PULMONARY ANATOMY AND PHYSIOLOGY

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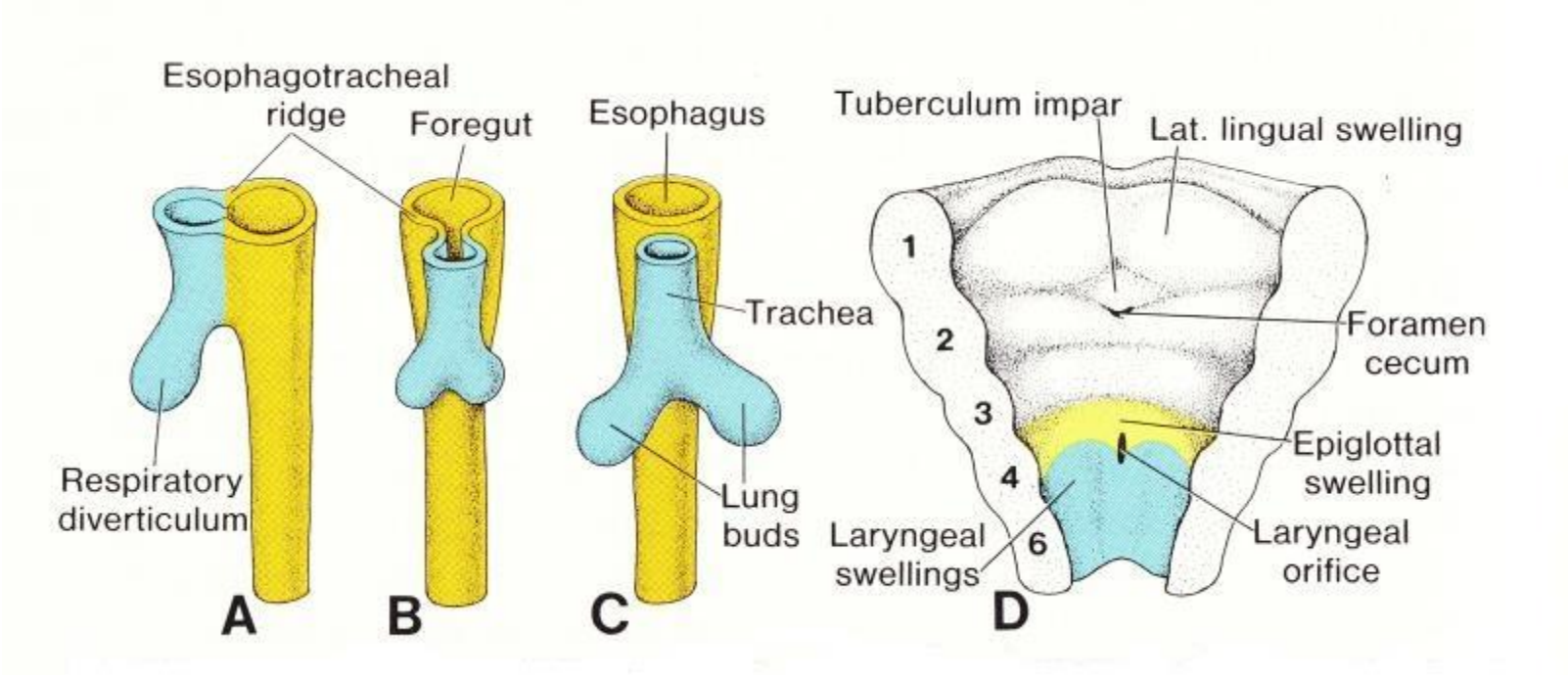
Embryology

- At the 4th week of gestation, the body cavity forms in the space between somatic and splanchnic layers of the lateral plate mesoderm.
- The rostral and caudal ends of the embryo gut tube end blindly.
- The yolk sac and allantois remain outside the embryo.
- The central opening of the gut tube remains in communication with the yolk sac through the vitelline duct .
- Diverticulum from pharynx gives rise to the larynx, trachea, bronchi, and lungs.



http://www.ultratwistersgym.com/Resources/Respiratory/Respiratory.html
Accessed 01/10/2020

Embryology

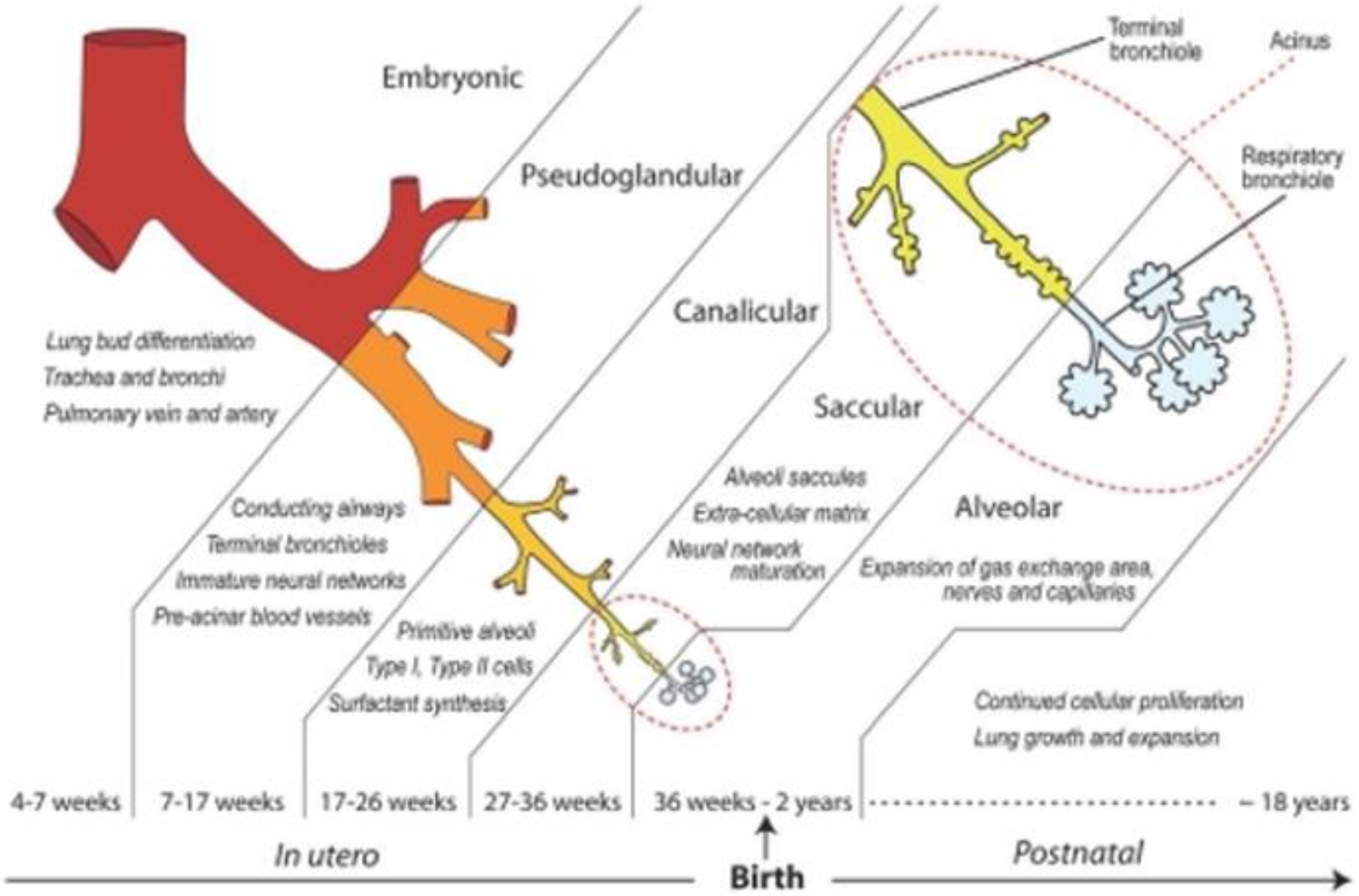
- At the 5th week, the coelom fuses, separating the embryo from the yolk sac, creating the intracoelomic space.
- It partitions further with the formation of the cardiac and pulmonary systems.
- Paired lateral ridges fuse to separate the respiratory from the digestive system.
- At 4-7 weeks gestation, secondary and tertiary bronchi form (embryonic stage);

Embryology

- At 5-16 weeks, conducting bronchi form (canalicular stage).
- Before 16 weeks the fetus cannot survive outside the womb as there is no structure for gas exchange
- At 17-26 weeks, respiratory bronchioles form (pseudoglandular stage);
- The production of surfactant from type II pneumocytes begins as early as week 24.
- At 24-26 weeks, terminal bronchioles reach primordial air sacs; the lung is well vascularized.
- Gas exchange is now possible outside the womb
- Steroids may accelerate maturation after 26 weeks gestation

Embryology

- From 27 weeks to 36 weeks, the blood-air barrier is established between the epithelial layer (Type I pneumocytes) and capillaries. (saccular stage)
- Type II pneumocytes are distributed among the Type I pneumocytes. Surfactant production increases
- Alveolar increase begins at week 32 (alveolar stage).
- Alveoli increase in number and volume until 2 years of age



http://basenat.u707.jussieu.fr/site_respirare/index.php?option=com_content&view=article&id=59&Itemid=30&lang=en&showall=1
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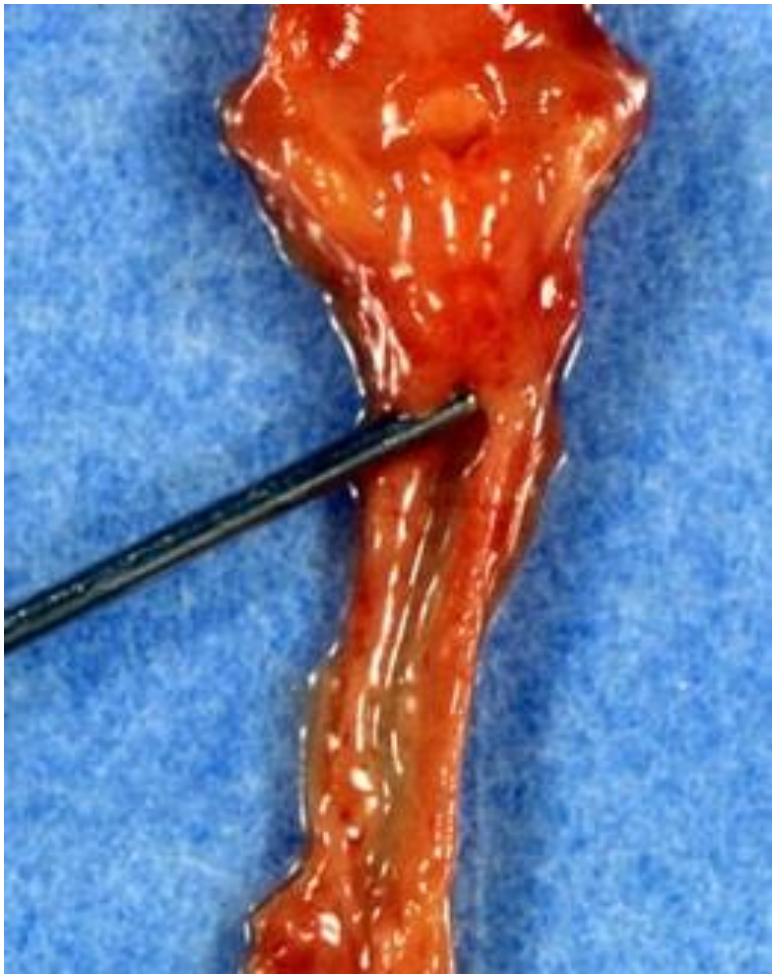
Laryngeal atresia



http://www.sonoworld.com/fetus/page.aspx?id=1250
Accessed 01/10/2020

Results from failure of the laryngeal lumen to recanalize.

Congenital or acquired narrowing of the airway that may affect the supraglottis, glottis, and/or subglottis

Features:

1) Obstruction of the upper fetal airway
2) Dilated airways below the obstruction
3) Enlarged lung and echogenic (due to accumulation of fluid)
4) Flattened or inverted diaphragm
5) Fetal ascites
6) Edema

Lung hypoplasia

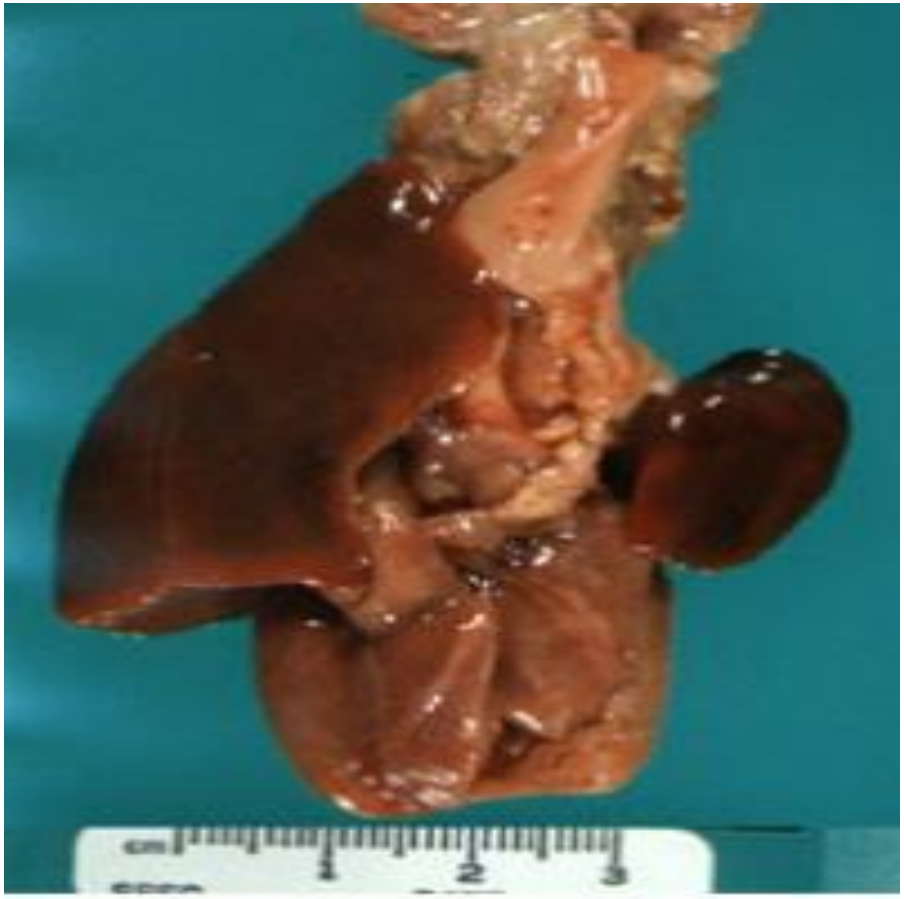


Figure 14. lunghypoplasia. Available at http://www.brown.edu/Courses/Digital_Path/systemic_path/pulmonary/ph2.html

Incomplete development of lung tissue.

Noted are the carina, a malformed bronchial stump, and absent or poorly differentiated distal lung tissue.

Associated with other cardiac, gastrointestinal, or skeletal abnormalities in 50% of cases.

Polyhydramnios.

Lung hypoplasia

- May be asymptomatic or may present with severe respiratory distress
- Older children may present with dyspnea and cyanosis may be present upon exertion, or have a history of respiratory infections.
- The external chest may appear normal or may be small and bell shaped, with or without scoliosis.
- A mediastinal shift is observed toward the involved side, and dullness upon percussion is heard over the displaced heart.
- Breath sounds may be decreased or absent on the side of hypoplasia, especially over the bases and axilla

Lung hypoplasia

- The Potter facies (hypertelorism, epicanthus, retrognathia, depressed nasal bridge, low set ears) suggest lung hypoplasia caused by the associated renal defects
- When the etiology of the hypoplasia is a neuromuscular disease, the patient may have myopathic facies, with a V-shaped mouth, muscle weakness, and growth retardation

Diaphragm

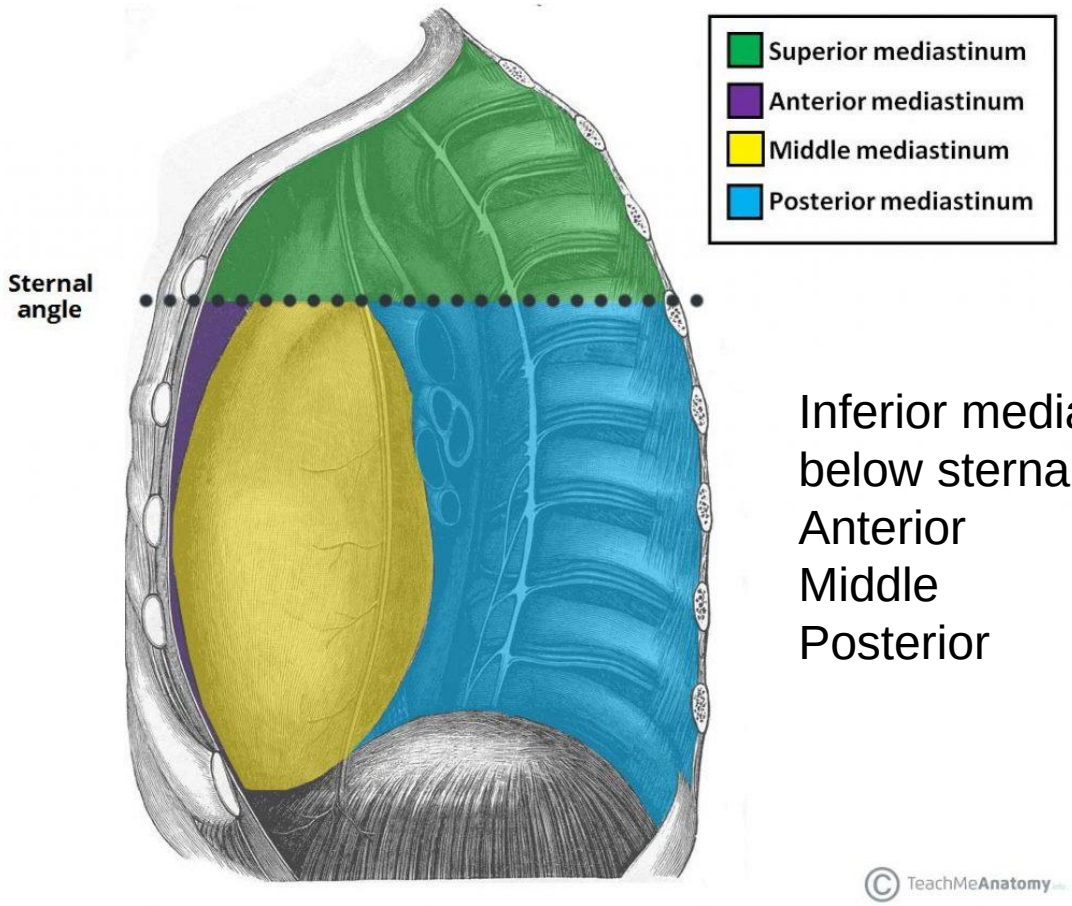
- At the 5th week, the transverse septum gives rise to the central tendon of the diaphragm;
- A small area lateral to the central tendon arises from the pleuroperitoneal membrane;
- The somatic mesoderm gives rise to the muscular part of the diaphragm
- The mesentery of the esophagus forms the crura of the diaphragm.

Diaphragm

- The phrenic nerve (C3-C5) is the sole motor nerve to the diaphragm.
- The phrenic nerve is sensory to the region of the central tendon.
- The lowest intercostal nerves are sensory to the remainder of the diaphragm.
- The diaphragm has openings for the inferior vena cava and right phrenic nerve at T8.
- The esophageal hiatus (and passage of the right and left vagus nerves) is at T10.
- The aorta and thoracic duct pass through at T12.

Mediastinum

- The plane between the sternal angle (junction of manubrium and body of sternum) and the intervertebral disc between T4 and T5 separates the superior and inferior mediastinum.
- The anterior mediastinum lies anterior to the pericardium.
- The fibrous pericardium attaches to both sternum and diaphragm.
- It is innervated by the phrenic nerve.
- The pericardium and related structures lie in the middle mediastinum.
- The posterior mediastinum lies posterior to the pericardium.

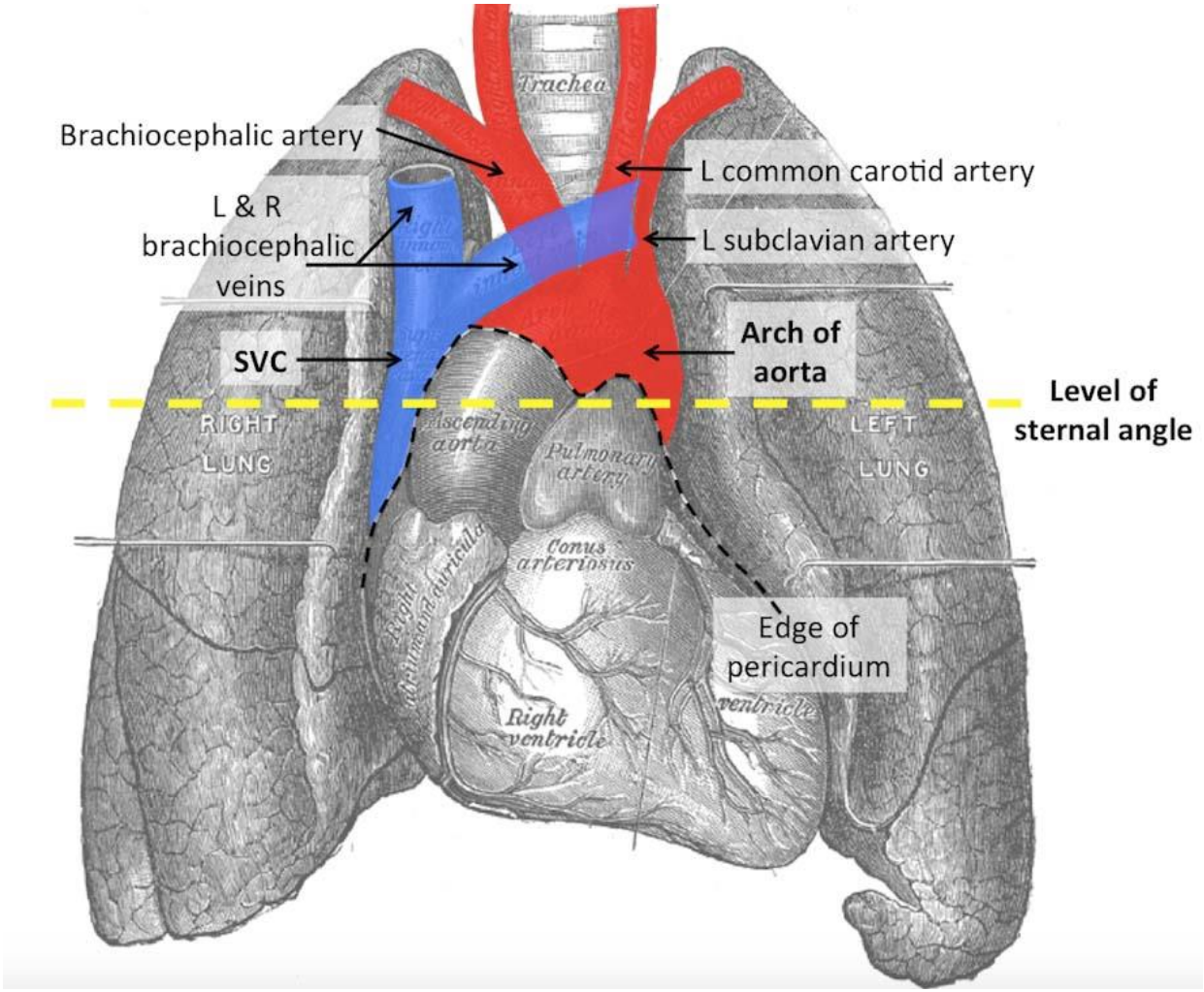


Inferior mediastinum is below sternal angle:
Anterior
Middle
Posterior

https://teachmeanatomy.info/thorax/areas/superior-mediastinum/
Figure 1
Accessed 01/15/2020

Found in the superior mediastinum

- Trachea;
- Esophagous;
- The aortic arch and its branches:
- Brachiocephalic, left common carotid, and left subclavian arteries;
- The left brachiocephalic vein crosses to join the right brachiocephalic vein to form the superior vena cava.
- Phrenic, vagus, and the left recurrent laryngeal nerves;
- Thoracic duct.
- The thymus gland is found in the anterior and superior mediastinum.



https://teachmeanatomy.info/thorax/areas/superior-mediastinum/
Figure 2
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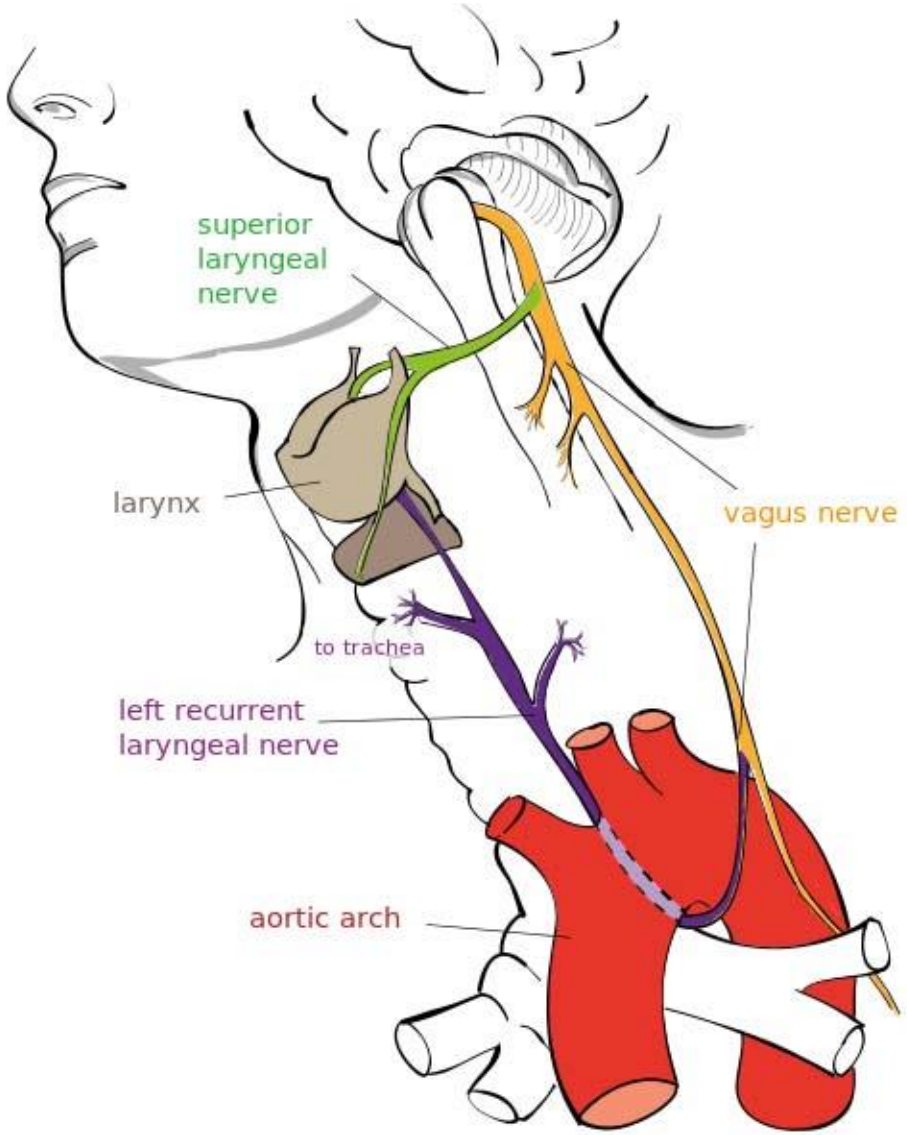


https://teachmeanatomy.info/thorax/areas/superior-mediastinum/
Figure 3
Accessed 01/15/2020

Found in the middle mediastinum

- The heart
- Pericardium

Found in the posterior mediastinum

- The thoracic aorta;
- The thoracic duct;
- Primary bronchi
- Tracheobronchial nodes;
- Azygos venous system;
- The azygos venous system communicates with the inferior vena cava.
- Drains the thoracic wall and thoracic organs except the heart and lungs.
- Esophagus;
- Vagus and splanchnic nerves.

Thoracic duct

- The thoracic duct originates from the cisterna chyli (abdominal cavity).
- Begins at L2.
- Ascends on right side in the thoracic cavity and crosses to the left side at T5.
- It continues to the superior mediastinum into the neck.
- Empties into the venous angle of the left jugular trunk and left subclavian trunk.

Chest wall

- Intermediate muscles of the back serve a respiratory function.
- Kinesiological monitor (proprioceptive).
- The serratus posterior superior elevates the 2^{nd}-5^{th} ribs. Innervated by T1-T4.
- The serratus posterior inferior depresses the 9^{th}-12^{th} ribs. Innervated by T9-T12.
- The intercostals function during forced respiratory maneuvers.
- The costal groove lies on the inferior surface.
- Contains the posterior intercostal vein, artery, and intercostal nerve.

Chest wall

- Intercostal nerves innervate the costal pleura.
- The phrenic nerve innervates the mediastinal pleura.
- The lungs and pleura extend above the first rib and clavicle anteriorly.
- Posteriorly the lungs only extend to the level of the first rib.

Chest wall

- Inferiorly, the lung extends anteriorly to the level of the 6th rib; the pleura, 8th rib.
- Inferiorly, the lung extends laterally to the level of the 8th rib; the pleura, 10th rib.
- Inferiorly, the lung extends posteriorly to the level of the 10th rib; the pleura, 12th rib.

Lungs

- The right lung has three lobes.
- The oblique fissure separates the upper and lower lobes, the lower and middle lobes.
- The horizontal fissure separates the upper and middle lobes.
- The left lung has two lobes separated by an oblique fissure.
- The oblique fissure begins at the level of the 2^{nd} rib. The horizontal fissure parallels the 4^{th} rib.

Lungs

- The right mainstem bronchus is nearly vertical.
- Post-ganglionic parasympathetic branches are from the vagus nerve.
- Pre-ganglionic sympathetic fibers are with T1-T5.

Normal chest anatomy

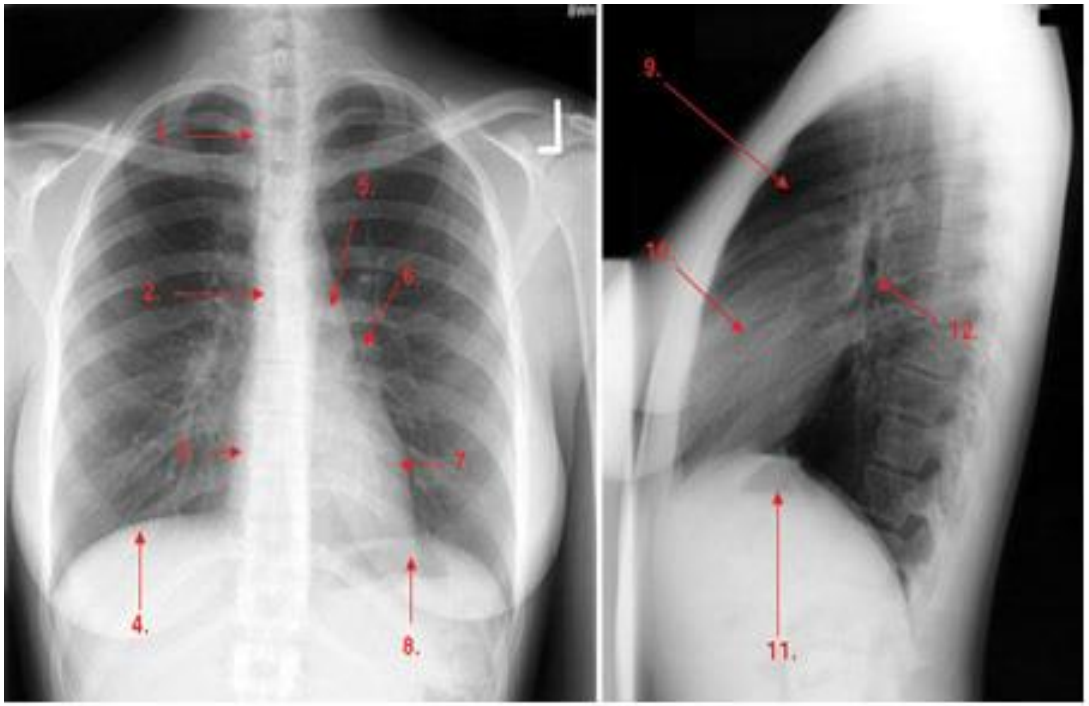


Fig. e24-1 Accesed 03/17/2010

1. Trachea. 2. Carina. 3. Right atrium. 4. Right hemi-diaphragm. 5. Aortic knob. 6. Left hilum. 7. Left ventricle. 8. Left hemi-diaphragm (with stomach bubble). 9. Retrosternal clear space. 10. Right ventricle. 11. Left hemi-diaphragm (with stomach bubble). 12. Left upper lobe bronchus.

Normal chest anatomy

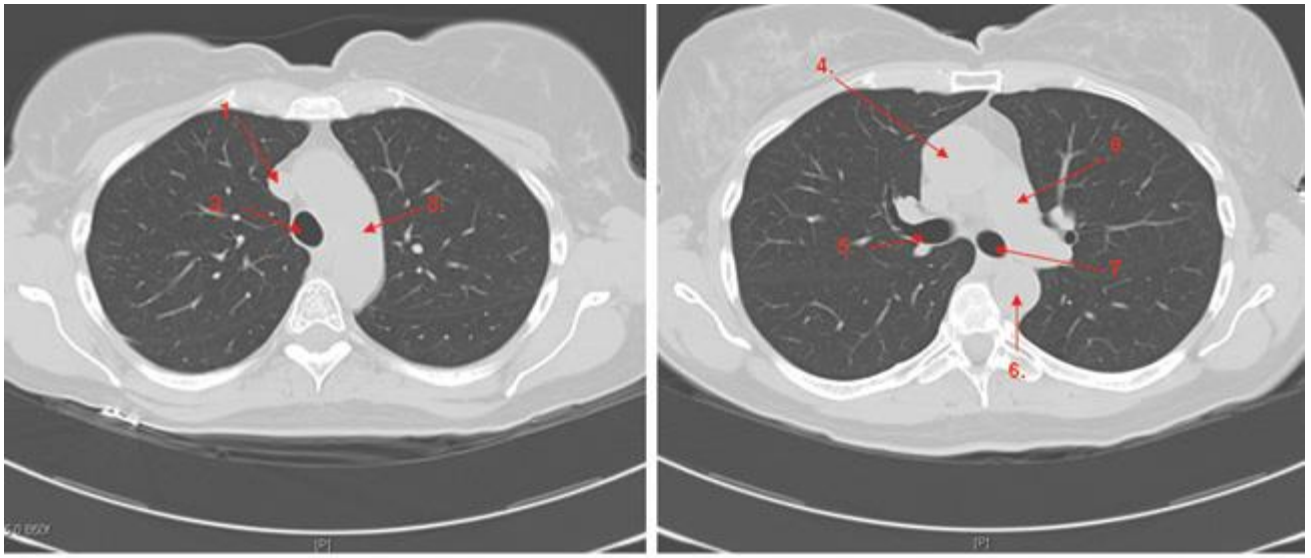
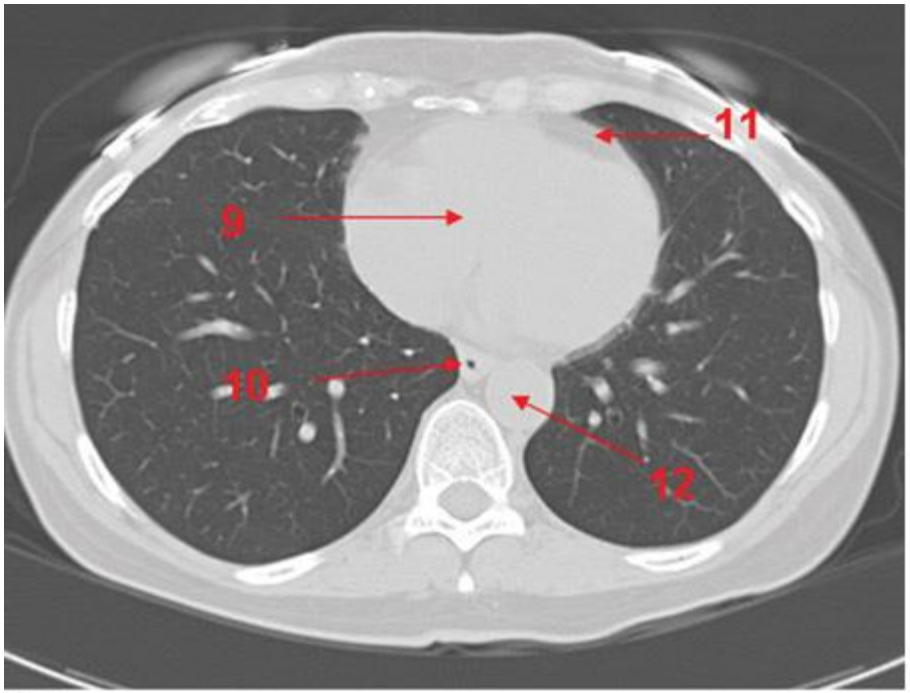


Fig. e24-2 Accessed 03/17/2010

1. Superior vena cava. 2. Trachea. 3. Aortic arch. 4. Ascending aorta. 5. Right mainstem bronchus. 6. Descending aorta. 7. Left mainstem bronchus. 8. Main pulmonary artery.

Normal chest anatomy



C

9. Heart.
10. Esophagus.
11. Pericardium.
12. Descending aorta.

Fig. e24-2 Accessed 03/17/2010

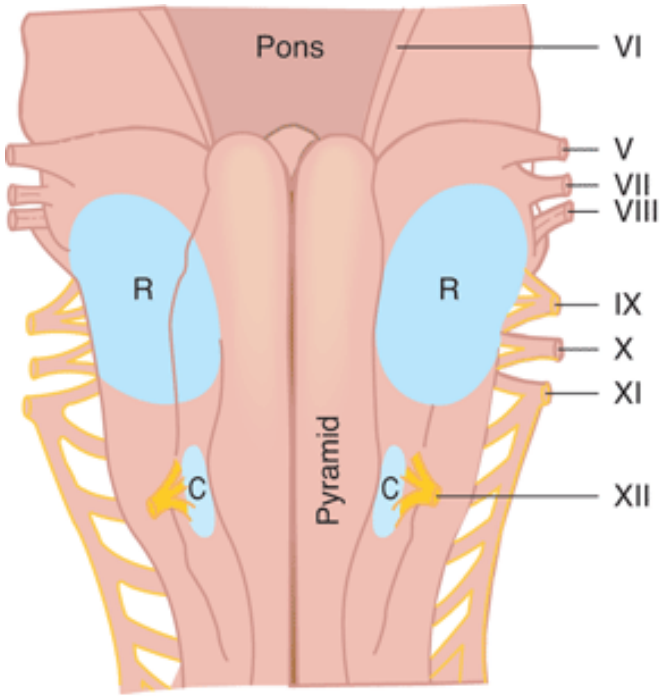
Respiratory Control System

- Controlled from the medulla.
- Dorsal respiratory nucleus (midlateral part of solitary nucleus) has inspiratory function.
- Phrenic motor neurons (contralateral) are activated by the dorsal respiratory nucleus.
- Receives excitatory projections from chemoreceptors in the medullary chemosensitive area and in the carotid body.

Respiratory Control System

- The chemosensitive area lies at the site of attachment of CN IX to the brainstem, where the choroid plexus extends through the lateral aperture of the 4th ventricle.
- At this juncture, the lateral reticular formation is exquisitely sensitive to H^+ concentration.
- Any increase stimulates the dorsal respiratory nucleus through direct synaptic contact.

Chemosensitive areas



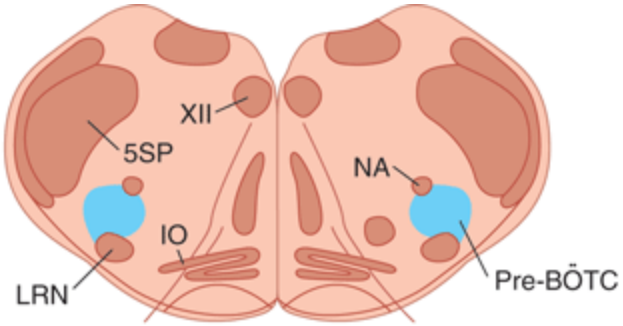
Rostral (R) and caudal (C) chemosensitive areas on the ventral surface of the medulla.

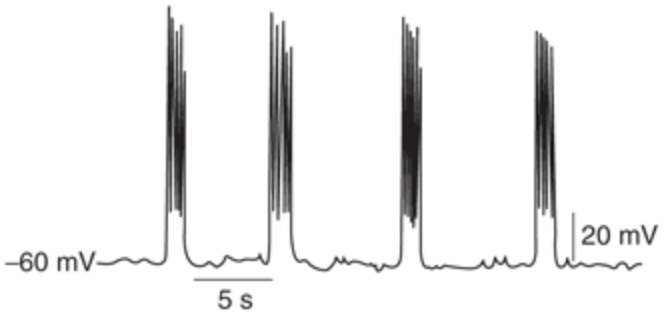
Fig. 37-7 Accessed 03/01/2010

Respiratory control system

- The ventral respiratory nucleus is expiratory
- Functions as an oscillator, engaged in reciprocal inhibition with the inspiratory center.
- Abdominal wall motor neurons (contralateral) are activated by the ventral respiratory nucleus (forced expiration).
- The medial parabrachial nucleus (adjacent to the cerulean nucleus) has a pacemaker function.
- Stimulated by the amygdala.

Respiratory control





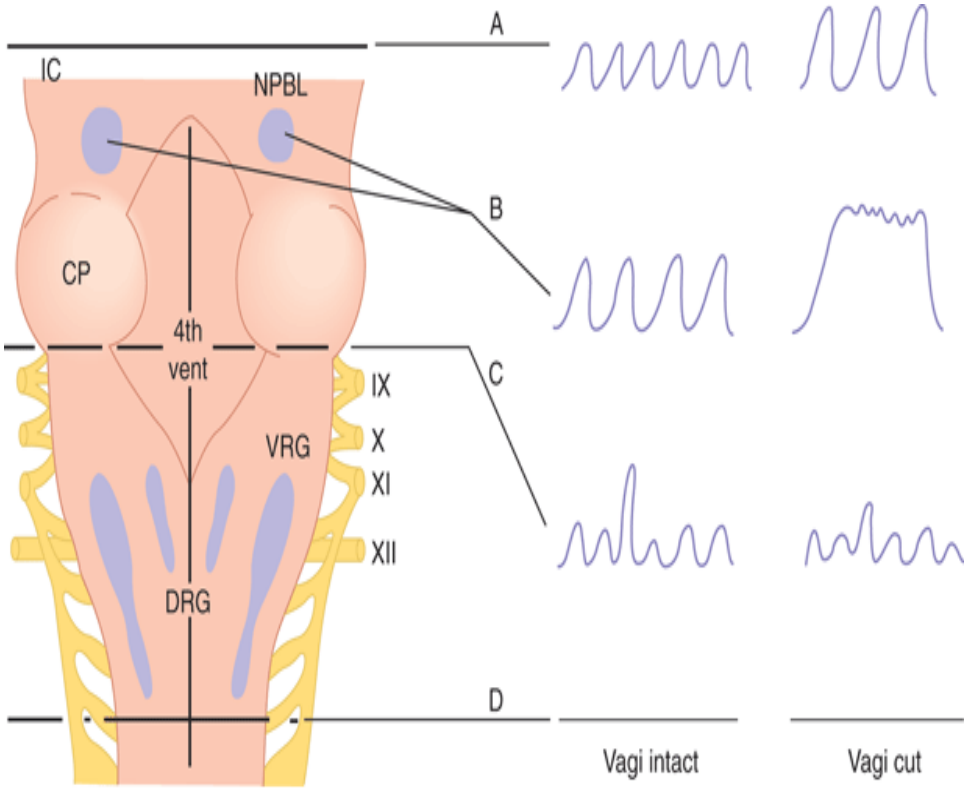
(Modified from Feldman JC, Gray PA: Sighs and gasps in a dish. Nat Neurosci 2000;3:531.) Fig. 37-1 Accessed 03/01/2010

Rhythmic respiration is initiated by a small group of synaptically coupled pacemaker cells in the pre-Bötzinger complex (pre-BÖTC) on either side of the medulla between the nucleus ambiguus and the lateral reticular nucleus.

They also contact the hypoglossal nuclei.

The tongue is involved in the regulation of airway resistance.

Brain stem control of respiration



Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

(Modified from Mitchell RA, Berger A: State of the art: Review of neural regulation of respiration. Am Rev Respir Dis 1975;111:206.) Fig. 37-2 Accessed 03/01/2010

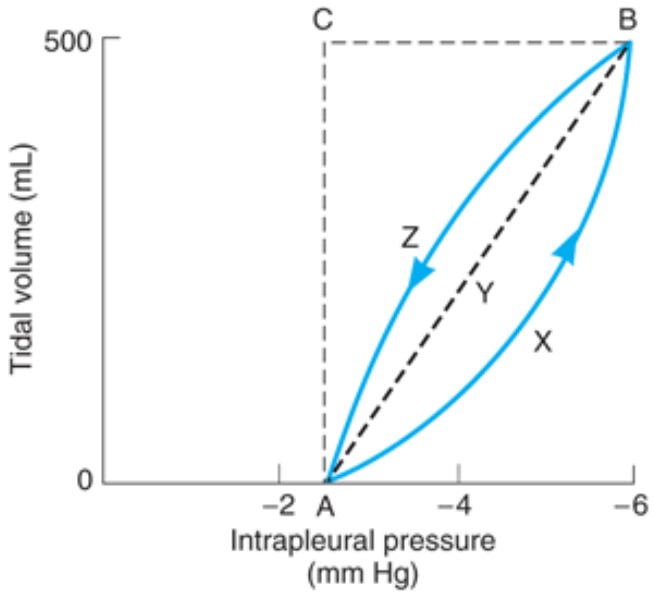
Respiratory control system

- Receptors in the airway are additionally innervated by slowly adapting and rapidly adapting myelinated vagal fibers.
- Slowly adapting receptors can be activated by lung inflation.
- Rapidly adapting receptors, or irritant receptors, can be activated by chemicals such as histamine and result in cough or even hyperpnea.

Respiratory control system

- Receptors in the airway are also innervated by unmyelinated vagal fibers (C fibers) that are typically found next to pulmonary vessels.
- They are stimulated by hyperinflation (or exogenous substances including capsaicin) and lead to the pulmonary chemoreflex.
- The physiologic role for this response is not fully understood.

Pressure-volume relationship in breathing



Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

Diagrammatic representation of pressure and volume changes during quiet inspiration (line AXB) and expiration (line BZA). Line AYB is the compliance line.

Fig. 35-15 Accessed 03/01/2010

Role of surfactant

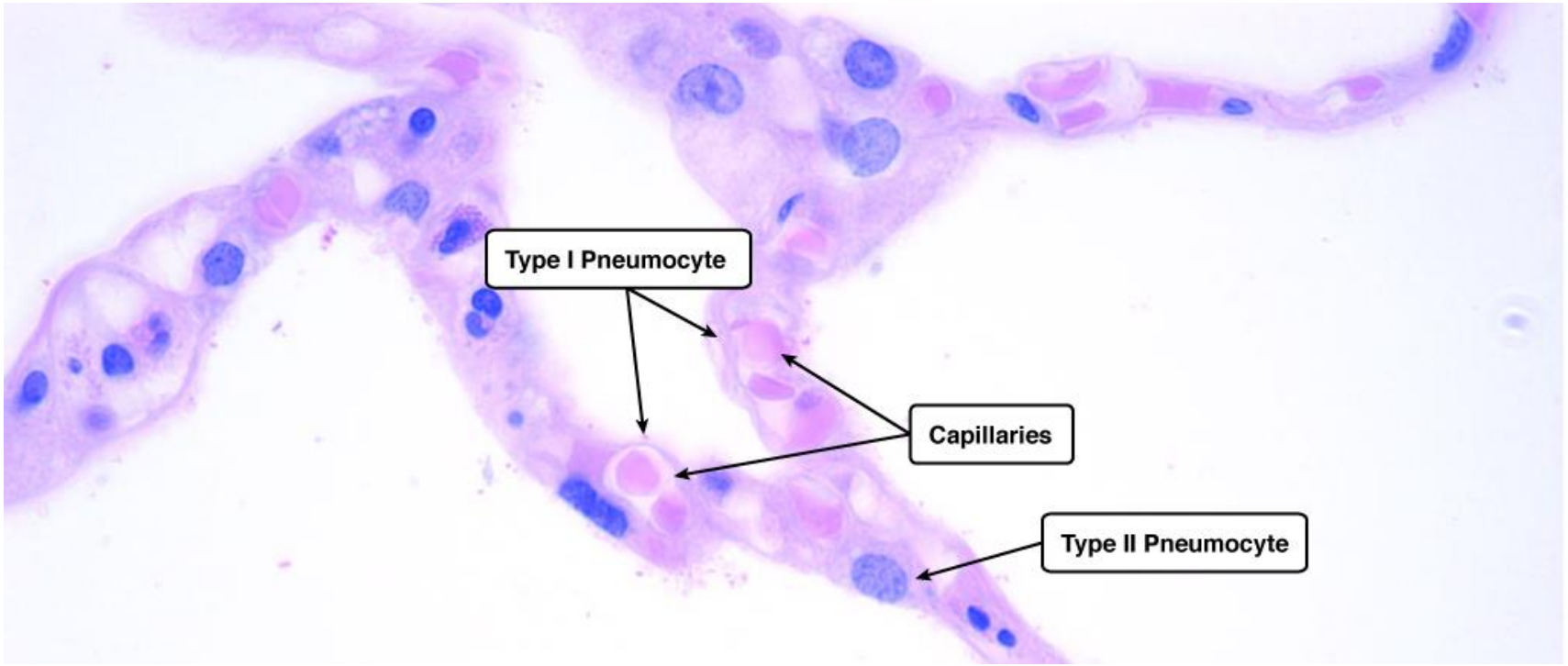
- Surfactant reduces surface tension at the air-liquid barrier in alveoli.
- With normal levels of surfactant, the lungs retain up to 40% of the residual air volume after the first breath.
- Subsequent breaths require less effort to maintain patency (no atelectasis).
- Surfactant production (type II alveolar cells) accelerates in 35th week of gestation.
- Minimal quantity present before 32 weeks

Surfactant

- Pulmonary surfactant consists of:
- 90% phospholipids
- Dipalmitoyl phosphatidylcholine (lecithin)
- Phosphatidylglycerol,
- 10% surfactant associated glycoproteins
- SP-A and SP-D (hydrophilic) are collectins and deal with innate immunity
- SP-B and SP-C (hydrophobic) affect surface tension
- Packaged into lamellar bodies and secreted into the alveolar space where it unravels to form a monolayer on alveolar surfaces
- Enters amniotic fluid

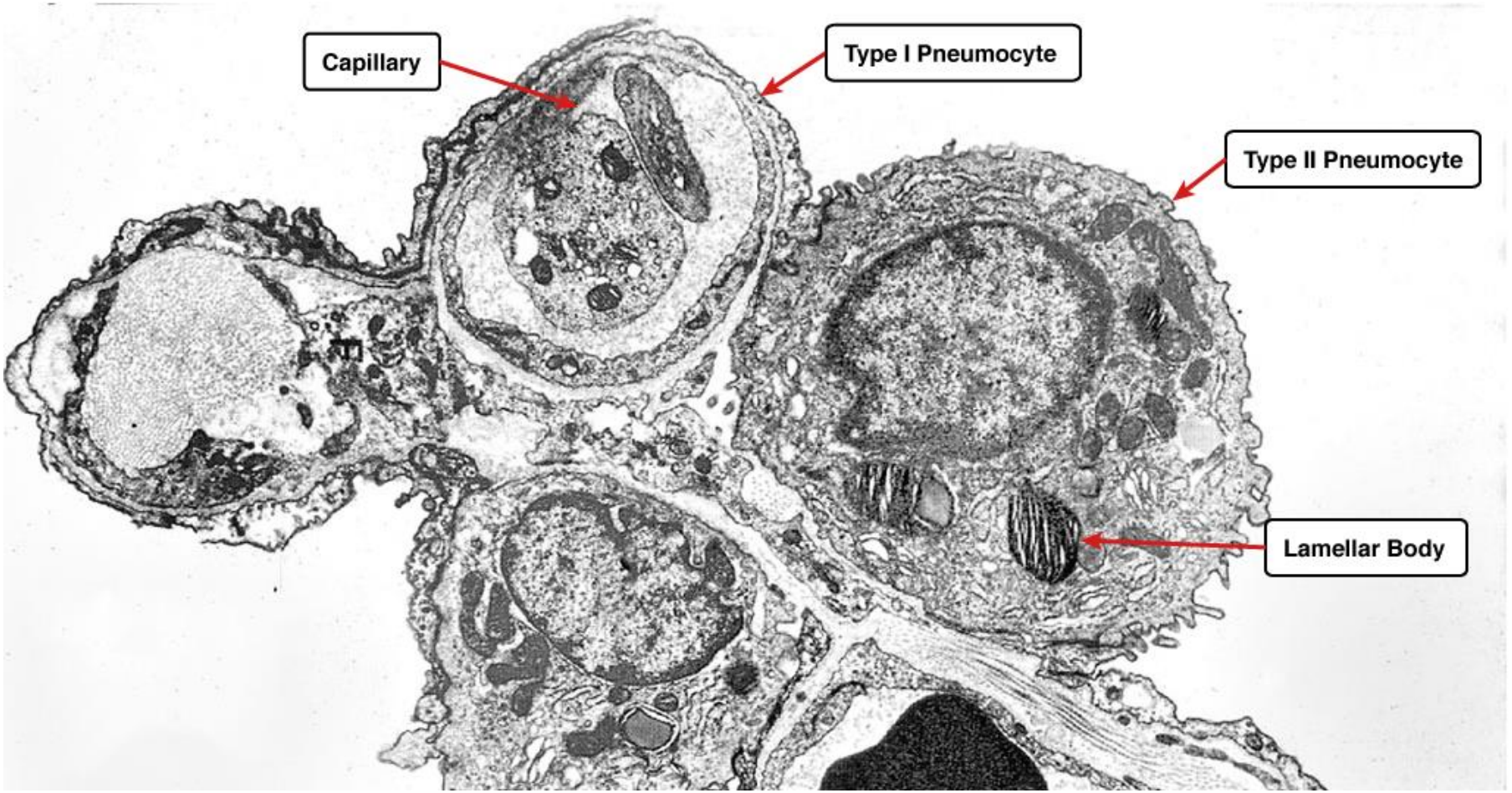
Surfactant

- Synthesis increased by:
- Cortisol
- Thyroxine
- Synthesis decreased by:
- Insulin



The type I pneumocytes form part of the barrier across which gas exchange occurs. They can be identified as thin, squamous cells whose most obvious feature is their nuclei. Type II pneumocytes are larger, cuboidal cells and occur more diffusely than type I cells. They appear foamier than type I cells because of they contain phospholipid multi-lamellar bodies, the precursor to pulmonary surfactant. Capillaries form a plexus around each alveolus.

http://medcell.med.yale.edu/histology/respiratory_system_lab/pneumocytes_em.php Accessed 02/20/2020



http://medcell.med.yale.edu/histology/respiratory_system_lab/pneumocytes_em.php
Accessed 02/20/2020

Pulmonary flow loops

- The expiration curve of an air-filled lung is steeper than the inspiration curve.
- The difference in the curves is hysteresis.
- The expiration limb is determined by lung compliance only
- Depends upon the amount of elastic tissue present).
- Surface tension alters the inspiration limb on the air-filled lung.
- The starting point is deflation (low lung volume, low alveolar radius).
- Elevated pressures are required to open the alveoli (and overcome intermolecular forces at the air-liquid interface).

Lung volume

- The volume of gas remaining in the lungs after a maximal forced expiration is the residual volume
- Cannot be measured by spirometry.
- The functional respiratory capacity is the expiratory reserve volume plus the reserve volume.
- It is the amount of air remaining in the lungs after a normal tidal volume is expired
- It is the equilibrium state in the lung.
- The volume is measured by inert gas dilution.
- The vital capacity is the tidal volume plus the inspiratory reserve volume plus the expiratory reserve volume.
- It is the volume that can be expired after maximal respiration.

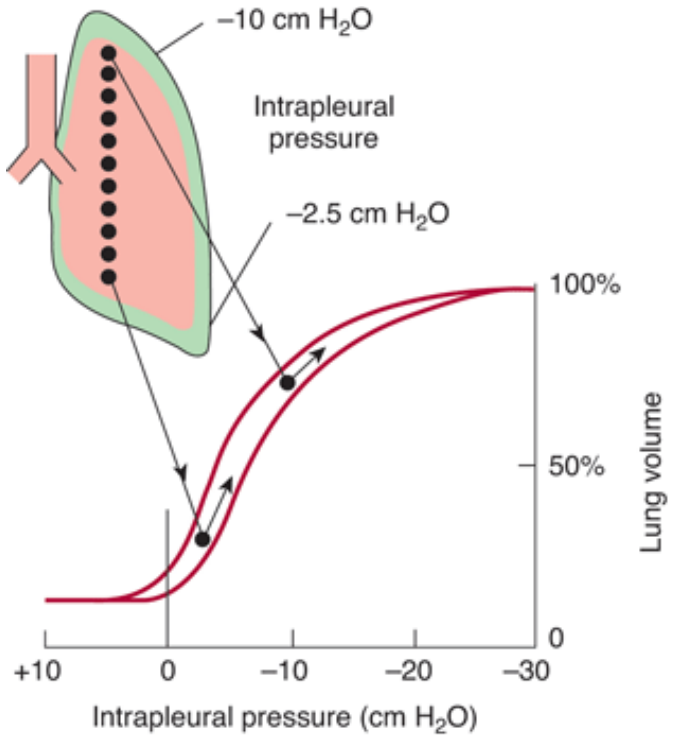
How To Measure Your Lung Capacity

- Take the deepest breath you can
- Inflate a balloon with a single breath.
- Tie it off
- Get a large, deep oven tray
- Weigh it
- Put it on the floor
- Fill an empty bucket with water and put it in the center of the oven tray
- The bucket must be filled to the very top

How To Measure Your Lung Capacity

- Gently dunk your balloon in the water.
- The water will start pouring out of the bucket and into the oven tray.
- Fully submerge the balloon
- Take the balloon and bucket away
- Weigh the oven tray with the water in it
- The difference in weight is your lung cappounds
- acity
- 1 mL water weighs 1mg
- 1 kg is 2.2

Intrapleural pressure



Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

(Reproduced with permission from West JB: *Ventilation/Blood Flow and Gas Exchange,* 3rd ed. Blackwell, 1977.)
Fig. 35-16 Accessed 03/01/2010

Because intrapulmonary pressure is atmospheric, the more negative intrapleural pressure at the apex holds the lung in a more expanded position at the start of inspiration.

Further increases in volume per unit increase in intrapleural pressure are smaller than at the base because the expanded lung is stiffer.

Lung resistance

- The medium sized bronchi are arranged in series and are the sites of highest airway resistance.
- Small airways are arranged in parallel.
- Reduces airway resistance
- Turbulent flow is converted to laminar flow
- Large cross-sectional area
- Favors gas exchange

Lung resistance

- Parasympathetic stimulation (muscarinic receptors) produces airway constriction.
- Smooth muscle is under tonic parasympathetic control.
- Sympathetic stimulation (β_2 receptors) produces airway relaxation.
- Its principal effect is on small airways.

Lung resistance

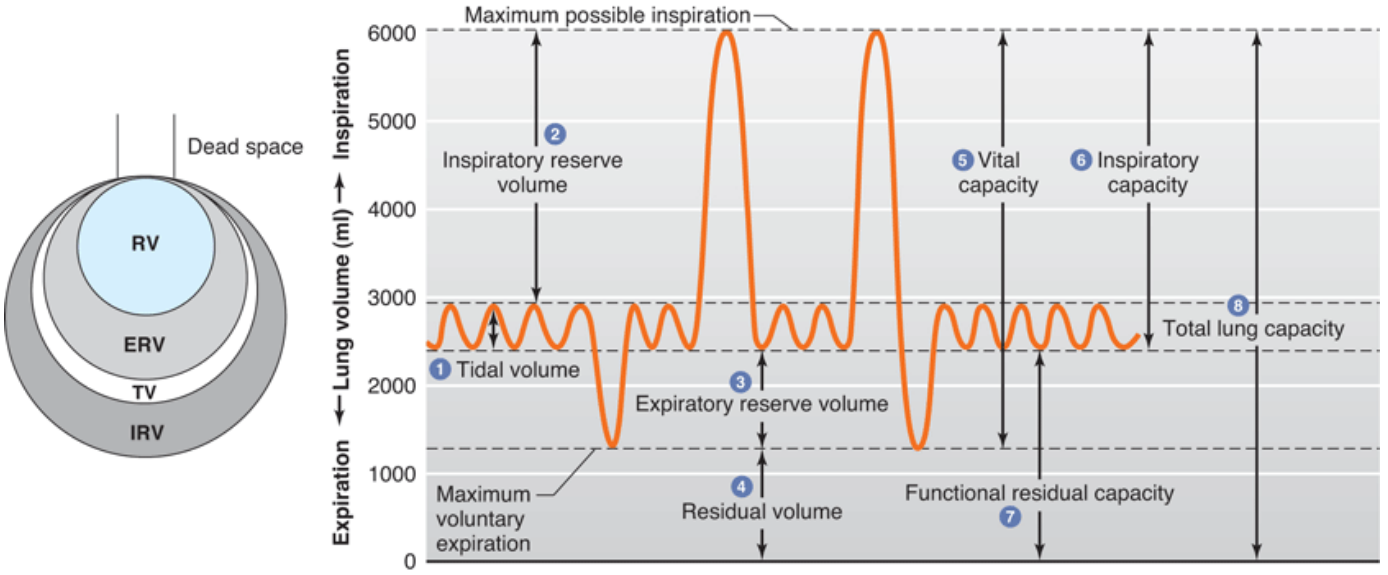
- In normal lungs, forced expiration generates intrapulmonary and intrapleural pressures higher than normal.
- The airways and alveoli do not collapse under that condition as the transmural pressure remains positive.

Lung resistance

- In restrictive lung disease, forced expiration generates normal intrapleural pressure
- However, there is diminished elastic recoil of airways and alveoli.
- Transmural pressure across the alveoli remains positive and they remain open.
- The transmural pressure gradient reverses across airways and they collapse.
- Airway resistance to flow increases.
- Increases in gas viscosity (diving at depth, dehumidified air) also produce increases in resistance.

Dynamic measurements

- Forced expiratory volume (FEV) is the volume of air that can be expired over time.
- Generally, the forced vital capacity (FVC) can be expired over 3 seconds.
- Pulmonary expiratory flow rate (PEFR) is the maximal effort exerted in the first 0.2 seconds of forced expiration.
- In obstructive airway disease, FVC and FEV at 1 second are decreased as well as the ratio FEV_1/FVC.
- In restrictive lung disease, FVC and FEV_1 are decreased; the ratio of FEV_1/FVC increases.



Respiratory Volumes and Capacities for an Average Young Adult Male		
Measurement	**Typical Value**	**Definition**
Respiratory Volumes		
1 Tidal volume (TV)	500 ml	Amount of air inhaled or exhaled in one breath during relaxed, quiet breathing
2 Inspiratory reserve volume (IRV)	3000 ml	Amount of air in excess of tidal inspiration that can be inhaled with maximum effort
3 Expiratory reserve volume (ERV)	1200 ml	Amount of air in excess of tidal expiration that can be exhaled with maximum effort
4 Residual volume (RV)	1200 ml	Amount of air remaining in the lungs after maximum expiration; keeps alveoli inflated between breaths and mixes with fresh air on next inspiration
Respiratory Capacities		
5 Vital capacity (VC)	4700 ml	Amount of air that can be exhaled with maximum effort after maximum inspiration (ERV + TV + IRV); used to assess strength of thoracic muscles as well as pulmonary function
6 Inspiratory capacity (IC)	3500 ml	Maximum amount of air that can be inhaled after a normal tidal expiration (TV + IRV)
7 Functional residual capacity (FRC)	2400 ml	Amount of air remaining in the lungs after a normal tidal expiration (RV + ERV)
8 Total lung capacity (TLC)	5900 ml	Maximum amount of air the lungs can contain (RV + VC)

(Right figure reproduced with permission from Widmaier EP, Raff H, Strang KT: *Vander's Human Physiology: The Mechanisms of Body Function*, 11th ed. McGraw-Hill, 2008.) Fig. 35-7 Accessed 03/01/2010

Pulmonary circulation

- The pulmonary circulation is a high pressure, high flow, low-resistance system.
- The vessels are more compliant.
- The pulmonary capillary bed is not a network of tubular vessels with some interconnections as is the systemic system
- Pulmonary capillaries mesh together in the alveolar wall so that blood flows as a thin sheet.
- Angiotensin I is converted to the potent vasoconstrictor angiotensin II in the pulmonary endothelial cells of the lungs
- Bradykinin, serotonin, norepinephrine and the prostaglandins E are inactivated in the lungs.

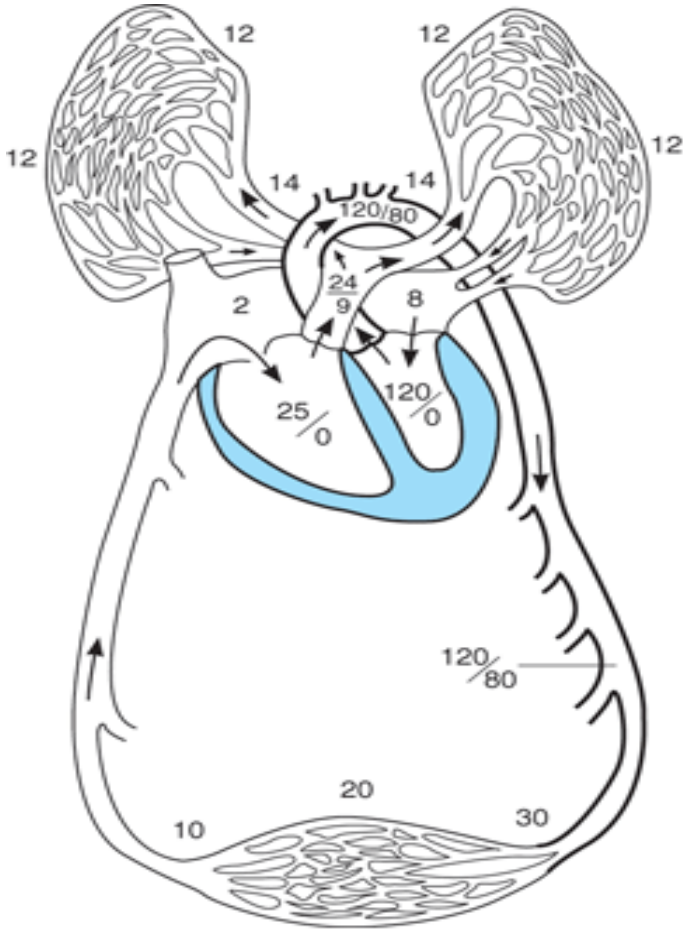
Pulmonary circulation

- Capillary recruitment and capillary distention cause the pulmonary vascular resistance to fall with increased cardiac output.
- This serves as a protective mechanism against pulmonary edema (increased hydrostatic pressure leading to extrusion of fluid into interstitial space).
- Low pO_2 increases pulmonary vascular resistance.
- Pulmonary vascular resistance is at its lowest at functional residual capacity (FRC).

Pulmonary circulation

- At high lung volumes, alveolar vessels are compressed.
- At low lung volumes, increased thoracic pressure compresses pulmonary vessels.

Pulmonary and systemic circulation pressures



(Modified from Comroe JH Jr.: *Physiology of Respiration,* 2nd ed. Year Book, 1974.)

Fig. 35-4 Accessed 03/01/2010

Gas transfer

- The volume of gas diffused is inversely proportional to membrane thickness.
- The diffusion coefficient of a gas is directly proportional to its solubility and inversely proportional to the square root of its molecular weight.
- Capillary blood flow limits O_2 uptake.
- Under steady state conditions, approximately 250 mL of O_2 per minute are transferred to the pulmonary circulation (VO_2) while 200 mL of carbon dioxide per minute are removed (VCO_2).

Alveolar gas equation

- The respiratory quotient, R, is the ratio of CO_2 production to O_2 consumption.
- The pressure of alveolar O_2 is directly proportional to the pressure of the inspired O_2 less the pressure of alveolar CO_2 divided by the respiratory quotient.
- When alveolar ventilation falls, the alvelolar pressure of O_2 falls, the alveolar pressure of CO_2 rises.

Arterial-alveolar difference in gas pressures

- The anatomic dead space is the volume of the conducting airways.
- No gas exchange occurs.
- Physiologic dead space includes that portion of the bronchiolar-alveolar system that is not involved in gas exchange.
- For the dead space, the difference in pressures of CO_2 in the systemic circulation and in the alveoli (or expired gas) is an approximation of the volume:

  Tidal volume X $(P_{art} – P_{alv}) / P_{art}$

Arterial-alveolar difference in gas pressures

- Normal Arterial-alveolar difference is <15 mmHg
- An elevated A-a difference with increased pCO_2
- Atelectasis
- Pulmonary edema
- Pleural effusion
- Pneumonia
- An elevated A-a difference with normal pCO_2
- Restrictive lung disease
- Interstitial lung disease

Alveolar ventilation

- Minute ventilation is tidal volume X breaths per minute.
- Alveolar ventilation is (tidal volume – dead space) x breaths per minute.
- Alveolar ventilation is directly proportional to the rate of production of CO_2 and inversely proportional to the arterial pressure of CO_2.

Alveolar ventilation

- If CO_2 production is constant, the arterial pressure of CO_2 is determined by alveolar ventilation.
- With increased metabolic rate (exercise, burn), CO_2 production is increased.
- Alveolar ventilation increases to maintain a stable pCO_2.

Gas exchange

- The exchange of CO_2 is diffusion limited.
- As long as the partial pressure of the gas is maintained, diffusion occurs along the length of the capillary.
- Under normal conditions, the exchange of O_2 is perfusion limited.
- The partial pressure of the gradient is not maintained and transfer is limited by blood flow.
- Higher blood flow is the only means of increasing exchange.

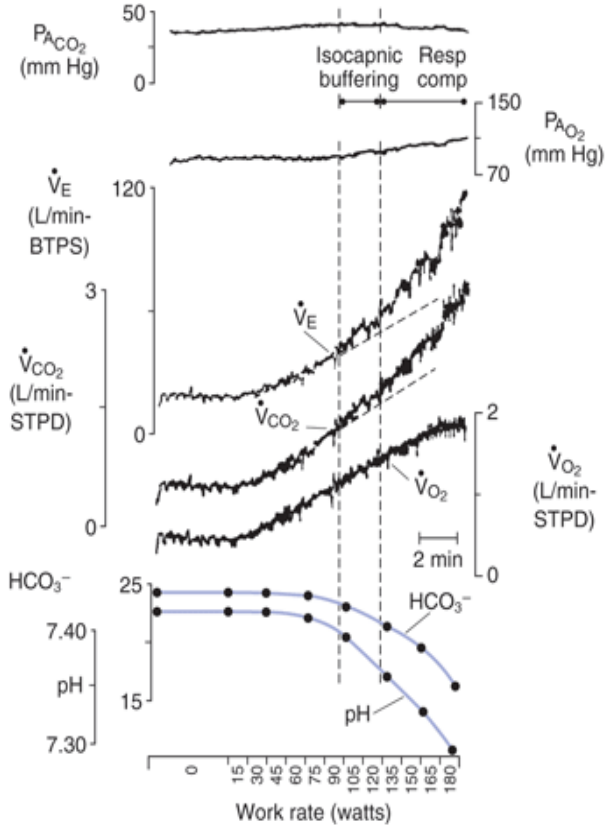
Gas exchange

- With pulmonary fibrosis or during strenuous exercise, O_2 exchange becomes diffusion limited.
- O_2 does not equilibrate along the capillary length
- This is also seen at high altitude.

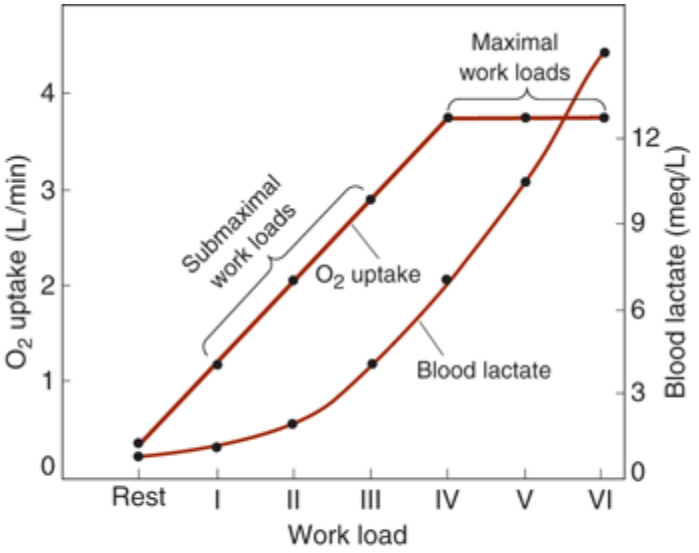
Ventilation perfusion ratio

- Ventilation improved at apex; perfusion improved at base
- At the apex
- $P_{\text{arterial alveolar pressure}} > P_{\text{artery pressure}} > P_{\text{venous pressure}}$
- Just above the level of the heart,
- $P_{\text{artery pressure}} > P_{\text{arterial alveolar pressure}} > P_{\text{venous pressure}}$
- Just below the level of the heart,
- $P_{\text{artery pressure}} > P_{\text{venous pressure}} = P_{\text{arterial alveolar pressure}}$
- At the base of the lung,
- $P_{\text{artery pressure}} > P_{\text{interstitial fluid pressure}} > P_{\text{venous pressure}} = P_{\text{arterial alveolar pressure}}$

Response in exercise



(Reproduced with permission from Wasserman K, Whipp BJ, Casaburi R: Respiratory control during exercise. In: *Handbook of Physiology.* Section 3, *The Respiratory System.*Vol II, part 2. Fishman AP (editor). American Physiological Society, 1986.) Fig 37-13 Accessed 03/01/2010



(Reproduced with permission from Mitchell JH, Blomqvist G: Maximal oxygen uptake. N Engl J Med 1971;284:1018.) Fig. 37-15 Accessed 03/01/2010

Altitude and pO_2

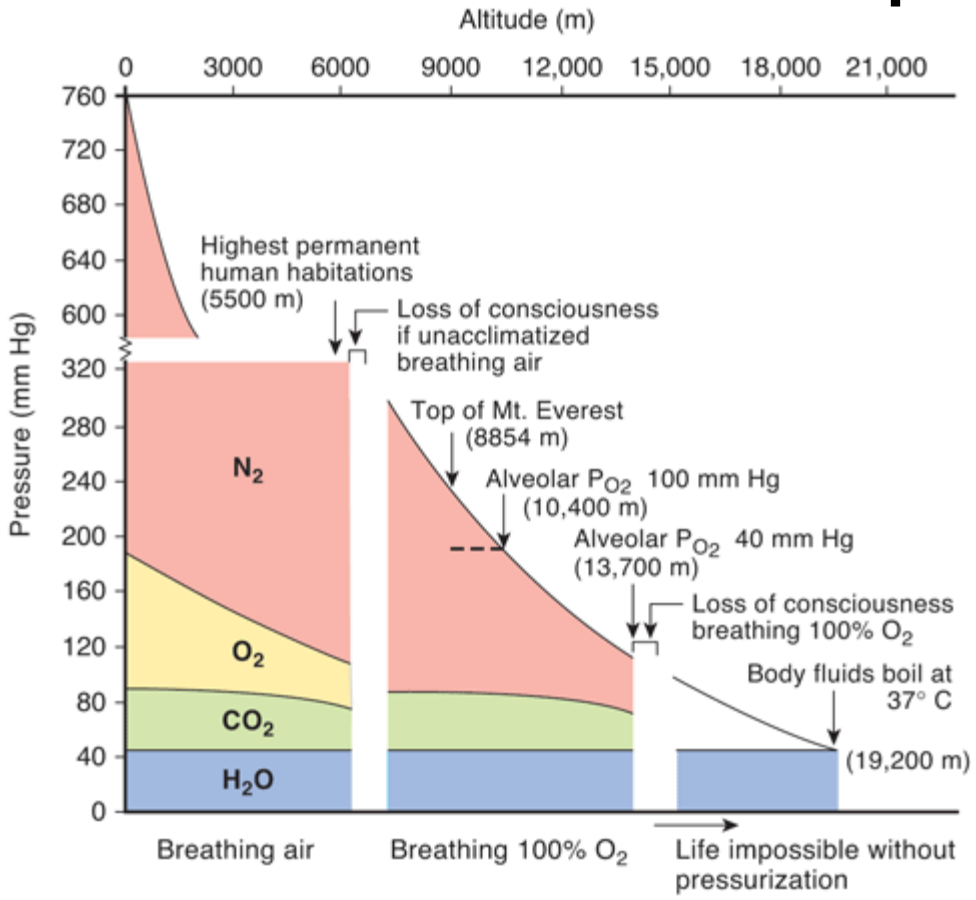


Fig. 36-12 Accessed 03/01/2010

With increasing altitude, the alveolar pCO_2 drops because of hyperventilation due to hypoxic stimulation of the carotid and aortic chemoreceptors.

The fall in barometric pressure with increasing altitude is not linear, because air is compressible.

Control of respiration

- Without training, breath-holding is possible for up to two minutes.
- With training, it may be possible to hold the breath for up to eleven minutes (physiological forces over-ride volitional control).
- With breath-holding and without training, it is possible to descend to 60 feet.
- The deepest free dive is 282 feet.
- The lowest pO_2 tolerable without loss of consciousness is 35-40 mmHg

Oxygen transport

- Hemoglobin can transport 70 times the amount of O_2 as that which is physically soluble in blood.
- The concentration of hemoglobin in erythrocytes is nearly double the concentration of plasma proteins in blood.
- Hemoglobin is responsible for the majority of the acid buffering capacity of plasma proteins.
- Hemoglobin A is a heterotetramer consisting of two α-chains and two β-chains, similarly folded.
- Each subunit carries a heme group with a central Fe^{2+}.
- Its oxidation state does not change with O_2 binding.

Oxygen transport

- Four of the six Fe^{2+} coordination sites in hemoglobin are occuppied by the Nitrogen atoms of the pyrrol rings
- and a fifth is occuppied by the (proximal) histidine of the globin molecule.
- The sixth is coordinated with Oxygen (or water if the hemoglobin is deoxygenated).
- Hemoglobin can exist in allosteric forms:
- The tense form has low O_2 affinity.
- As O_2 is bound, more molecules change to the high affinity relaxed form.
- The Oxygen saturation curve is sigmoidal.

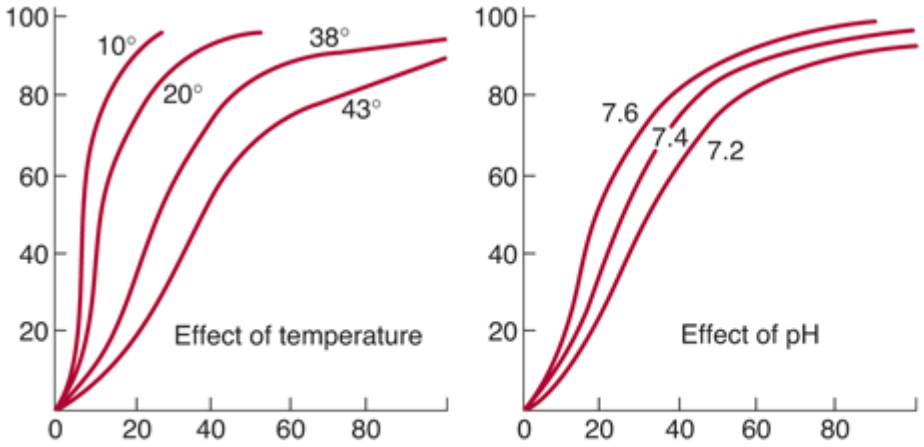
Oxygen transport

- CO_2 and H^+ are heterotropic effectors of hemoglobin.
- 2,3 diphosphoglycerate (synthesized from an intermediate of glycolysis) also acts as a heterotropic effector of hemoglobin.
- It can be returned to glycolysis as 2-phosphoglyceracetate, but without making ATP
- 2,3-DPG binds selectively to deoxy-hemoglobin, effectively increasing the release of O_2 at a constant pO_2. (right shift)
- The effects of CO_2 and 2,3-DPG are additive.

Oxygen transport

- Increased pCO_2 and decreased pH (metabolism) decrease the affinity of hemoglobin for O_2 and increase its supply to tissues. (Bohr effect)
- Increases in temperature as well as increases in 2,3-DPG concentration (hypoxemia) also decrease the affinity of hemoglobin for O_2 and increase its supply to tissues.
- 2,3-DPG is bound less well to the γ-chain of fetal hemoglobin.
- O_2 is more tightly bound and not available for unloading to the tissues.

Oxygen dissociation curves



$$pH = 6.10 + \log \frac{[HCO_3^-]}{0.0301\ P_{CO_2}}$$

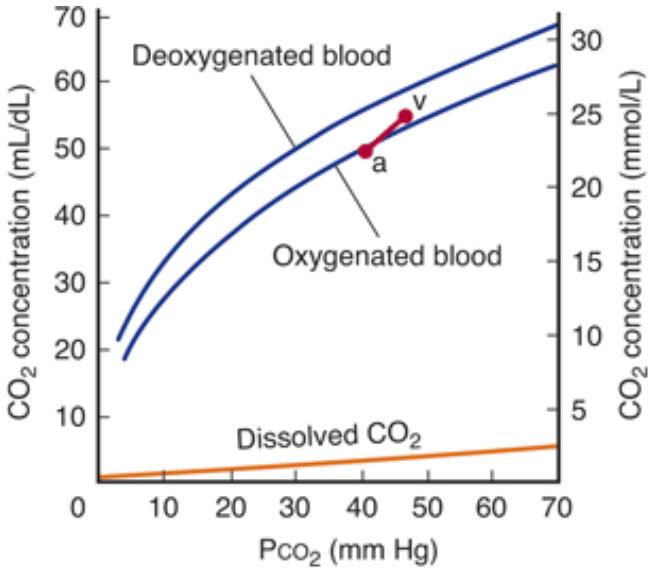
pH arterial blood ≅ 7.40
pH venous blood ≅ 7.36

Fig. 36-3 Accessed 03/01/2010

Carbon dioxide transport

- 5% of CO_2 arising in tissues is soluble in blood.
- 5% of CO_2 arising in tissues is covalently bound to the N-terminus of hemoglobin (carbaminohemoglobin).
- 90% of CO_2 arising in tissues is first converted into HCO_3^-.
- In the lungs, CO_2 is regenerated.

Carbon dioxide dissociation curve



(Modified and reproduced with permission from Schmidt RF, Thews G (editors): *Human Physiology.* Springer, 1983.)
Fig. 36-7 Accessed 03/01/2010

The arterial point (a) and the venous point (v) indicate the total CO_2 content found in arterial blood and venous blood of normal resting humans.

Note the low amount of CO_2 that is dissolved (orange trace) compared to that which can be carried by other means.

Carbon dioxide transport

- CO_2 is converted to HCO_3^- and is released into the plasma via an antiport in the red cell membrane in exchange for Cl^-
- Passes from the plasma to the lungs.
- Deoxy-hemoglobin is a stronger base than is oxyhemoglobin.
- It therefore binds additional protons and promotes the formation of HCO_3^- from CO_2 in the peripheral tissues.

Carbon dioxide transport

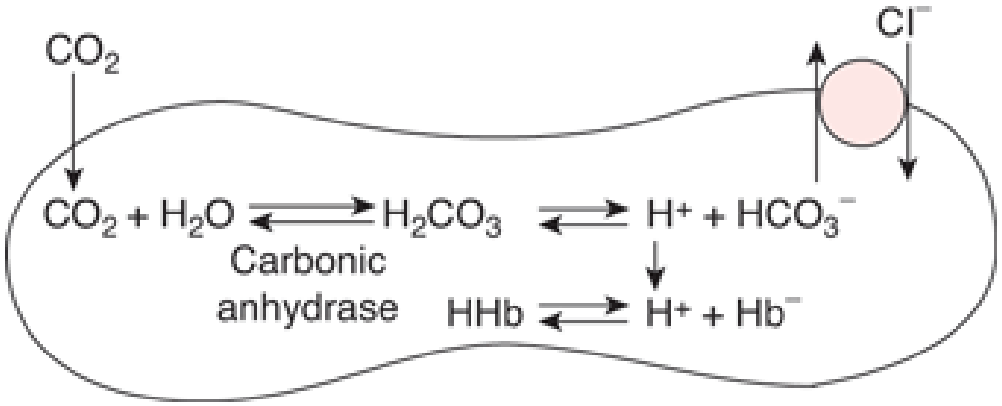
- In the lung, deoxy-hemoglobin is oxygenated, causing a release of protons.
- This shifts the HCO_3^-/ CO_2 equilibrium to the left, promoting CO_2 release.
- In the erythrocyte, the equilibrium is catalyzed by carbonic anydrase.

Carbon dioxide transport

- O_2 binding, then, is regulated by the pH.
- High CO_2 concentrations lead to elevated numbers of protons, reducing the affinity of hemoglobin for O_2, promoting O_2 release.

- Myoglobin does not release O_2 until $pO_2<20$ mmHg.
- Myogoblin does not have a quartenary structure

Gas transport



Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

Fig. 36-6 Accessed 03/01/2010