Overview

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Anatomy and Physiology of the Lung

The lung is the human body's respiratory organ, responsible for supply of all tissues and organs with vital oxygen (O_2) and for disposal of carbon dioxide (CO_2), the end product of internal respiration and of several metabolic pathways.

The lung, located in the upper thorax, consists of two parts, the right lung further comprising three lobes and the left lung comprising two. Left and right lungs are individually surrounded by a pleural cavity, which consists of two pleurae and the cavity in between. The parietal pleura lines the rib cage, whereas the visceral pleura covers the surface of the lungs. The space between the pleurae is filled with pleural fluid. The pleurae are critically important for breathing motions (see below).

The lungs represent the functional anatomical part of the respiratory system consisting of the upper and lower respiratory tract, also called upper and lower airways (Fig. 1a). The upper airways comprise nasal cavity, pharynx, and larynx. Their role is to warm and moisten the inhaled air and to protect from noxious agents, mainly filtering them via the nasal turbinates. The nasal cavity also allows smelling. The pharynx is part of both digestive and respiratory systems (see chapter "Overview" under the part "Gastrointestinal tract") and offers an alternate route of air supply via the mouth. The larynx contains the vocal cords (vocal folds), necessary for human speech. It continues into the lower respiratory tract.

The lower respiratory tract consists of the trachea and the lungs. The trachea bifurcates first into primary bronchi, subsequently into bronchioles, and finally into terminal and respiratory bronchioles, which ultimately give rise to alveolar ductus and sacs (Fig. 1b). In total, the lower respiratory tract branches up to 20 times.

The main function of the lung is to allow gas exchange with the blood, which takes place in respiratory bronchioles and subsequent lung regions and is most pronounced in the alveoli.

On a cellular level, the wall of the conducting airways (trachea, bronchia, and bronchioles) consists of mucosa, submucosa, and adventitia. The mucosa contains a mucus layer (see below) and pseudostratified columnar, ciliated epithelium with mucus-secreting goblet cells, columnar cells, and basal cells. Underneath, the lamina propria is located, a layer of connective tissue, which harbors large amounts of elastin (Fig. 1c). The submucosa contains submucosal glands, which

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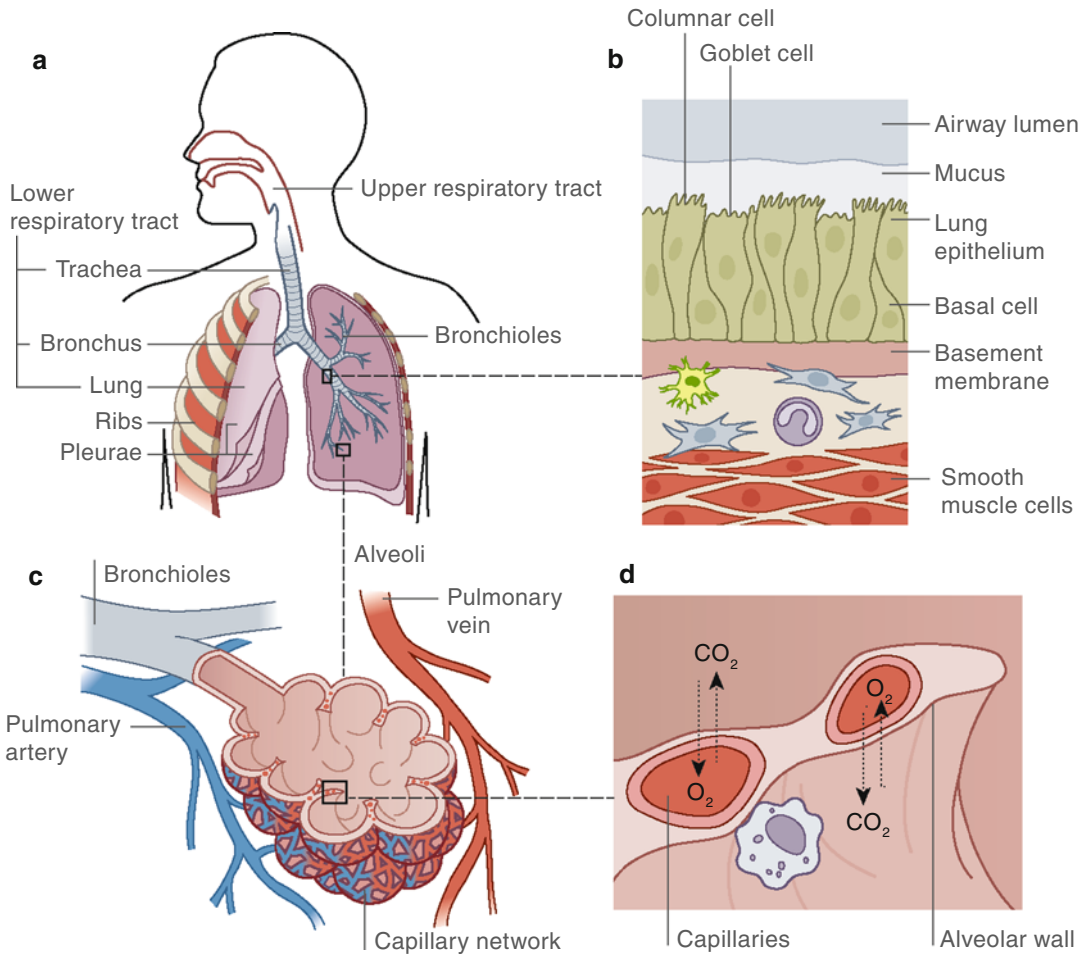

Fig. 1 Anatomy of the respiratory system. (**a**): Macroscopic overview of upper and lower respiratory tract. (**b**): Magnification of a section through a bronchial wall showing the mucosa and the underlying tunica muscularis. In the mucosa, basal, ciliated columnar cells, and mucus-secreting goblet cells are shown. A submucosal gland is not included due to space constraints albeit the glands are present in bronchia. Whereas goblet cells, glands, and elastic fibers decrease in number concomitant with the length of the cilia towards the smaller airways, the muscle layer transiently increases. (**c**): Anatomy of an alveolar sack showing the approximate arrangement of individual alveoli and the surrounding dense capillary network. Note that in the lung vasculature, arteries carry oxygen-deficient blood, whereas veins carry oxygen-rich blood (shown in *blue* and *red*, respectively). (**d**): Detailed view of a section through an alveolar wall showing thin respiratory surface, movement of gases, and an alveolar macrophage

are connected to the mucosa and also contribute to mucus secretion. In addition, this submucosal layer includes fibroblasts, dendritic cells, and neutrophils, the latter two of which participate in host defense. The adventitia, a fibroelastic connective tissue layer, confines the airways towards the outside. C-shaped rings of hyaline cartilage provide a semirigid outside support to prevent collapse of the airway during inspiration.

As the bronchi decrease in diameter, a gradual transition in the architecture of the epithelium can be observed. The epithelial layer transforms from pseudostratified, columnar epithelium towards a ciliated, simple columnar and finally simple cuboidal epithelium (the shape of a typical respiratory epithelium). Concomitantly, a gradual decrease in the number of goblet cells as well as submucosal glands is seen, whereas Clara

cells emerge. Clara cells, although their function is not completely understood, are thought to play a role in the secretion of surfactant proteins (see below). Furthermore, the amount of elastic tissue decreases and a muscularis mucosae begins to take shape between the lamina propria and the submucosa. The cartilage skeleton is also absent from the bronchioles and smaller airways.

Alveoli (Fig. 1c, d) feature an extremely thin wall of specialized respiratory epithelium to facilitate gas exchange. Most of the alveolar epithelium is covered by small, squamous-like type I pneumocytes. It also includes larger cuboidal type II pneumocytes that produce surfactant (see below) and are thought to be stem cells for both types of pneumocytes. Alveolar macrophages in the alveolar lumen scavenge particulate matter and microorganisms.

In order to perform its function, the lung is extensively vascularized; the alveoli are surrounded by a dense capillary network (Fig. 1c) that can be compared to a columnar hallway. Due to its potential volume and sophisticated regulation, the pulmonary capillaries can act as a large blood reservoir.

The ~300 mio alveoli, each 0.2–0.3 mm in diameter, sum up to a functional area of gas exchange of up to 140 m^2. The alveolar wall, consisting of alveolar epithelium, minimal interstitium, and endothelium (Fig. 1d), totals to less than 1 µm.

Mechanism of Breathing

Breathing can be initiated by two similar actions, upward rib movement (chest breathing) or downward movement of the diaphragm (abdominal breathing). As the outer pleura is physically connected to both, it will follow the movement passively. Consequently, during inspiration, the existing low pressure (below atmospheric pressure) in the intrapleural cavity is further decreased and will cause the inner pleura and eventually the lung tissue to follow (as interpleural fluid cannot be expanded). This effectively increases the lung volume and results in an inward movement of air. Puncturing of the pleura is extremely dangerous as lack of the negative intrapleural pressure effectively hinders lung expansion and thus inhalation (pneumothorax). In contrast, exhalation occurs mainly passively as the lung has the intrinsic tendency to retract due to surface tension in the alveoli and distension of its elastic fibers in the lung tissue. The total lung capacity can amount up to 6 l of air. Yet, even after maximal exhalation, a residual volume of 1.25 l will remain, reflecting the volume of the conducting airways, which do not participate in gas exchange [1].

Any change leading to an obstruction of the airways, like those in asthma and COPD (see chapters "Asthma" and "COPD") will have detrimental effects. Ventilation deficiencies can be divided into restrictive and obstructive disorders. The former describes a disturbed expansion of the airways (accompanied by reduced total capacity), whereas the latter describes difficulties in conduction and increased inflow or outflow resistance.

Ventilation, diffusion, and convection (blood flow) are of central importance to gas exchange, meaning a constant delivery of fresh air, passive gas exchange with the blood, and ongoing propulsion of the oxygenated blood to keep a stable gradient over the alveolar membrane (see below) [2].

It should be noted that gas exchange with the blood never reaches complete equilibration. Whereas the inhaled gas mixture contains 21 % O_2 and around 0.05 % CO_2, the exhaled gas mixture still contains 14–16 % O_2 and around 4 % CO_2.

The respiratory quotient is the relation between exhaled CO_2 and inhaled consumed O_2 (CO_2/O_2). It is indicative of the primary metabolic fuel (carbohydrates or fatty acids) at the moment of measurement. As fatty acids require more oxygen for complete oxidation of a single carbon atom, preferential metabolism of fatty acids decreases the respiratory quotient [3].

Lung-Specific Metabolic/Molecular Pathways and Processes

Mucus Production

Mucus is secreted from goblet cells and submucosal glands in the bronchial epithelium as a viscous fluid containing mucins, water, ions, and

antimicrobial substances such as immunoglobulin A (IgA, see also chapter "Overview" under the part "Immune system") and lysozyme. Mucins are heavily glycosylated proteins of high molecular weight.

Mucus is essential to trap inhaled particles and microorganisms and prevent them from reaching and damaging the respiratory epithelium (Fig. 1). Mucus containing bacteria, debris, and inflammatory cells and products is referred to as phlegm. Rhythmic upward propulsion by the cilia on the bronchial epithelium transports mucus and captured particles towards the larynx, where most of it is swallowed or expectorated. Cough is a physiological reflex that aids to eject particles and mucus or phlegm that would otherwise damage or block the airways. Consequently, damage to cilia causes accumulation of mucus and increased ventilatory resistance resulting in obstructive pathology.

Surfactant Production and Function

Alveoli are subject to dramatic surface tension resulting from the attraction between the molecules of the fluid film that covers the alveolar cell surface. This force supports exhalation but would drive all liquids within the airways to retract, the lung to collapse, and the alveoli to merge into larger vesicles (prohibiting functional gas exchange). However, the stability of the alveoli is ensured by a surface-active agent (surfactant) decreasing surface tension and lubricating the alveolar epithelium. Surfactant is a mixture of proteins and lipids, mainly consisting of lecithin derivatives. Its main lipid components are dipalmitoylphosphatidylcholine (DPPC) molecules that tend to repel each other, thus counteracting the surface tension of the fluid film on the alveolar cell surface; surfactant also contains ~40 % of other phospholipids and ~5 % surfactant-associated proteins and is secreted by type II alveolar epithelial cells.

Gas Exchange

Gas exchange across the alveolar wall occurs by passive diffusion; a process that can be described by Fick's law of diffusion. According to the law, a large exchange area, short diffusion distance, and a constant gradient of substances (across the membrane) facilitate diffusion. All these prerequisites are provided by the unique setup of the alveoli (Fig. 1c, d). Nature of the gas also influences diffusion rate, with CO_2 diffusing more freely over the alveolar membrane than O_2.

The substance gradient is expressed by the partial pressure of gases (pO_2, pCO_2) in the alveolar lumen and in the blood. In order to provide a constant gradient that is as steep as possible, constant and coordinated ventilation and perfusion are of utmost importance. The ratio between ventilation and perfusion, called the ventilation-perfusion coefficient, is relatively constant (0.8–1) among healthy subjects to secure a proper partial pressure gradient and thus gas exchange but can change significantly in some pathologies, e.g., when pulmonary shunts are created by perfusion of non-ventilated alveoli (see chapter "Community-acquired pneumonia").

Hemoglobin helps to maintain the gradient by binding of O_2 and thus effectively removing it from the pool of free O_2. Interestingly, the binding capacity of hemoglobin for O_2 is dependent on pO_2, with the high partial pressure in the lungs increasing its binding affinity (see chapter "Overview" under the part "Blood"). Consequently, the contact time of 0.3–0.7 s between an individual erythrocyte and the alveolar wall is already sufficient for saturation of hemoglobin with O_2.

Outside-In: Metabolites of Other Tissues Affecting the Lung

Regulation of Breathing

Regulation of breathing is mediated primarily via the sympathetic and parasympathetic nervous system. Sympathetic activity causes relaxation of smooth muscle cells and thus bronchodilation aiding in inspiration. Parasympathetic activity can constrict the airways, a feature used during exhalation. Overactivation of the parasympathicus often causes pathological constriction.

However, constriction is more commonly caused by local inflammation, as occurs during asthma and COPD (see chapters "Asthma" and "COPD", respectively).

The central nervous control center of breathing is represented by neural oscillators located in the medulla oblongata, called the ventral respiratory group. These neurons trigger breathing autonomously but are adjustable and react to systemic need and metabolism (as indicated by the blood gas status). Detection of the blood gas status occurs mainly by arterial chemosensors located in the carotid artery (called glomus caroticum) and also by central chemoception in the brainstem. Among the three prime indicators triggering breathing (i.e., reduced pO_2, increased pCO_2, and increased H^+/decreased pH), increased pCO_2 is the most important signal. There is an almost linear correlation between pCO_2 and breathing induction. At high concentrations, however, CO_2 acts narcotic and may reduce breathing.

The tight chemosensation of pCO_2 has important metabolic implications. Upon hyperventilation (increased/frequent breathing), pCO_2 can be drastically reduced, reducing or even completely inhibiting further breathing. The latter can lead to hypoxemia (reduced pO_2 in the blood) and might remain undetected until unconsciousness occurs. Additionally, hypoxemia-induced breathing lowers pCO_2, which will in turn decrease breathing activity more efficiently than required based on pO_2 status. Dramatic alterations of blood gases can occur in divers or at high altitudes [4, 5].

Increased H^+ is compensated by hyperventilation, causing an increased exhalation of CO_2. By this mechanism, the lung is a major regulator of blood pH along with the kidneys (see below). Again, the expected response to high H^+ is stymied by the "more effective" response to altered pCO_2.

Breathing and Pathologies

Observation of breathing patterns can hint at specific underlying pathologies and disturbances.

For example, in altitude sickness, reduced pO_2 in the atmosphere causes increased heart rate and deep and more frequent breathing (to incorporate sufficient O_2). However, this effectively lowers pCO_2 in the blood causing decreased breathing, which again causes hypoxemia, or even apnea (lack of breathing). The resulting periodic breathing pattern is known as Cheyne-Stokes breathing.

Decreased atmospheric pressure at high altitudes can cause pulmonary edema. If the intrapulmonary pressure is too low compared to the blood pressure, plasma fluid leaks into the alveoli. More frequently, left ventricular heart failure results in pulmonary edema, which is characterized by superficial breathing.

In contrast, hypercapnia (abnormally increased pCO_2 in the blood) and acidosis are characterized by extremely deep breathing called Kussmaul breathing (see below).

Breathing and Treatment

It should be noted that drug delivery via the lungs, e.g., using inhalation devices, offers great therapeutic potential, not only for treatment of asthma and COPD. Inhaled drug delivery harnesses immediate contact to mucosal surfaces and easy translocation to the blood across the alveolar membrane [6].

Inside-Out: Metabolites of the Lung Affecting Other Tissues

Function Under Extreme Conditions

Hypercapnia not only increases breathing but also causes arousal and initiates head turning during sleep. It can be caused by lung function deficits (as in several lung diseases), breathing depression, inhalation of increased concentrations of CO_2 (as in rebreathing), and long-term artificial respiration. It is often accompanied by respiratory acidosis due to the formation of carbonic acid (H_2CO_3) and subsequent dissociation to H^+ and bicarbonate (HCO_3^-).

Respiratory acidosis (blood pH <7.35) causes clinical symptoms, such as blue, cyanotic lips; increased heart rate (tachycardia); and pulmonary

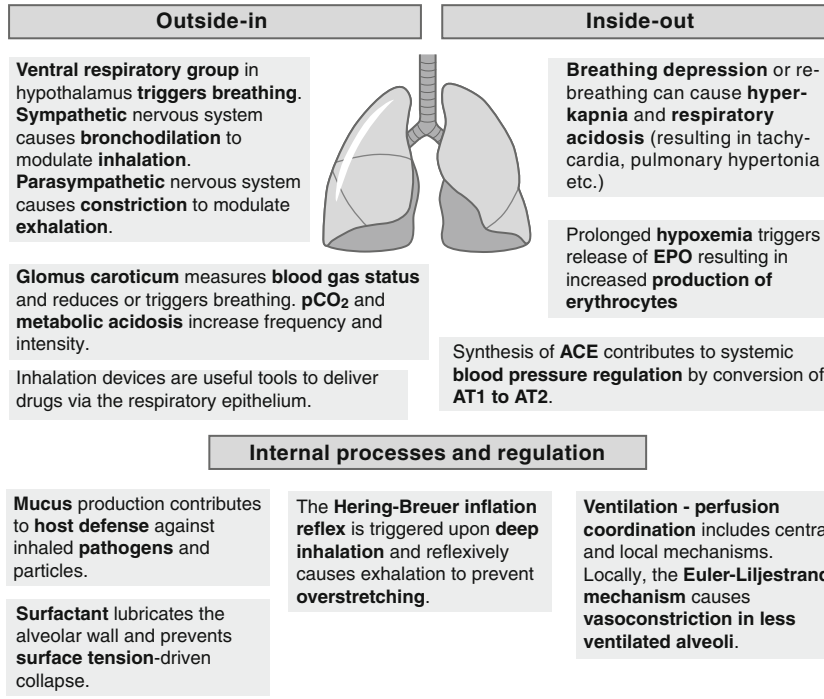

Fig. 2 Specific metabolism of the lung and interaction with other organs and tissues. pCO_2 partial pressure of CO_2 in the blood, *EPO* erythropoietin, *ACE* angiotensin-converting enzyme, *AT* angiotensin

hypertonia (Fig. 2). Respiratory acidosis is commonly corrected by H^+ excretion in the kidney (see chapter "Overview" under the part "Kidney").

Acidosis can also occur due to increased anaerobic glycolysis (causing increased lactic acid concentrations) and ketone body synthesis resulting in ketoacidosis (due to increased acetoacetic acid and 2-hydroxybutyric acid concentrations). This metabolic acidosis occurs during shock or, more commonly, deregulated diabetes (coma diabeticum, see chapter "Diabetes mellitus"). Other forms of metabolic acidosis originate from decreased H^+ excretion (as occurs in kidney disease, see chapter "Chronic kidney disease"), increased HCO_3^- excretion, or acid intoxication (e.g., by acetylsalicylic acid).

If acidosis exceeds the buffer capacity of the blood, it can be fatal. In general, metabolic deregulation is antagonized by respiratory mechanisms, and vice versa. Thus, severe metabolic acidosis is characterized by Kussmaul breathing, a deep and gasping breathing pattern, which is a sign of life-threatening conditions.

Prolonged reduced oxygen levels (hypoxemia) trigger release of erythropoietin (EPO) via hypoxia-inducible factor (HIF)-1α. This increases production of hemoglobin and thus facilitates oxygen transport (see chapter "Overview" under the part "Blood"), e.g., during adaptation to high altitudes [7].

Other Functions

Finally, the lung also performs functions different from gas exchange. For example, lung endothelium synthesizes angiotensin-converting enzyme (ACE) that converts angiotensin I to angiotensin II (Fig. 2). This conversion is of critical importance to blood pressure homeostasis (see chapters "Overview" under the part "Kidney" and Hypertension) and a protective role of ACE in the lung has been reported [8].

Coordination with Other Organs

The function of the lung needs to be coordinated with other organs in particular with the cardiovascular system. For example, increased breathing is only useful if heart rate and blood

convection are also increased. Coordination with sensory reactions, such as speech and cough reflex (see above), is also mandatory. These coordinating responses involve multiple centers in the CNS and are too complex to elaborate in this brief introduction [9].

Inside-In: Metabolites of the Lung Affecting Itself

Lung Perfusion and Usage of Alveoli

As mentioned above, the ventilation-perfusion coefficient is critical for gas exchange. Concomitantly, only ~50 % of alveolar capillaries are perfused at rest as only a similar amount of alveoli is ventilated. Increased oxygen demand increases perfusion and activates reserve capillaries. Simultaneously, breathing is intensified to ventilate corresponding alveoli (via central regulatory mechanisms). While standing, the base of the lung is much more perfused than the tips, due to a gradient in hydrostatic blood pressure.

Perfusion is also regulated locally, as less ventilated alveolar regions cause local vasoconstriction (called hypoxic pulmonary vasoconstriction) to prevent perfusion of non-ventilated alveoli and shunting of deoxygenated blood to the heart. This mechanism is known as the Euler-Liljestrand mechanism and is driven by local hypoxia (Fig. 2). Hypoxia is sensed by oxygen-sensitive potassium channels, which close and thus cause depolarization of smooth muscle cells leading to Ca^{2+} influx and vasoconstriction.

Reflexes and Internal Regulation

Several internal reflexes are directed at pulmonary protection. These originate from the lung and are mediated by the nucleus tractus solitarius in the CNS. A major mechanism is the Hering-Breuer inflation reflex, which is induced upon deep inhalation and aims to prevent overstretching of lung tissue. In reflexive manner, it triggers exhalation (Fig. 2). Another protective mechanism is the reflex induction of coughing in response to inhaled particles, fluids, or noxious gases.

Final Remarks

The lungs are critical regulators but also effectors of human metabolism, as they are both starting and end point of internal respiration. By supplying O_2 and removing CO_2, the lungs are implicated in virtually all metabolic pathways of which energy metabolism surely is the most influential. Due to the unique composition and organization of the conducting and respiratory tracts that permit its efficient function, the lung is also susceptible to both extrinsic and intrinsic pathologies. Microorganisms can easily enter with the airflow, and pathological disturbance of the delicate balance between ventilation, diffusion, and convection has an immediate and sometimes dramatic effect on respiratory function and associated metabolism.

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