Regulatory Physiology course

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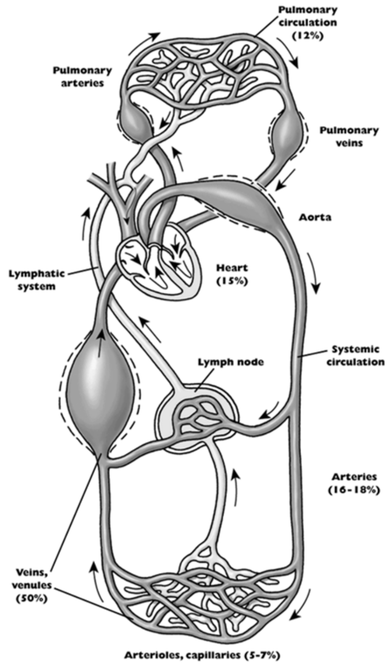
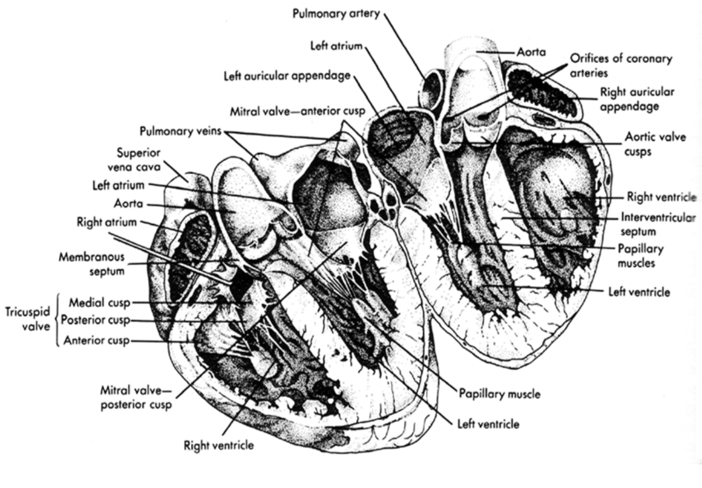
Circulation

Mammalian circulatory system



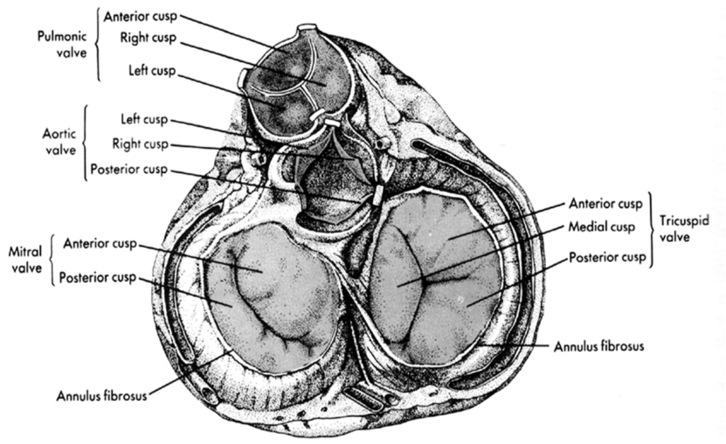
Eckert: Animal Physiology, W.H.Freeman and Co., N.Y.,2000, Fig. 12-3.

Human heart



Berne and Levy, Mosby Year Book Inc, 1993, Fig. 24-10

Valves in the heart

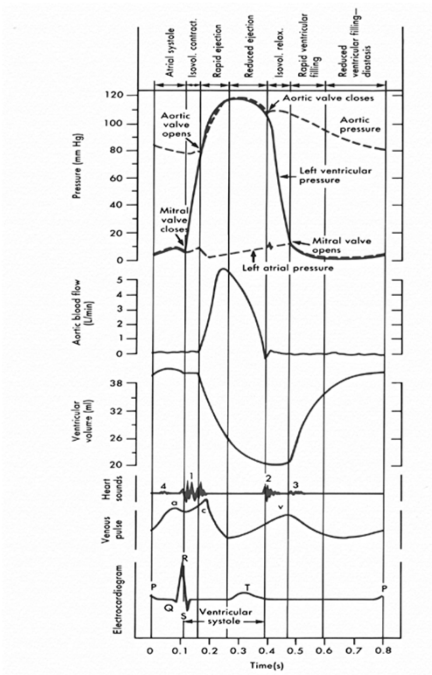


Berne and Levy, Mosby Year Book Inc, 1993, Fig. 24-11

Electrical activity of the heart

- vertebrate heart is miogenic – see Aztec rituals
- principal pacemaker: sinoatrial node
- 2x8 mm, built up by modified muscle cells
- AP is followed by slow hypopolarization – hyperpolarization activated mixed channels (Na^+, Ca^{++}) and K^+ inactivation
- NA and ACh changes the pacemaker potential in different directions through cAMP effecting the hyperpolarization activated channel
- in the atrium – rudimentary conduction system
- AV-node, 22x10x3 mm, in the interatrial septum
- bundle of His, bundle branches (Tawara), Purkinje fibers
- SA, AV nodes 0.02-0.1 m/s, muscle cell 0.3-1 m/s, specialized fibers 1-4 m/s (70-80 vs. 10-15 μ)

Cardiac cycle



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Regulation of cardiac output I.

- cardiac output = heart rate x stroke volume
- heart rate is regulated mainly by the autonomic nervous system
- stroke volume depends on the myocardial performance that in turn depends on intrinsic and extrinsic factors

- heart rate at rest is about 70/minute
- during sleep it is less by 10-20, in children and small animals it can be much higher (hummingbird)
- emotional excitation, exercise: 120-150
- parasympathetic inhibition dominates in rest arriving through vagal nerves – ganglion on the surface or in the wall of the heart
- asymmetric: right - SA, left - AV
- acting through muscarinic receptors
- beat-to-beat regulation – fast elimination

Regulation of cardiac output II.

- sympathetic innervation: lower 1-2 cervical, upper 5-6 dorsal segments
- relay in stellate ganglion
- beta adrenergic effect through cAMP - positive chronotropic, inotropic, dromotropic, batmotropic effects
- slow effect, slow elimination
- asymmetric innervation: right - frequency, left – strength of contraction
- other effects:
  - baroceptor reflex
  - respiratory sinus arrhythmia: rate increases during inspiration, decreases during expiration
    - vagal outflow decreases during inspiration because of the increased activation of stretch receptors
    - Bainbridge-reflex: increased filling of the heart (preload) due to lower pressure in the chest increases heart rate

Myocardial performance

- intrinsic factors: Starling´s law of the heart, or the Frank-Starling mechanism - 1914
- myocardial performance increases with preload length of skeletal muscles is optimal at rest, length of heart muscles optimal when stretched
- increased preload:
  - first the heart cannot pump out the increased venous volume – end-systolic volume increases
  - larger end-diastolic volume – stronger contraction – new equilibrium, increased volume is pumped out
- increased peripheral resistance:
  - first less blood can flow out of the aorta against the increased resistance – pressure increases – heart cannot pump the same volume against this - end-systolic volume increases
  - larger end-diastolic volume – stronger contraction – new equilibrium, the original volume is pumped out
- extrinsic factors: most importantly sympathetic effect – strength of contraction increases

The arterial system

- large volume, distensible wall, terminated by a large resistance - “Windkessel”
- punctured tire, Scotch pipe, etc.
- small variation in pressure, continuous flow
- terms: systolic/diastolic pressure, pulse pressure, mean arterial pressure
- mean arterial pressure depends on the blood volume in the arterial system and on the distensibility of the walls of the arteries
- pulse pressure depends on stroke volume and compliance
- heart copes with increased venous return and increased peripheral resistance through the arterial system

Microcirculation I.

- in most tissues cells are less than 3-4-cells distance from the nearest capillary
- length 1 mm, diameter 3-10 μ
- arteriole - metarteriole - precapillary sphincter - capillary - pericytes
- arteriovenous anastomosis (shunt)
- nutritional and non-nutritional circulation (thermoregulation) – rat’s tail, rabbit’s ear
- growth of capillaries depends on demand – babies born before term are put into incubators – upon removal, lens are invaded by capillaries, retina damaged - blindness
- capillary permeability depends on location (function)
- easy penetration for lipid soluble substances
- for hydrophilic ones it depends on capillary type

Microcirculation II.

- **continuous capillary**
  - continuous basal membrane, gaps of 4 nm, 7 nm pinocytotic vesicles
  - muscle, nervous tissue, lung, connective tissue, exocrine glands
- **fenestrated capillary**
  - continuous basal membrane, pores
  - everything can penetrate, except proteins and blood cells
  - kidney, gut, endocrine glands
- **sinusoidal capillary**
  - large paracellular gaps crossing through the basal membrane
  - liver, bone marrow, lymph nodes, adrenal cortex
- **hydrostatic pressure difference - filtration (2% out, 85% back) – exchange of materials**
- **filtration - reabsorption – Starling's hypothesis**
- **edema: gravidity, tight socks, heart failure, starving, inflammation, elephantiasis**

Regulation of peripheral circulation

- **central and local regulation – location-, and time-dependent**
- **target: arteriole, metarteriole, sphincter muscles**

- **central regulation**
  - sympathetic innervation: strong, long-term vasoconstriction – single-unit smooth muscle cells without Na^+-channels
  - parasympathetic effect e.g. on saliva glands is indirect (bradykinin)

- **local regulation**
  - basal miogenic tone – smooth muscles contract, when stretched; blood flow remains constant (kidney, brain)
  - metabolic regulation – intense activity: accumulation of metabolites, i.e. CO_2, adenosine

Venous system

- veins have thin-walls and large volume – capacity vessels
- maximal pressure is about 11 mmHg, but contains half of the blood volume
- effect of gravitation: U-shaped tube, pressure difference is the same standing and laying – hydrostatic pressure is huge at the turn
- role of the muscle pump and the valves
- inspiration helps venous return – negative pressure
- Valsalva's maneuver; in trumpet players - pressure can be around 100-400 mmHg
- thrombus and embolus
- venomotor tone – standing in attention, fighter pilots, circulatory shock, returning of astronauts
- jumping out of bed - 3-800 ml displaced into legs – cardiac output decreases by 2 l

Central regulation I.

- regulator neurons are in the medulla (formerly: pressor and depressor centers) – that is why any increase in brain volume can be fatal
- input: reflex zones, direct CO_2, H^+ effect
- output: vagal nerve and the sympathetic nervous system – tonic activity at rest: slow heart beat, vasoconstriction in muscle, skin, intestines
- chemo-, and mechanoreceptors – information for the control of breathing and for the long-term regulation
- part of the receptors found in compact zones, they induce circumscribed reflexes
- receptors in the high-pressure system (baroceptors): carotid and aortic sinuses – „buffer nerves" carry the information to the n. tractus solitarius (belongs to the caudal cell group)

Central regulation II.

- receptors in the low-pressure system (atrial volume receptors): at the orifice of the v. cavae and the v. pulmonalis, as well as at the tip of the ventricles
- activated by volume increase, effect similar to baroceptor effect, but long-term responses are more important – production of ADH (vasopressin) and aldosterone decreases
- special receptor group in the atrium: Bainbridge -reflex
- chemoreceptors: glomus caroticum and aorticum activated by CO_2 increase and O_2 decrease (below 60 mmHg) – latter is more important as CO_2 acts also directly in the medulla – heart frequency decreases, vasoconstriction
- „sleeping pill" for native people (and biology students): pressing the sinus caroticum

Respiration

Anatomy of the lung I.

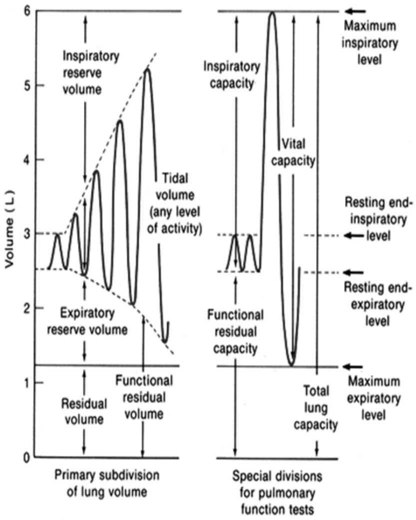
- 2 halves, 900-1000 g together, right half is somewhat larger, 40-50 % blood
- airways:
  - trachea – bronchi – bronchioles – alveolar ducts - alveoli
  - branching is always fork-like, cross-sectional area of the two „child" bronchi is always larger - 22-23 branching
  - trachea and large bronchi (up to 1 mm) are supported by C-shaped, or irregular plates of cartilage
  - below 1 mm – bronchioles, connective tissue and muscle
  - function: warming, saturation with water vapor (expiration in cold, dehydration in dry air)
- exchange of gases occurs in alveolar duct-alveolus (300 million) - surface 50-100 m^2
- during evolution more and more septum in this part – surface increases
- emphysema – heavy smokers, trumpet players, glass blowers
- barrier: endothelium, epithelia, fibers

Anatomy of the lung II.

- lungs are covered by the parietal and visceral pleurae
- thin fluid layer (20 μ) couples the pleurae (pleuritis, pneumothorax, treatment of tuberculosis)
- the lung has a collapsing tendency (surface tension + elastic fibers)
- surfactant in alveoli (produced by epithelial cells: dipalmitoyl-phosphatidylcholine)
- respiratory muscles:
  - inspiration active, expiration passive normally
  - intercostal muscles, T1-11, external: inspiration, internal: expiration
  - diaphragm, C3-5 (n. phrenicus), at rest 1-2 cm movement: 500 ml, it can be 10 cm – damage of the spinal chord – jumping into shallow water!
  - abdominal wall (birthday candles, trumpet, always important above 40/minute)
  - accessory muscles – help inspiration in case of dyspnea

Lung volumes

- lung volumes can be measured by spirometers - spirogram
- anatomical and physiological dead space
- in swans and giraffes it is huge, large tidal volume
- tidal volume (500 ml) – anatomical dead space (150 ml) = 350 ml dilutes functional residual volume: steady O_2 concentration
- total ventilation: 14 x 350 ml = 4900 ml/minute



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Gas concentrations

	pO_2 (mmHg)	pO_2 (%)	pCO_2 (mmHg)	pCO_2 (%)
dry air	160	21.0	0.3	0.04
wet air	150	19.7	0.3	0.04
alveolus	102*	13.4	40	5.3
pulmonary artery	40	5.3	46	6.1
pulmonary vein	100**	13.2	40	5.3

atmospheric pressure: 760 mmHg
partial pressure of water vapor: 47 mmHg

* effect of O_2 consumption, and anatomical dead space
** bronchiolar veins join here

Transport of O_2

- physical solubility of O_2 is very low – 0.3/100 ml
- hemoglobin increases O_2 solubility 70-fold - 20 ml/100 ml
- oxyhemoglobin bright red, deoxyhemoglobin dark red-purple – see difference of venous and capillary blood during blood tests
- affinity is characterized by half-saturation: Hgb: 30 mmHg, myoglobin 5 mmHg
- saturation of Hgb at 100 mmHg 97.4%, at 70 mmHg 94.1% - almost no change
- affinity is decreased by:
  - increased temperature – active tissues are warmer
  - decrease of pH, increase of CO_2 - applies to active tissues and organs
    - Bohr's-effect: H^+ uptake - affinity decreases, on the other hand uptake of O_2 increases acidity Haldane's-effect

Transport of CO_2

- CO_2 is more soluble physically, but it also reacts with water
- transport mainly in the form of HCO_3^- (88-90%), some as CO_2, H_2CO_3, or CO_3^{2-}, some attached to proteins (carbamino)
- most of the released CO_2 from HCO_3^- (80%)
- CO_2 - H_2CO_3 transformation is slow (several seconds) – carbonic anhydrase enzyme inside the red blood cell – speeds up reaction
- H+ ion is taken up by the deoxyhemoglobin that is weaker acid than the oxyhemoglobin
- HCO3- is exchanged for Cl^- - facilitated diffusion with antiporter - Hamburger-shift
- opposite process in the lungs

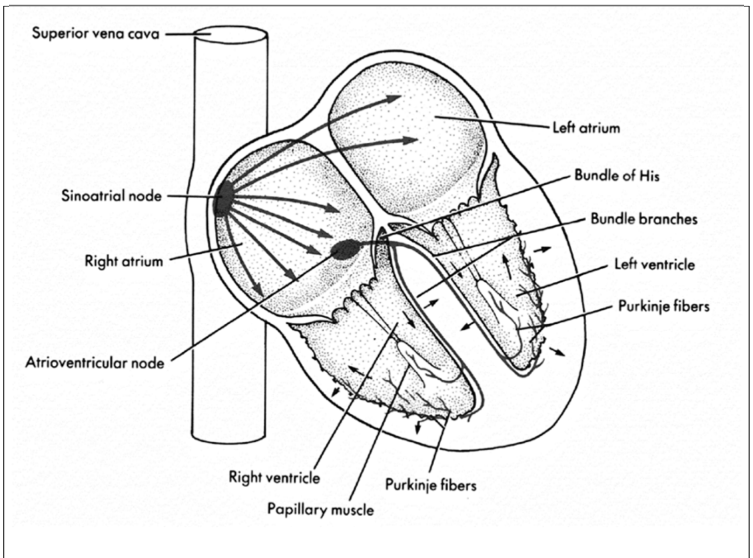
Regulation of breathing I.

- mammals use 5-10% of all energy consumption for the perfusion and ventilation of the lung
- closely matched processes to avoid wasted perfusion or ventilation
- alveolar hypoxia - local vasoconstriction
- in high mountains low O_2, general constriction – increased resistance – higher blood pressure in pulmonary artery – lung edema
- central regulation: inspiratory and expiratory neurons in the medulla – other functions as well, thus not a center
  - dorsomedial neurons, close to the nucl. tractus solitarius: inspiratory neurons
  - ventrolateral expiratory neurons
- descending effects: talking, singing, crying, laughing, etc.

Regulation of breathing II.

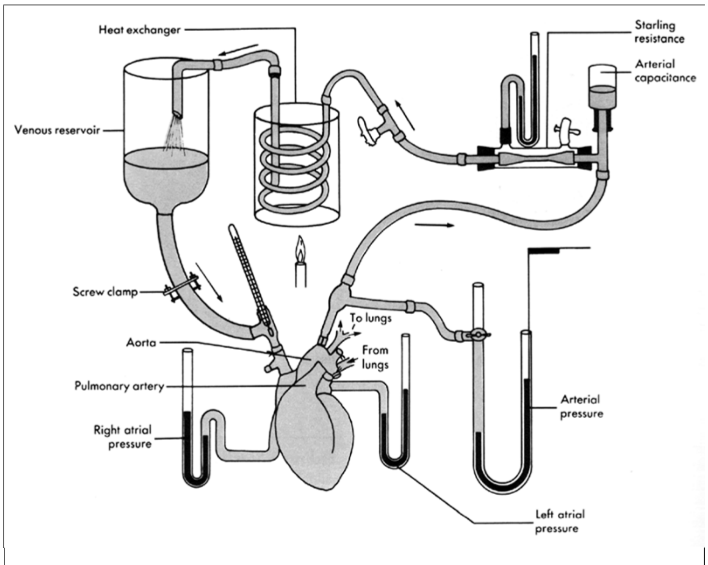
- output: motoneurons innervating the diaphragm and the intercostal muscles
- trigger for inspiration:
  - increase of CO_2 and H^+ - central receptors; no breathing below a certain CO_2 threshold
  - decrease of O_2 , increase of CO_2 and H^+ - glomus caroticum and aorticum
  - in terrestrial animals CO_2 is regulated, in aquatic animals O_2 – its concentration changes more; if O_2 exchange is sufficient, than that of the more soluble CO_2 should be also OK
- trigger for expiration: stretch receptors in the lungs - Hering-Breuer reflex
- these information serve not only gas exchange and pH regulation, but such reflexes as swallowing, coughing, etc.

Conduction system of the heart



Berne and Levy, Mosby Year Book Inc, 1993, Fig. 23-25

Heart-lung preparation



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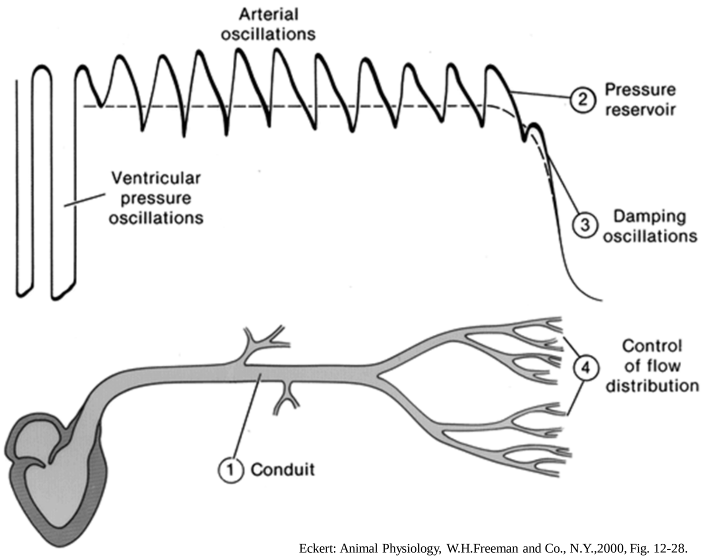
Windkessel function



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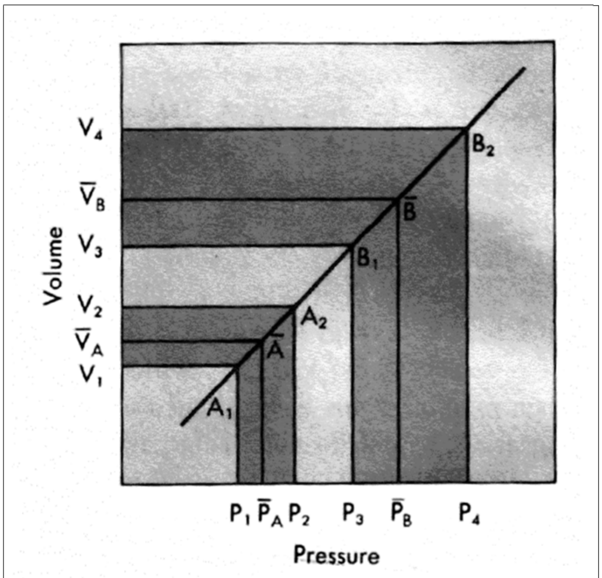
Effect of increased venous return



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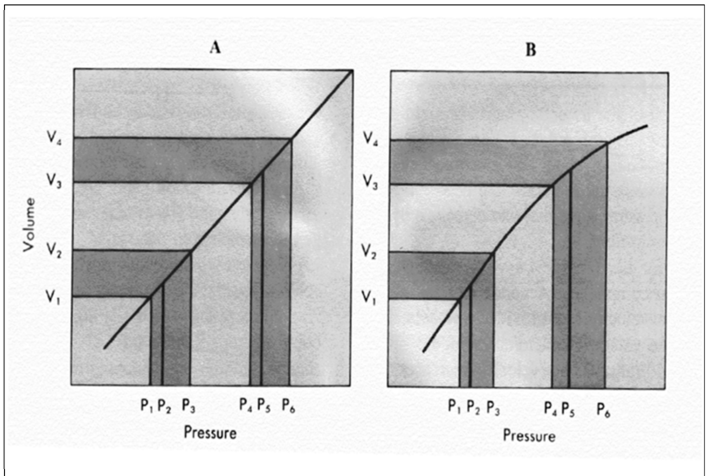
Effect of increased resistance



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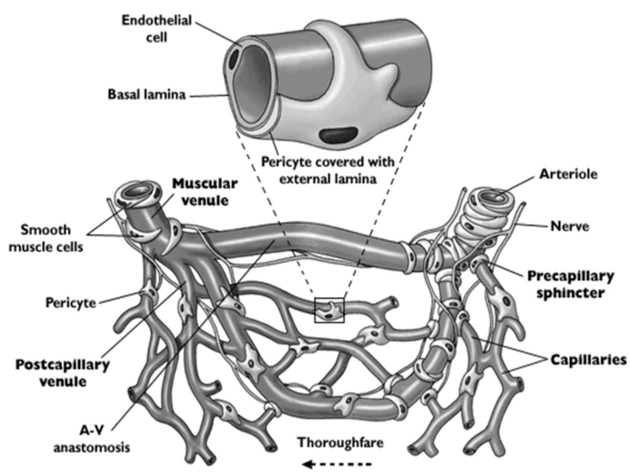
Microcirculation



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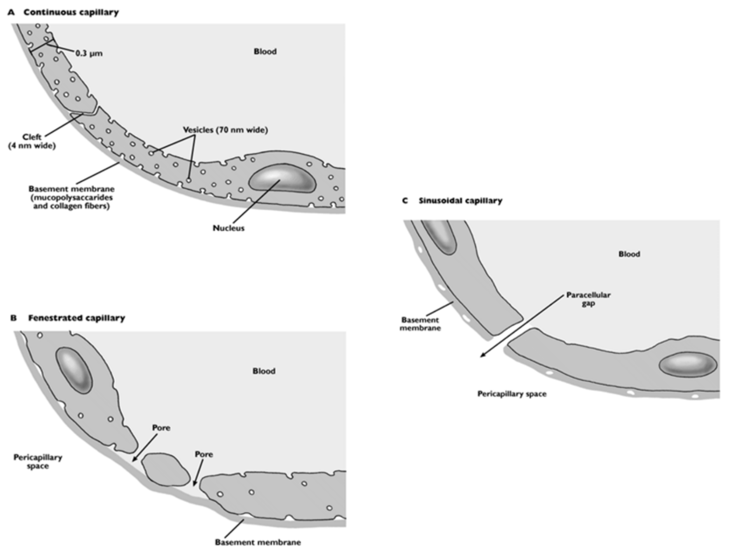
Types of capillaries



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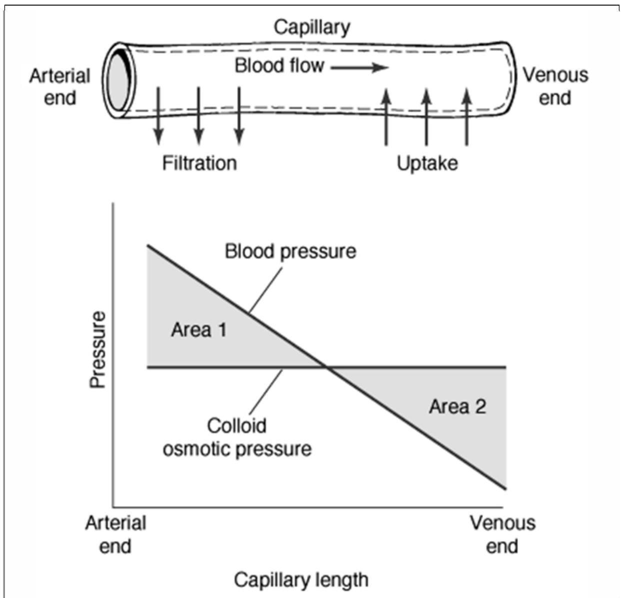
Starling's hypothesis



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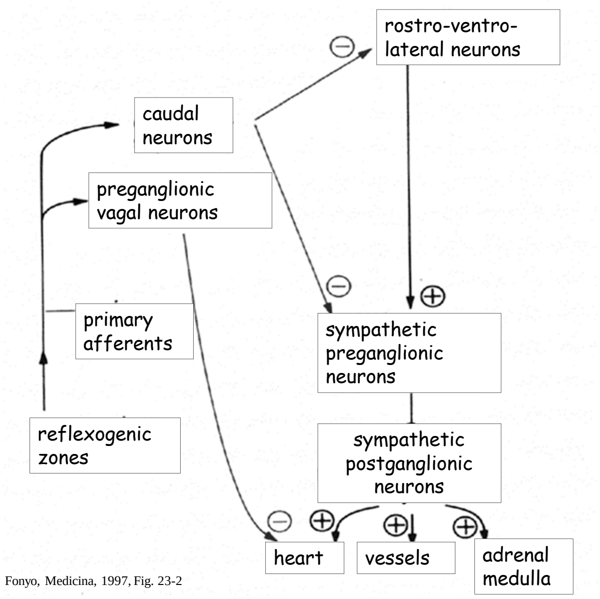
Elephantiasis I.

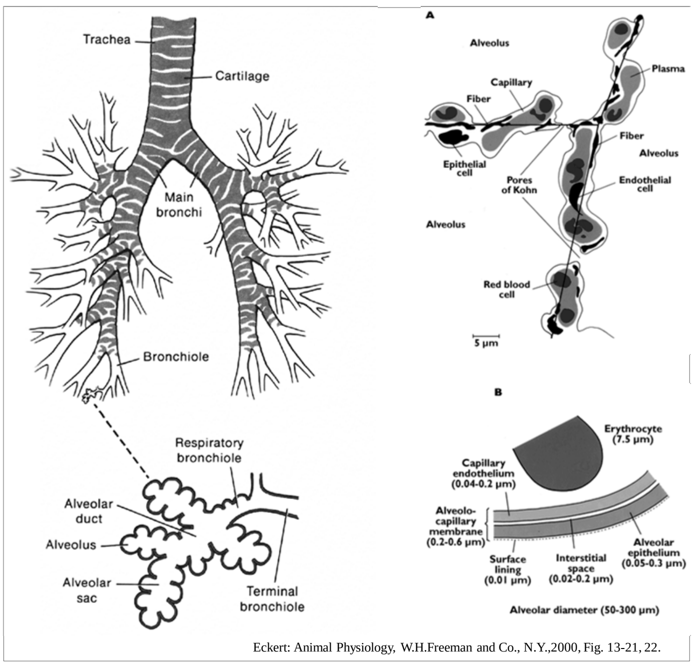
Elephantiasis II.

Regulation of circulation



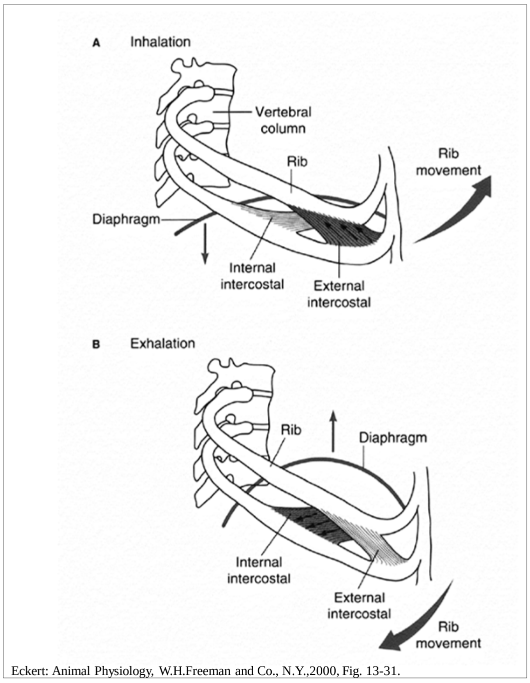
Fonyo, Medicina, 1997, Fig. 23-2

The mammalian lung



Eckert: Animal Physiology, W.H.Freeman and Co., N.Y.,2000, Fig. 13-21, 22.

Respiratory muscles



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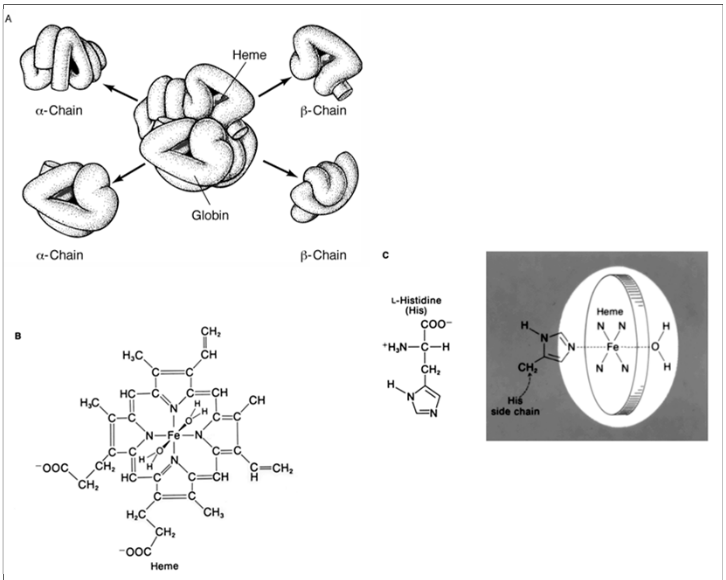
Structure of hemoglobin



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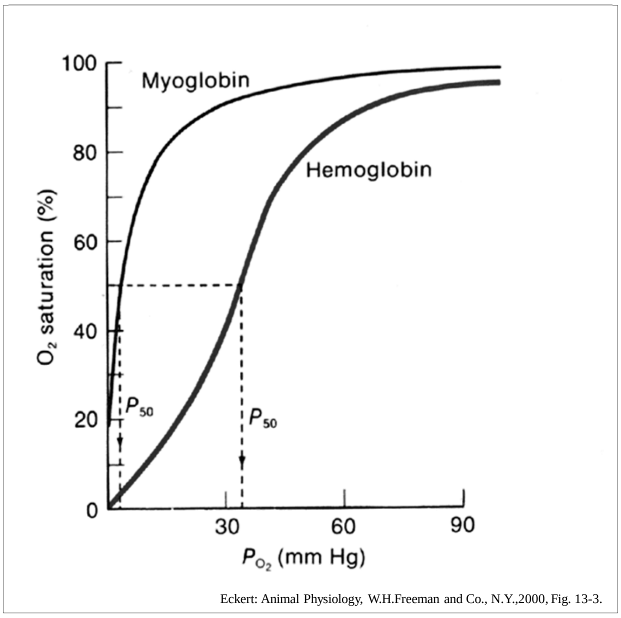
Saturation of hemoglobin



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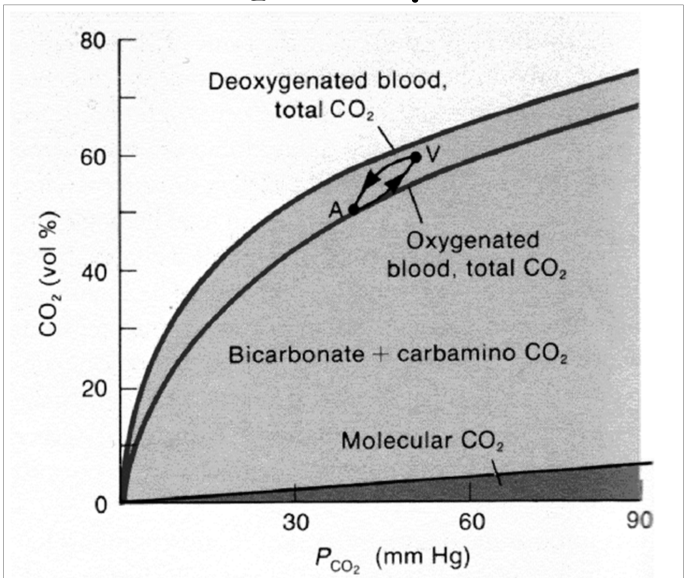
CO_2 transport



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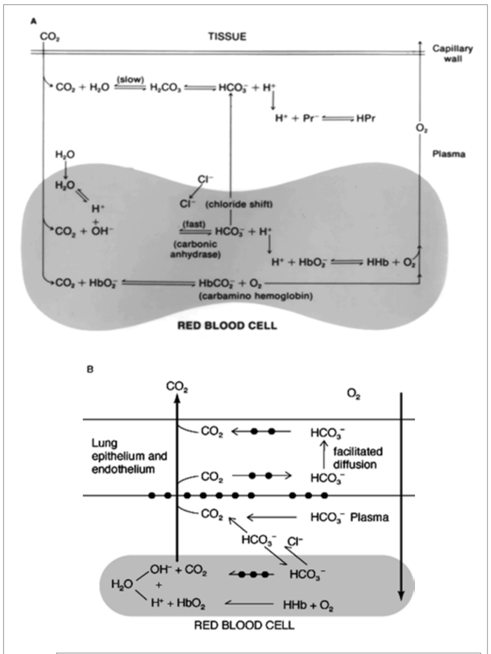
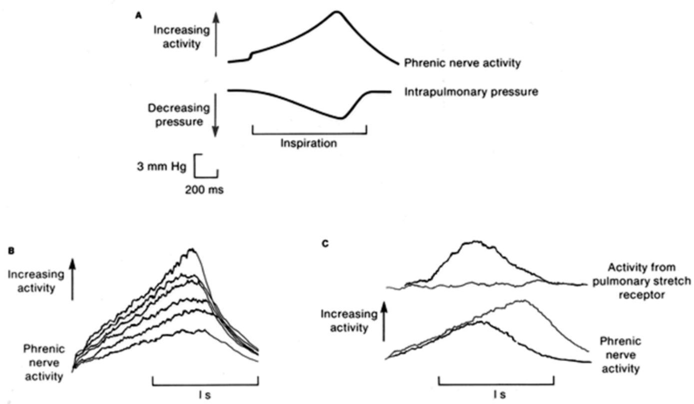
Red blood cells in CO_2 transport



Animal Physiology, W.H.Freeman and Co., N.Y.,2000, Fig. 13-11.

Activity of the phrenic nerve



Eckert: Animal Physiology, W.H.Freeman and Co., N.Y.,2000, Fig. 13-49.