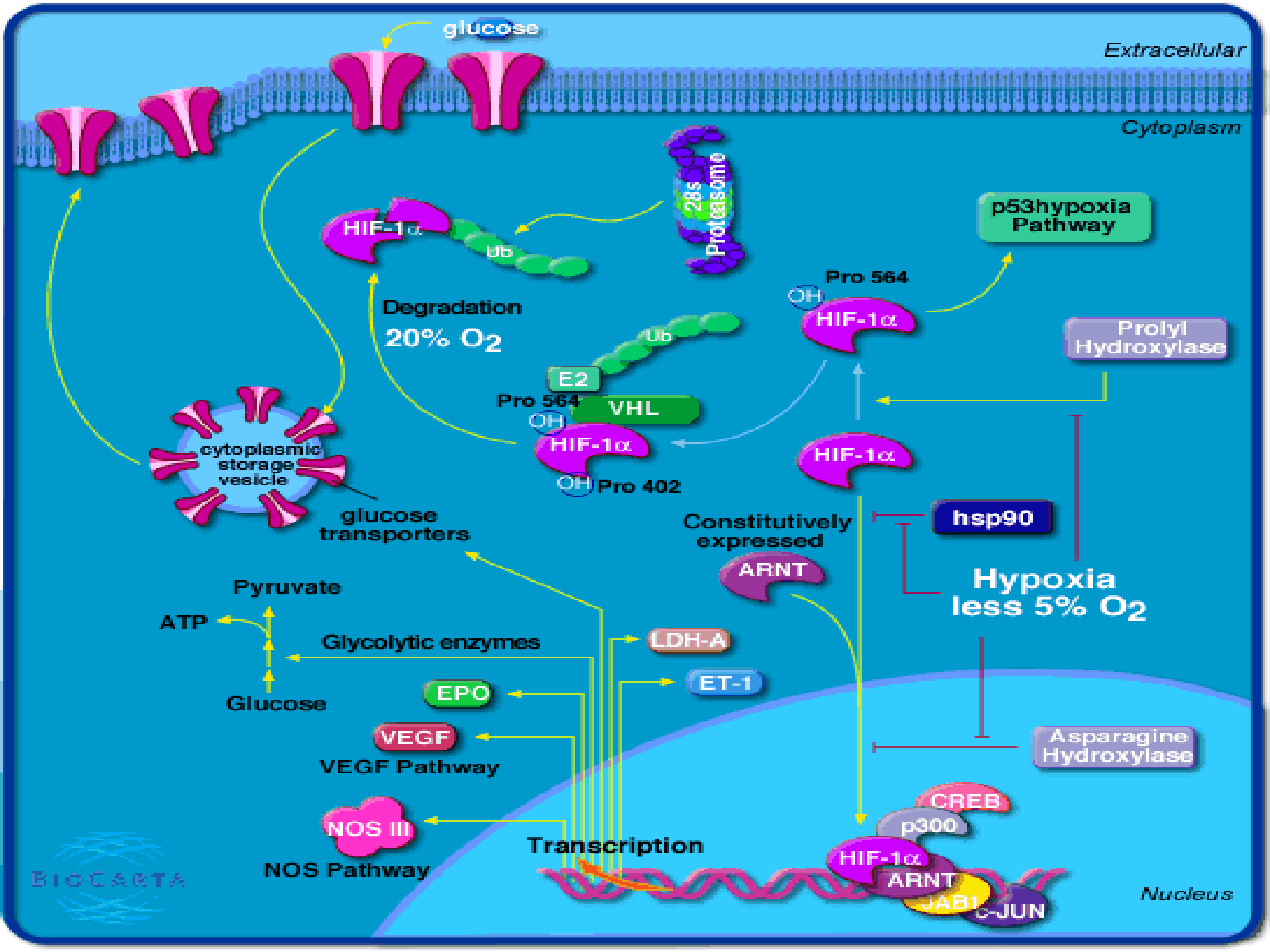
HIF-1α regulation by proline hydroxylation

Hypoxia and gene transcription

- The dynamics of HIF-1 expression also appears to be quite rapid both in its onset of expression and its decay characteristics.

- For example, evidence of decay of HIF-1 after reoxygenation of lung tissue occurs in <1 min. Such rapid dynamics could provide the ability for short bouts of intermittent hypoxia to produce adaptations at the level of gene transcription that promote ***angiogenesis, erythropoiesis, and glycolysis***.

- Thus, although no data are available regarding whether tissues respond differently to continuous or intermittent hypoxia, it seems reasonable to expect that HIF-1 expression is a critical determinant in initiating and reversing the adaptive and/or maladaptive responses to intermittent hypoxia.


glucose
Extracellular
Cytoplasm
HIF-1α
Ub
26s Proteasome
Degradation
20% O2
p53hypoxia Pathway
Pro 564
OH
HIF-1α
Prolyl Hydroxylase
Ub
E2
Pro 564
VHL
OH
HIF-1α
OH
Pro 402
HIF-1α
cytoplasmic storage vesicle
glucose transporters
Constitutively expressed
ARNT
hsp90
Hypoxia less 5% O2
Pyruvate
ATP
Glycolytic enzymes
LDH-A
ET-1
Glucose
EPO
VEGF
VEGF Pathway
Asparagine Hydroxylase
NOS III
NOS Pathway
Transcription
CREB
p300
HIF-1α
ARNT
JAB1
c-JUN
Nucleus
BIOCARTA

Thank you for your attention