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Structure and Function of the Respiratory System

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ABSTRACT

The atmosphere is a mixture of gases that surround any celestial body that has sufficient gravitational force to prevent the gases from escaping from their environment. At first probably it consisted of volcanic emanations with almost no oxygen. The appearance of oxygen in the atmosphere enabled aerobic life as we know it today. The original gill system of fish was replaced by lungs when oxygen dissolved in seawater was converted into the gaseous state of the atmosphere. The respiratory system developed and evolved over eons to serve its most ancient function: gas exchange. The structure of the respiratory system is designed to serve this function. Other functions subsequently emerged during evolutionary development. Cellular respiration, in the intimacy between the capillary and the cell, and external respiration are discussed to understand the architectural design serving this and other functions of the respiratory system.

Keywords: Oxygen, mitochondria, cellular respiration, external respiration, structure, function.

INTRODUCTION

The atmosphere as we know today is approximately 4.5 billion years old. At first it consisted of volcanic emanations, however current volcanic eruptions are a mixture of water vapor, carbon dioxide (CO_2), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), hydrogen, ozone, methane, krypton and xenon, but without oxygen. The first living organisms that appeared on Earth were essentially anaerobic. If this is the same mixture that existed in the early atmosphere, several processes must have occurred to produce what we have today, basically to acquire the oxygen that constitutes 21% of breathable air (1). One of these processes was condensation. As the planet cooled it is possible and probable that some of the volcanic water vapor condensed passing from the gaseous state to the liquid and formed the oceans and seas. The CO_2 reacting with the rocks of the Earth's crust produced calcium carbonate minerals, part of which could dissolve in the new oceans. The most primitive marine organisms acquired chlorophyll, a pyrrolic pigment capable of converting light energy into chemical energy, through the photosynthetic combination of water and CO_2, generating carbohydrates and oxygen dissolved in the water. The following equation expresses this relationship:

$$6\ CO_2 + 12\ H_2O + \text{LIGHT} + \text{CHLOROPHYLL} = C_6H_{12}O_6 + 6\ H_2O + 6\ \mathbf{O_2} + E.$$

E=Energy.

Approximately 570 million years ago, the oxygen content of the oceans was sufficient to support marine life through gill respiration. About 400 million years ago, the Earth's atmosphere

acquired enough oxygen in the gaseous phase for marine animals to reach the Earth's crust and breathe air. This is how the lungs appeared for this gaseous respiration, which were possibly air sacs, with blood vessels in their walls that served as primitive organs of gas exchange to supplement the oxygen obtained through gill respiration (2). Subsequently, with evolution and phylogenetic development, the lung acquired other functions to maintain homeostasis, such as immunological and endocrine functions, hormone and peptide synthesis and metabolism, excretion of volatile metabolic waste products, and filtering of cellular aggregates, all of which contribute to proper primary function, namely, gas exchange. The integrity of the system guarantees its functions, and these, in turn, determine its structure (3).

THE DISCOVERY OF OXYGEN

The discovery of oxygen would have to wait the appearance in the European scientific firm of the French chemist Antoine-Laurent Lavoisier (1743-1794), the English minister Joseph Priestley (1733-1804) and the Swedish German chemist and pharmacist Carl Wilhelm Scheele (1742-1786), the fathers of "pneumatic chemistry" (the chemistry of gases). Lavoisier, with his precise and methodical approach, directed chemistry in the same way that physics had taken a century before with the monumental work of Issac Newton and separated chemistry from alchemy. He was admitted to the Academy of Sciences when he was just 25 years old and embarked on a career that was, in essence, that of a scientific civil servant. He was part of the group that devised the metric system, helped draw the first geological maps of France, and was involved in many other practical applications of science, from the introduction of street lighting to increasing crop yields. One of his most important official duties as director of the state factories was the development of gunpowder, which was then vital to France's military power because the blockade prevented the import of raw materials. Studying combustion with “mercury lime” (mercury oxide) found that an acid formed every time a substance bound with a gas active in the air and baptized it with the Greek roots meaning “gas producer”, OXY-GEN. The idea that oxygen is the “acid-generating principle” is erroneous, but the element was already discovered and had name. He also coined the name of HYDROGEN, which means water producer (had shower that water is hydrogen oxide). Lavoisier came from a wealthy Parisien family and become a tax collector, which was an aristocratic privilege in prerevolutionary France. He used the money raised to fund his experiments, but the system was unpopular and corrupt. In 1794 a Revolutionary Court condemned him for having participated in this collection system. Despite the pleas of his friends and the great services rendered to science and France, he was condemned to death and the judge commented “The republic does not need sages”. The guillotine claimed one of its greatest victims (4).

In 1774, Joseph Priestley heated mercuric oxide, and when he studied the gas that was produced, he wrote, “What surprised me more than I can well express, was that a candle burned in this air with a remarkably vigorous flame. . . . I was utterly at a loss to account for it.” He added, “From the greater strength and vivacity of the flame of a candle in this pure air, it may be conjectured that it might be peculiarly salutary to the lungs in certain morbid cases.” Priestley remarked that “a moralist, at least, may say that the air which nature has provided for us is as good as we deserve.” (5). Prestly announced, perhaps without realizing it, the foundations for the later use of what we would know as medical oxygen. That is, oxygen is a medication to treat respiratory failure. Priestley discovered two nitrogen oxides, sulfur dioxide and soda water (carbon dioxide easily dissolved in water under pressure), resulting in a

pleasant-tasting beverage. He fully supported the American colonists' revolution against George III of England and his prime minister, Lord North, and later expressed his support for the French Revolution. This earned him much animosity in his country, and he emigrated to the United States the same month that Lavoisier died in France. He set up a laboratory in Pennsylvania and made his final contribution to "pneumatic chemistry" by discovering carbon monoxide. He died in 1804, weakened by the effects of inhaling the last "new kind of air," carbon monoxide.

Carl Wilhelm Scheele, Swedish pharmacist, discovered lactic acid in 1772, (manganese and chlorine too), the same discovery Priestly made. However, he didn't publish it until 1777, after Lavoisier and Priestley. Lavoisier proved the existence of oxygen, named it, and published it first in 1777. A correspondence between Scheele and Lavoisier, which remained forgotten and dated 1772, was discovered only in 1992 (218 years later), proving that Scheele was the father of the discovery (6). However, Scheele is rarely mentioned in science textbooks as part of this select group that discovered oxygen. The historical eye is sometimes farsighted.

O_2 began to be used indiscriminately and ritualistically and is used as a cure for many respiratory diseases. By the late 1890s, rigorous scientific evaluation had demonstrated that there were deleterious effects from the use of supplemental oxygen (7). Later, West would teach us that there are 5 mechanisms of alveolar hypoxia and hypoxemia: diffusion disorders, hypoventilation, right-left intrapulmonary shunt, imbalance ventilation/perfusion, and decrease oxygen inspired fraction (8).

THE INTERNAL RESPIRATION

Despite the ancient acquisition of oxygen from the atmosphere and the discovery by Lavoisier, Priestely and Scheele 250 years ago, the cellular and nuclear mechanism of the coordinated response to hypoxia has been unraveled in the last 30 years. The key to this knowledge is the family of HIFs (hypoxia-inducible factors), which are transcription regulators or master-switch that respond primarily to oxygen levels and bind to specific DNA sequences.

Molecular Biology of Normoxia and Hypoxia

All nucleated cells sense and respond to hypoxia and not just the glomus cells of the carotid body, as was originally believed. One of the first key elements was the discovery of the role of HIFs as proteins that bind to the hypoxia response element (HRE) of the gene encoding erythropoietin (EPO) synthesis under conditions of hypoxia (9). It was then defined that HIF-1 is a heterodimer formed by two subunits: HIF-1α (oxygen regulatory unit) and HIF-1β (constitutional unit). HIF-1β is ubiquitous and is transcribed continuously, but HIF-1α is restricted, and under normoxic conditions, is present at very low levels in the cytoplasm (10). Under *normoxic* conditions, prolyl-hydroxylases (PHDs) in the presence of oxygen, iron and 2-oxoglutarate, hydroxylates the HIF-1α proline, creating a binding site with the von Hippel-Lindau protein, which recruits the ubiquitin E3 ligase. Polyubiquitination signals protein for degradation by proteasome 26S (11). (Figure 1). HIF inhibitory factor (FIH) is an oxygen-dependent asparagine-hydroxylase (hydroxylates asparagine residue) that reduces HIF activity (12). Therefore, both metabolic pathways reduce HIF activity, and both are oxygen dependent, which explains the reduced expression of HIF in the presence of normal oxygen concentrations (Figure 2A). HIF-2 consists of two subunits: HIF-1β and HIF-2α which is a

paralogue of HIF-1α and expressed mainly in normal tissue macrophages and plays an important role in erythropoiesis and vascularization. Its expression is also regulated by oxygen-dependent hydroxylation (13).

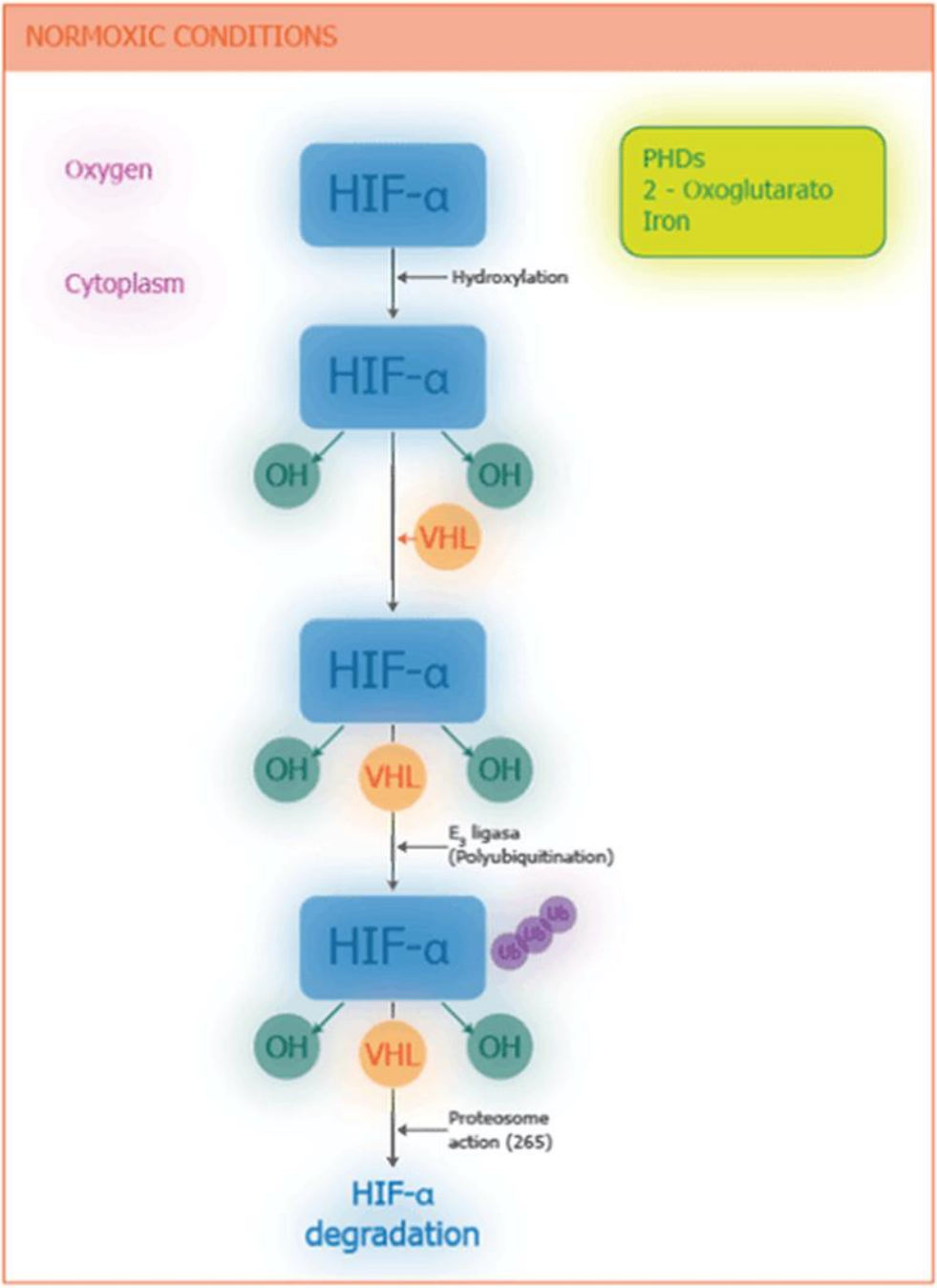

Figure 1: Role oh Hypoxia-Inducible Factors α (HIF-α) under Normoxic conditions.
Legend. Under normoxic conditions, HIF-α is hydroxylated by prolyl-hydroxylase domain 2 protein (PHD_2). It then interacts with von Hippel-Lindau protein (VHL), and recruits' ubiquitin E_3 ligase. The polyubiquitination of HIF-1α flags the protein for degradation by the 26S proteasome.

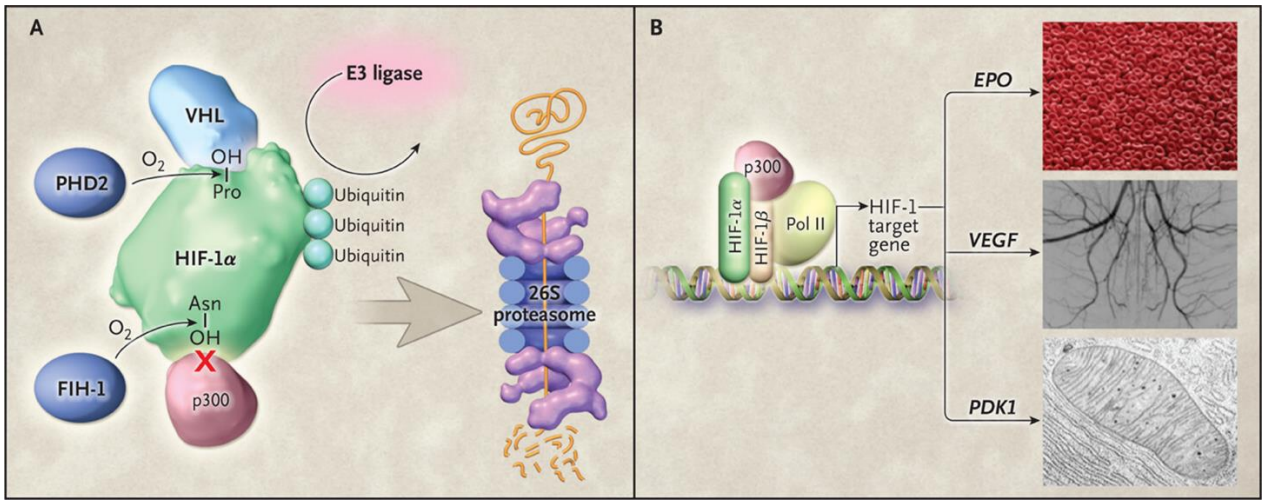

Figure 2: Factor inhibiting HIF-1.

Legend. (Panel A). Factor inhibiting HIF-1 (FIH-1) also uses oxygen to hydroxylate HIF-1α on an asparagine residue (Asn–OH). HIF-1α containing Asn–OH cannot be bound by the coactivator protein p300, thereby preventing HIF-1α from activating gene transcription.

Under *hypoxic* conditions, hydroxylation of proline and asparagine is not activated, and HIF-1α accumulates rapidly, translocated to the nucleus, dimers with HIF-1β, recruit p300 (coactivating protein), binds to HRE and activates RNA polymerase II from hundreds of target genes (Figure 3). For example, EPO, which is the hormone that stimulates the production of red blood cells, VEGF encoding vascular endothelial growth factor (which is the angiogenic factor that stimulates the formation of blood vessels) and glycolytic enzymes, for example PDK1 (pyruvate dehydrogenase-kinase 1, which adapt cellular metabolism to conditions of hypoxia) (14). Other genes that are activated by HIFs are those encoding the synthesis of nuclear factor Kβ (NF-kβ) (a pro-inflammatory factor) and Toll-like receptors (TLRs). Normally NF-kβ is inactive in the cytosol because there is a molecule that inhibits its activity, IKβα, but when hypoxia conditions (e.g., EPOC) are present, HIFs on translocation to the nucleus (in alveolar macrophages) activate the gene of the IKKβ, a kinase that phosphorylates IKβα and the inactive, releasing the control that was on NF-Kβ. NF-Kβ translocated to the nucleus and in turn, activates genes encoding the synthesis of pro-inflammatory proteins such as tumor necrosis factor-alpha (TNF-α) and interleukin-8 (IL-8), the largest chemotactic mediator and activator of neutrophils that infiltrate the airway, capitalizing the inflammation (Figure 4). Hypoxia therefore produces inflammation and this in turn tissue hypoxia generates a vicious circle (15). In general, hypoxia amplifies the cell activity of innate immune response while suppressing the adaptive immune system response (16). The TLRs are a family of protein receptors that play a key role in recognizing molecules in the immune system (17).

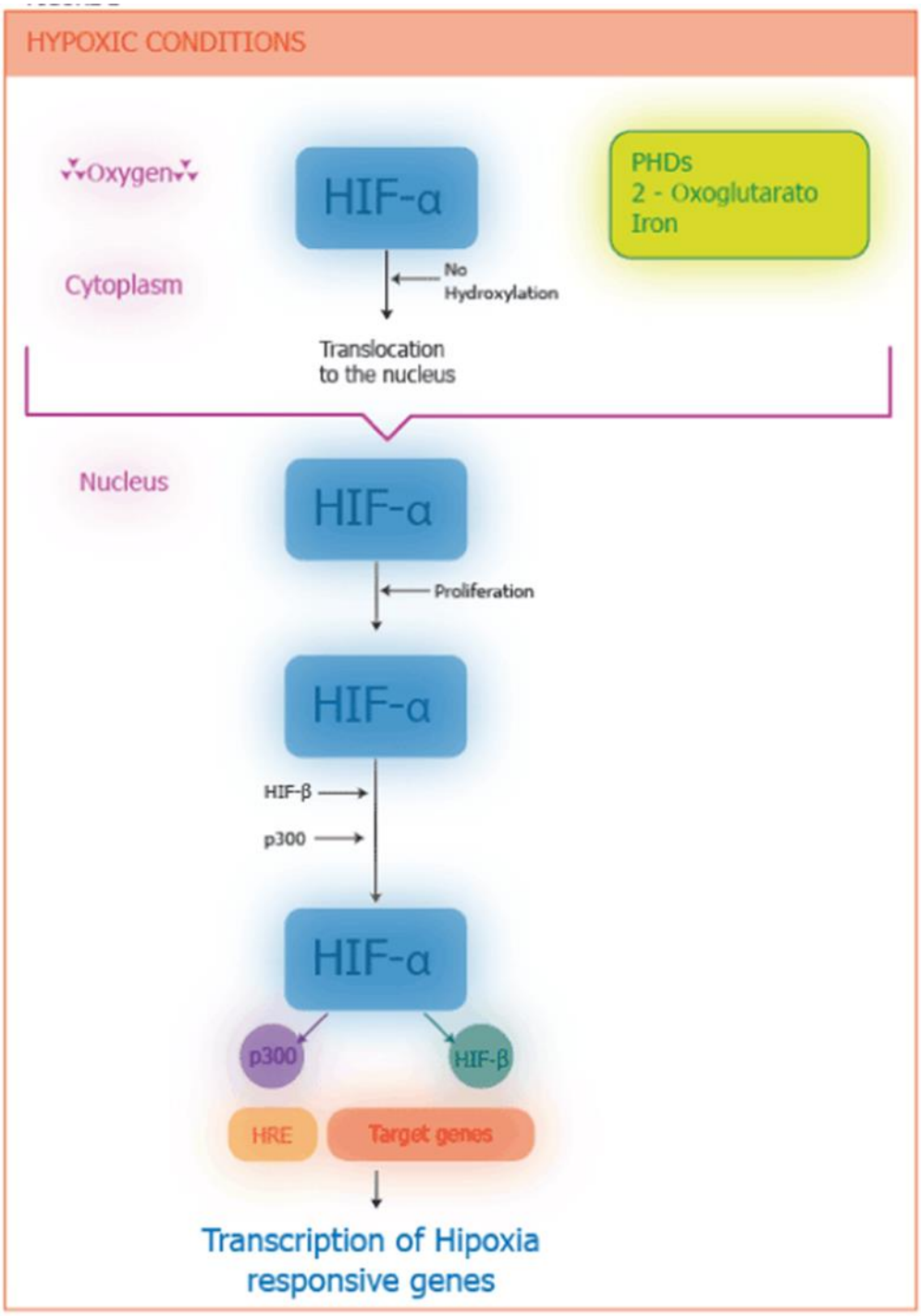

Figure 3: Role of the HIF-1α under Hypoxic conditions.

Legend. Under hypoxic conditions, HIF-α does not undergo degradation and rapidly accumulates but instead translocated to the nucleus where it dimerizes with HIF-β and the recruits´ coactivators (p300), binds to hypoxia response elements (HRE), and activates the transcription by RNA polymerase II of hundreds of target genes.

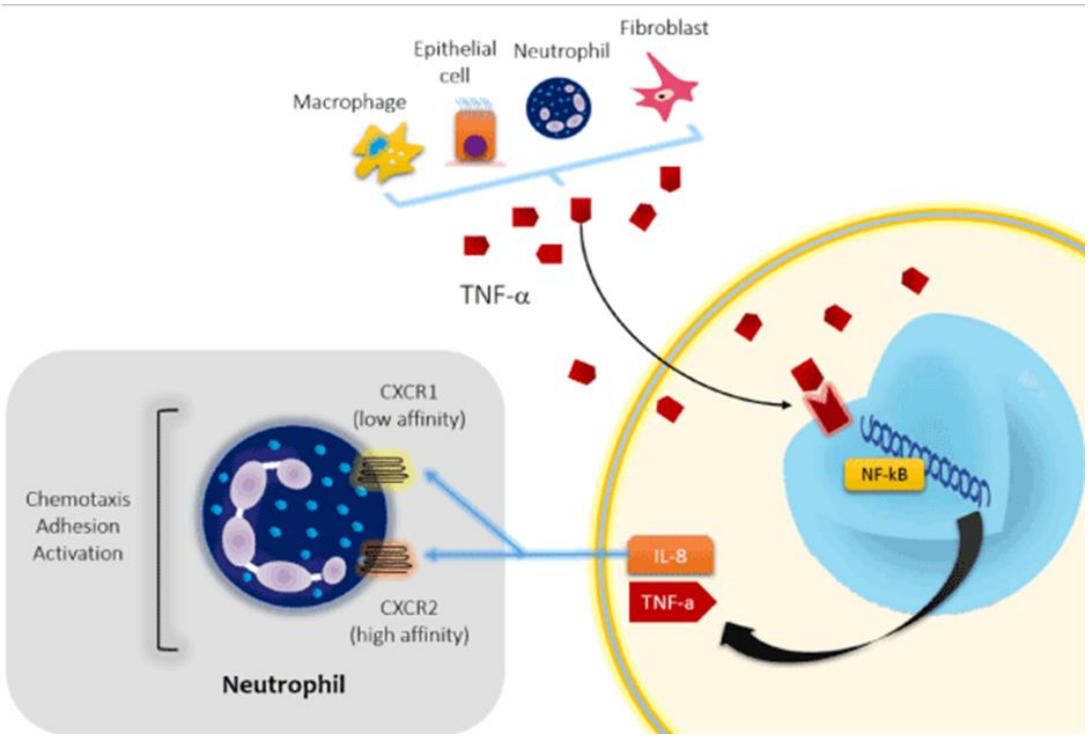

Figure 4: Activation of the Nuclear Factor kβ (NF-kβ).

Legend. NF-kβ has a central role in orchestrating the inflammatory response in respiratory pathologies. NF-kβ is activated by oxidants and inflammatory mediators such as TNF-α produced by macrophages, epithelial cells, neutrophils, and fibroblast. Most of the inflammatory proteins that are upregulated in macrophages are regulated by NF-kβ. Interleukin-β (IL-β) is ubiquitous inflammatory chemokine that mediates several inflammatory events in the lungs. It is a major chemotactic and activating mediators of neutrophils. TNF-α= tumor necrosis factor-α. NF-kβ= Nuclear Factor kβ. CXCR1= chemokine C-X-C motif receptor 1. CXCR2= chemokine C-X-C motif receptor 2.

Solid tumors contain increased levels of HIF-1α and HIF-2α, and these elevated levels correlate with cancer-related death. Inflammatory cells also contribute to the abnormal growth and activity of blood vessels in tumors by the release of VEGF (18,19).

Mitochondria

The human lung is composed of approximately 40 cell types, regionally and spatially located through the organ, and contains several levels of mitochondria (20). The mitochondrial genome was inherited through the maternal germ line and was inherited from aerobic prokaryotes bacteria (no defined nucleus) more than a billion years ago and retains many of the morphological and biochemical characteristics of their bacterial ancestors. They are an icon of convoluted double-crested structures that are present in all cells of the body and have their own genome, transcriptome and proteome (21). According to the endosymbiotic theory, mitochondria are descendants of old bacteria that entered symbiotic relation with the cells of the host (22). Conceptualized as “cell batteries” (and consistent with this analogy subject to change), mitochondria are complex cellular organelles assembled from proteins encoded by two distinct genomes: nuclear chromosomal DNA and the mitochondrial genome, i.e., mitochondrial DNA (mt-DNA). Despite the small size of the mt-DNA (16.5 kb in humans), it encodes 13 potential oxidative phosphorylation subunits (OXPHOS) which interact with more

than 70 units encoded by nuclear DNA: their concerted action is necessary to produce ATP (adenosine triphosphate), which is required for all active cellular processes (23). Historically, the major role of mitochondria has been to catalyze the oxidation of metabolites to produce ATP, via OXPHOS (see later). Additional critical functions of mitochondria such as regulation, proliferation, differentiation, cell death, redox and calcium homeostasis have been revealed during the last three decades. Recently, research has pointed out mitochondria as controlling the immune responses and determinants of immune cell phenotypes and their functions, including CD4+ T cell differentiation and CD8+ memory T cell formation (24). Mitochondrial aerobic glycolysis is required for effective activation of T cells through the generation of mt-ROS (reactive oxygen species), which are necessary for optimal activity of nuclear factor of activated T cell (NF-AT) and proximal T-cell receptor-mediated signaling (25). Within the mitochondrial proteome are key proteins such as mitochondrial antiviral signaling protein (MAVS), which is the first protein located in the mitochondria involved in innate immune response and inflammatory response (26).

The presence of two genomes in human cells - the nuclear genome and the tiny mt-DNA - is a curiosity of evolution. Altered mt-DNA diseases (more than 400 mutations or deletions in the 16,569-bas-pair mitochondrial chromosomes that contain only 32 genes), are heterogeneous disorders with well-known genetic causes (27). The possibility of mitochondrial replacement in certain individualized cases is a viable therapeutic option. In fact, on December 15, 2016, the Human Fertilization and Embryology Authority in the United Kingdom approved the use - in certain specific cases - of an in vitro fertilization (IVF) technique involving donation of mitochondria (28). The discovery of pathogenic defects of mt-DNA occurred in the 1980s, but since then much research has revealed several common diseases, in which mitochondrial dysfunction is a pathogenic and/or perpetuating mechanism of the process underlies. COPD does not escape this fact (29).

Oxidative and Glycolytic Metabolism

When arterial oxygen reaches tissue capillaries, O_2 diffuses to the mitochondria, where PO_2 is much lower. "Textural" or tissue PO_2 likely varies greatly from tissue to tissue at the peripheral level, but in some cells, tissue PO_2 drops as low as 1 mm Hg (30). Under normoxic conditions, HIF-1α and HIF-2α will not translocate to the nucleus and glucose metabolism will occur via the aerobic pathway (Fig- 5). Glycolytic enzymes convert glucose into pyruvate, which can be converted, in well-oxygenated cells, into acetyl coenzyme A (CoA) (by the enzyme pyruvate dehydrogenase (PDH). Acetyl CoA is oxidized in mitochondria to tricarboxylic acid (TCA) (Krebbs cycle), generating electrons that are transferred through a series complexes, electron transport chain (ETC), and are eventually transferred to oxygen to form water. The proton gradient established by ETC is used to synthetize ATP (31). NADH (nicotine adenine dinucleotide) and FADH2 (flavine and adenine dinucleotide) are intermediate compounds that store energy and transfer it to ADP to form ATP (ATP synthase), through the proton gradient hat was generated for ETC. (31). These processes occur in the inner membrane of mitochondria. When ATP is hydrolyzed at its phosphate bonds (energy ‘store), ADP, inorganic phosphorus, and energy are released. It is this energy that the cell uses for its metabolism and cellular processes such as muscle contraction, ion transport, molecular synthesis, protein synthesis, lysosomal enzyme activity, propagation of nerve impulses, etc.

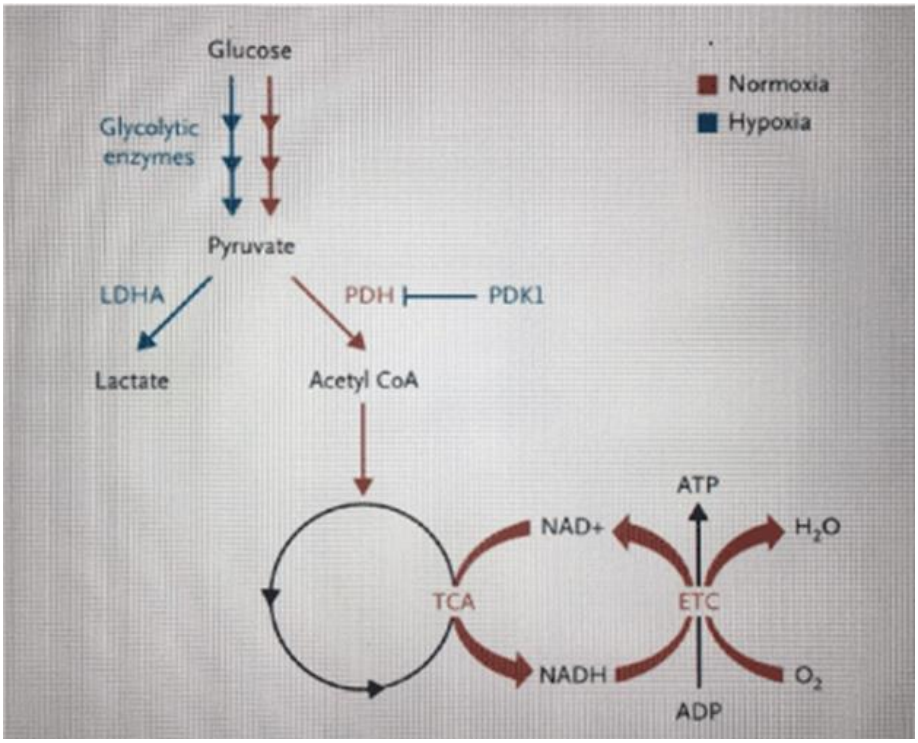

Figure 5: Regulation of Glucose metabolism in response to changes in cellular oxygen levels.
Legend. Glucose is converted to pyruvate by the action of glycolytic enzymes. In well-oxygenated cells (red pathway), PDH converts pyruvate to acetyl coenzyme A (CoA), which is oxidized in the mitochondrial tricarboxylic acid (TCA) cycle, generating electrons that are transported through a series of protein complexes (ETC) and are eventually transferred to oxygen to form water. The proton gradient established by the ETC is used to synthetize ATP. Under hypoxic conditions (blue pathway) PDK1 inactive PDH, and LDH converts pyruvate to lactate (15).

Under hypoxic conditions, pyruvate dehydrogenase kinase 1 (PDK1) inactivates PDH, and lactate dehydrogenase A (LDHA) converts pyruvate to lactate. HIF-1 activates the expression of LDHA and PDK1 genes, thus tipping the balance from oxidative to glycolytic metabolism (32). Although anaerobiosis is a relatively inefficient path to produce ATP (oxidative metabolism generates 18 times more ATP per mole of glucose than glycolytic metabolism), it can keep the cell alive as it reduces oxygen consumption. A critical event added to the relative inefficiency of the anaerobic pathway is its product. In the aerobic pathway, the end products are endogenous water and CO_2. The lungs eliminate more than 10,000 mEq/day of carbon dioxide. The kidneys eliminate less than 100 mEq of acid/day. The lungs exert considerable control over acid-based balance. Anaerobically, it produces lactic acid, which produces intracellular acidosis by reducing the pH. This leads to dysfunction of enzymes vital to cellular metabolism, densification of proteins and lipids, and alterations in the transport of ions and molecules across the cell membrane, all of which lead to cell death, particularly if the pH drops below 7. Acidosis also activates several mechanisms of programmed cell death, which accelerates cellular failure to maintain metabolism and leads to cell death.

Anaerobic today are presumably descendants of those primitive organisms, "adapting" to increased atmospheric levels of oxygen for restricted themselves to environments where oxygen does not penetrate. Other organisms have developed defense systems to protect

themselves from oxygen toxicity using the same as metabolic transformations (hydroxylase, oxidase and oxygenase enzymes are examples) and for efficient energy production by using electron transport chains with oxygen as the terminal electron acceptor-such as those present in the mitochondria. Mitochondria produce 80% of our cellular adenosine triphosphate (ATP) (33). It is remarkable that we have developed antioxidant defenses against concentrations of 21% oxygen, but not more. All aerobic species suffer injury when exposed to higher concentrations of 21%. For example, humans breathed pure oxygen and as early as six hours to develop chest tightness, cough, and sore throat (34). Exposure periods over the alveoli of the lung damage and premature infants exposed to high doses of oxygen develop fibroplasia lenticular (which may occur with blindness) (35).

In 1954, Gerschman and colleagues in the United States (US) proposed that the harmful effect of oxygen was due to the formation of oxygen radicals, superoxide oxygen theory, followed in 1968 the discovery of the enzyme superoxide dismutase (SOD), specific for the removal of a free radical substrate. In its simplest form, this theory states that oxygen toxicity is due to excess formation of superoxide radical ($O_2^{\bullet -}$) and the SOD enzymes are important antioxidant defenses (36).

THE EXTERNAL RESPIRATION

Humans have evolved complex circulatory, respiratory, and neuroendocrine systems to ensure that oxygen level are precisely maintained, since a deficiency or excess may result in death of cells, tissue, or the organism. No other molecular factor has had a singular influence on the development and progress of animal life as oxygen. PO_2 falls as the gas moves from the atmosphere in which he lived until the mitochondria where it is used. At sea level the PO_2 of inspired air is 150 mm Hg. When systemic arterial blood reaches the capillary tissue, oxygen diffuses into the mitochondria where PO_2 is very low (36,37). All processes of external respiration, however simple or complex, are designed to capture atmospheric oxygen (and export CO_2 to the atmosphere), and supply it to mitochondria for aerobic metabolism. These processes are briefly discussed below, essentially as a chain of events that contribute to mitochondrial respiration.

Ventilation

The primary function of the respiratory system is to allow gas exchange between the circulatory system (which carries O_2 to the mitochondria) and the environment. This occurs between alveolar gas and the blood contained in the pulmonary capillaries. The process described above is called alveolar ventilation ($A\dot{V}$). Total ventilation (pulmonary ventilation or minute ventilation) is given by the product of tidal volume and respiratory rate, but $A\dot{V}$ corresponds to the volume of air that reaches the gas exchange units (alveoli) and participates in the fresh gas exchange (that is, it provides O_2 and extracts CO_2); so, the air retained in the dead space must be discounted. Due to the availability of O_2 from the alveolar space, the alveolar cells do not rely on pulmonary perfusion for oxygen delivery. For this reason, in adults, O_2 consumption of lungs only represents 0.5-4% of the total oxygen consumption (39). The cells of the major conducting bronchi represent an exception to the generalization concerning the sources of oxygen for lung cell metabolism. While the bronchial epithelium obtained the O_2 diffusion from the lumen of the airway, oxygen consumed by the deep tissues of these pathways is delivered by the systemic circulation through the bronchial arteries (40). According to the Weibel model, the airways

branch systematically forming an average of 23 generations of dichotomies, the first 16 being purely conductive generations and the last 6-7 related to gas exchange. However, it should be noted that these conduction pathways, through the bronchial venous plexus (the bronchial arteries supply blood to the plexus), are located beneath the mucosa and another part beneath the adventitia and drain their blood into the bronchial veins and are part of the airway water exchange system. They add moisture and heat to the inspired air, which are necessary not only for water balance, but also, and above all, for the proper functioning of the epithelia lining the conducting airways, the function of the cilia, and ASL (airways surface liquid) (41).

Dead space corresponds to the portion of the respiratory tract where gas exchange does not occur. There are two "types" of dead space. Anatomical dead space: this corresponds to the conducting airway, which does not have alveolar units, that is, up to the terminal bronchioles. Physiological dead space: this corresponds to the areas of the lung that are ventilated but not perfused and therefore do not participate in gas exchange. In other words, it is the sum of the anatomical dead space and the alveolar dead space (42). In healthy individuals, the anatomical dead space and the physiological dead space are practically equal; however, in pathological conditions, the latter can increase considerably depending on the differences between blood flow and ventilation in the different lung areas. These alterations are beyond the scope of this review. Total ventilation is relatively easy to determine by measuring tidal volume with an expiratory valve and multiplying by the respiratory rate. However, to quantify alveolar ventilation, we need to know the amount of dead space, which is not possible using conventional spirometry maneuvers. Thus, two methods for measuring dead space emerge: Fowler's method, which measures anatomical dead space, and Bohr's method, which measures the physiological dead space (43).

As air moves from the atmosphere to the alveoli, PO_2 decreases, so that at the alveolar level it is about 100 mmHg (at sea level) or has decreased by one-third. This occurs in part because, as it passes through the airway, the cells lining it consume O_2 for aerobic metabolism, water vapor and gases such as CO_2 coming from the capillaries are added and because at the alveolar level, O_2 is taken up by the pulmonary venous capillary blood for oxygenation. Therefore, alveolar PO_2 (PAO_2) is a product of the balance between uptake by the capillaries (which in turn depends on O_2 consumption by the tissues) and continuous replenishment by alveolar ventilation. Therefore, PAO_2 is largely determined by $V\dot{A}$. Inspired air circulates at high speed to the terminal bronchioles, but beyond that, the cross-sectional area of all the airways increases to such an extent, due to the large number of bifurcations, that the velocity of the gas decreases significantly.

- **PAO_2**= PIO_2- ($PACO_2$/0.8). PIO_2= (PB-47) FIO_2.
- **PAO_2**= Alveolar O_2. **$PACO_2$**= Alveolar CO_2 pressure= Normal= 40 mmHg
- **0.8**= R=respiratory quotient= Relationship between CO_2 production (250 cc/minute)/oxygen consumption (300 cc/minute).
- **PIO_2**= Inspired oxygen pressure.
- **PB**= (760 mmHg sea level).
- **47**= 47 mmHg= Water vapor pressure. PAO_2 is calculated in dry air, so H_2O vapor is subtracted. $PACO_2$ must also be subtracted.
- **FIO_2**= Inspired O_2 Fraction = 0.21% at ambient air.

Therefore, at sea level if the barometric pressure is 760 mmHg and the vapor pressure of H_2O is 47 mmHg (at body temperature of 37°C), the pressure of inspired air will be 149 mmHg ([760-47]x0.21) and by subtracting 50 (40 mmHg of $PACO_2$/0.8) we will get a PAO_2 of 100 mmHg.

The mechanism that conveys air from the terminal bronchi to the outermost wall of the alveoli (the acini are 5 mm long) is gaseous diffusion (molecular diffusion), in which contact between the molecules and with the walls accelerates the particles. This mechanism guarantees air flow within the acinus, which is truly the functional unit of the respiratory system. Lungs with 5 million alveoli have approximately 150,000 acini. This process of molecular gaseous diffusion within the airway should not be confused with diffusion across the blood-gas membrane, which allows the transport of gases between alveoli and capillaries (44).

Diffusion

Diffusion across the blood-gas membrane occurs passively and primarily involves O_2, which moves toward the capillary, and CO_2, which moves toward the alveoli. Diffusion of O_2 is slower than that of CO_2 due to its lower solubility. CO_2 and O_2 have similar molecular weights, but CO_2 is 24 times more soluble in the liquid phase. For a given gas to diffuse through the alveolar-capillary membrane, it must pass from a gaseous to a liquid interface, which is determined by Henry's law. This law states that "the amount of gas (C) absorbed by a liquid in which it chemically combines is directly proportional to the partial pressure (P) of the gas to which the liquid is exposed and the solubility (k) of the gas in the liquid" (C = k x P). The gas must then transit to the alveolar-capillary membrane, sequentially diffusing through the pulmonary surfactant, the alveolar epithelium, the interstitium, and the capillary endothelium to reach the erythrocyte. The diffusion rate of a gas is determined by Fick's law, which states that "the volume of a gas moving through a membrane per unit time is directly proportional to the area of the barrier (A), the diffusion constant (D), and the pressure difference (P1-P2) between the two sides, but is inversely proportional to the thickness of the barrier (T)" according to the following formula: $\dot{V}$ gas = AD (P1 – P2)/T. In the alveolar-capillary membrane, these determinants have unique characteristics that facilitate diffusion. The surface area is large, between 60 and 100 m^2 in a healthy adult. This area increases with the recruitment of capillaries during exercise and decreases under conditions of low venous return. The barrier thickness (T) is minimal (0.2 to 0.5 μm) and facilitates diffusion. The diffusion constant (D) depends on the properties of the alveolar-capillary membrane and the gases. Finally, the partial pressure gradient (P1 – P2) is the main determinant of the diffusion rate of a gas (45).

The time it takes for the red blood cell to travel from the venous side to the arterial side along the capillary is 0.75 seconds. At rest, the equilibrium of the O_2 partial pressure gradient across the alveolar-capillary barrier is achieved in one-third of the time it takes for an erythrocyte to pass through the capillary, about 0.25 seconds. O_2 easily passes through the alveolar-capillary barrier and binds to hemoglobin in hundredths of a second, saturating it; dissolved O_2 increases the capillary O_2 partial pressure, which begins at about 40 mmHg in mixed venous blood and quickly reaches the alveolar O_2 partial pressure (100 mmHg). This would be true in a perfect lung, where the PO_2 of arterial blood would be the same as that of alveolar oxygen (PAO_2), but this is not exactly the case. As O_2 diffuses, some of the molecules are consumed by alveoli, the interstitium, and the vessel walls for aerobic metabolism. Therefore, while it is true that blood

PO_2 rises ever closer to PAO_2 as the blood travels through the pulmonary capillary, it can never reach it. This difference is minimal under normal conditions but can be amplified in pathological conditions. After 0.25 seconds, there is no further passage of O_2 from the alveoli to the blood-gas membrane which means that it has 0.5 seconds of reserve for diffusion. In exercise time decreases the blood remains in the capillary, but O_2 transfer increases as the barrier area increases by recruiting previously un-perfused capillaries and improving the ventilation/perfusion ratio. But during regular exercise, it takes a red blood cell a third of a second to cross the capillary, just the time it takes for oxygen to diffuse. Therefore, PaO_2 (arterial PO_2) should not be significantly reduced with exercise, unless PAO_2 is reduced (as at altitude) or there is a pathology of the alveolar-capillary membrane that delays diffusion. Basal and post-stress blood gas analysis is a test used to functionally assess the integrity of the alveolar-capillary membrane. The diffusion of CO_2 is much more efficient than that of O_2 since CO_2 diffuses 20 times faster in the alveoli-capillary membrane. Therefore, when diffusion is impaired, the passage of O_2 is affected first. The pressure gradient across the membrane is equilibrated at approximately the same time (0.25 seconds), even though the partial pressure gradient of CO_2 is only 5 mmHg: much lower than the 60 mmHg of O_2. Since O_2 and CO_2 diffusion is limited by perfusion, they are not used to measure diffusion capacity in the laboratory. DLCO (diffusion of carbon monoxide=CO) is used, whose passage through the membrane is essentially limited by diffusion (46,47). Normal value of DLCO at rest is 25 mL/minute/mm Hg (8 mmol/minute/Kpa) and increases 2-3 times during exercise.

Pulmonary Circulation

A red blood cell takes 4 to 5 seconds to travel through the pulmonary circulation under resting conditions and remains for about 0.75 seconds within the pulmonary capillaries. Pulmonary capillaries have an average diameter of 6 μm, making them slightly smaller than a red blood cell, so they must change shape to pass through them. Each red blood cell passes through multiple capillaries during its passage through the lungs. Approximately 280 trillion pulmonary capillaries supply 300 million alveoli in an adult, resulting in an estimated potential gas exchange area of 50 to 100 m^2 (48). The lungs receive blood through the bronchial and pulmonary circulations. The *bronchial circulation* constitutes a very small portion of the left ventricle's cardiac output (2%) and supplies part of the tracheobronchial tree and other lung structures up to the level of the terminal bronchioles with systemic arterial blood. The bronchial arteries emerge variably, either directly from the aorta or from the intercostal arteries. The venous drainage of this circulation is unusual; some bronchial veins drain into the azygos and hemiazygos veins, while a substantial portion of venous drainage enters the pulmonary veins. The blood in the pulmonary veins has already participated in gas exchange and is therefore already oxygenated. Thus, the drainage of the bronchial veins into the pulmonary venous flow is part of the anatomical right-to-left shunt. Another component of the right-to-left anatomical shunt is a small amount of blood from coronary veins that drain directly into the left ventricle via the Thebesian veins. The combined effect of both shunts adds poorly oxygenated (venous) blood to the arterial blood, depressing arterial PO_2. *Pulmonary circulation* constitutes the entire cardiac output of the right ventricle and supplies the lung with mixed venous blood from all tissues of the body. It is this blood that participates in gas exchange with alveolar air in the pulmonary capillaries. The pulmonary circulation begins in the main pulmonary artery, which receives deoxygenated blood from the right ventricle. The pulmonary artery and its branches have much thinner walls, with less smooth muscle, than the arteries of

the systemic circulation, as well as larger internal diameters. The pulmonary artery branches successively (28 generations) like the airway system to the terminal bronchioles, subsequently passing into the capillary bed. The pulmonary capillaries form a dense network in the wall of the alveoli, allowing gas exchange. Oxygenated blood is collected from the capillary bed by small pulmonary veins that eventually join to form the four large pulmonary veins that empty into the left atrium.

The pressures in the pulmonary circulation, unlike systemic pressures, are remarkably low, being in harmony with the walls of the pulmonary artery and its branches, which are very thin and have little smooth muscle, offering much less resistance to blood flow. They give the pulmonary vessels greater distension than the arteries of the systemic circulation. These factors lead to much lower intravascular pressure, which makes them more compressible. PVR (pulmonary vascular resistance) is equal to mean pulmonary artery pressure minus mean left atrial pressure, which is then divided by pulmonary blood flow. Normal pulmonary vascular resistance is one-tenth of systemic vascular resistance (17 mmHg/L/minute). In an adult, pulmonary blood flow is about 6 L/min, so pulmonary vascular resistance is 10 (15-5)/6, or about 1.7 mmHg/L/ minute. (49). Mean pulmonary artery pressure (15 mmHg) is measured by placing a catheter in the pulmonary artery or indirectly using echocardiography by measuring right ventricular systolic and diastolic pressures. Left atrial pressure is 5 mmHg. This difference in right ventricular output pressure minus left atrial input pressure is divided by pulmonary blood flow to obtain PVR. This is more relevant to cardiovascular physiology. PVR has its lowest overall value at the level of functional residual capacity (FRC) and increases at high or low lung volumes. Therefore, lung volume influences resistance. What should be clear is that under physiological breathing conditions (FRC), breathing and air intake promote a reduction in PRV so that blood flow can flow through the pulmonary circulation. In turn, as blood flow increases, PRV decreases through two mechanisms: recruitment and distension of pulmonary blood vessels. Under resting conditions, a proportion of the capillaries are poorly perfused. As the right cardiac output increases, these capillaries are recruited, opening parallel pathways, which decreases PVR. Furthermore, given the anatomy of the pulmonary vessels, increased blood flow produces an increase in caliber or distension of individual capillary segments, which also decreases resistance. In addition to the passive factors previously described, the muscle tone of the pulmonary vessels can actively modify PVR and is influenced by neural and humoral factors. The pulmonary vasculature is innervated by sympathetic and parasympathetic fibers of the autonomic nervous system. The catecholamines epinephrine and norepinephrine increase PVR, while histamine is a powerful vasoconstrictor. Certain prostaglandins, thromboxane, and endothelin also have a vasoconstrictor effect. Acetylcholine, beta-glucans, nitric oxide, and certain prostaglandins also have a vasodilatory effect. This is particularly relevant in the pathophysiology and treatment of the various forms of Pulmonary Arterial Hypertension (50-52).

Pulmonary blood flow can be determined using various techniques, both invasive and indirect. Invasive methods include measuring the volume of blood circulating through the lung every minute, using Fick's principle.

- $\dot{V} = \dot{Q}\ (CaO_2 - CvO_2)$
- $\dot{Q}$: flow

- $\dot{V}O_2$: average O_2 consumption per minute at the mouth (it would be equal to the amount of O_2 captured by the blood in the lungs per minute). It is measured by collecting exhaled air in a spirometer and measuring its concentration.
- CvO_2: concentration of oxygen in the blood entering the lungs. Deoxygenated blood is measured with a catheter in the pulmonary artery.
- CaO_2: blood leaving the lung. It is measured by arterial puncture.

Among the noninvasive methods for measuring blood flow, transcutaneous and transesophageal Doppler ultrasound stands out, being the most widely used clinically. Regional blood flow can also be determined by pulmonary angiography or pulmonary computed tomography.

Blood flow is not distributed evenly throughout the lung but is affected by gravity. When standing, blood flow progressively decreases from the bases to the apices, reaching very low levels in this area. In the supine position, blood flow in the posterior regions is greater than in the anterior region. If we consider the pulmonary arterial system as a column of blood, the pressure difference between the highest part (pulmonary apex) and the lowest part (pulmonary bases) of a 30 cm high lung will be about 30 cm of water (23 mmHg). This pressure difference is very large for a low-pressure system such as that of the pulmonary circulation. It is obvious that the bases are better perfused than the pulmonary apices in a standing individual. Under normal circumstances, passive factors dominate vascular resistance and flow distribution in the pulmonary circulation. However, when PAO_2 drops below 70 mmHg, significant hypoxic pulmonary vasoconstriction can occur (53,54). During this phenomenon, the smooth muscle contraction of the walls of the small arterioles, located very close to the alveoli, occurs in the hypoxic region. An increase in the concentration of cytoplasmic calcium would be the main trigger of this contraction. Alveolar hypoxia can cause the release of vasoactive substances from the lung parenchyma or mast cells present in the affected area. Histamine, serotonin, catecholamines, and prostaglandins have been suggested as mediators of this reaction, but none fully explains the response to hypoxia, so it is likely the combination of various mediators that produces this vasoconstriction. Nitric oxide (NO), an endothelium-derived vasodilator, also plays a role in controlling circulation. It is produced from L-arginine catalytically, through the action of endothelial NO synthase. NO activates guanylate cyclase and increases the synthesis of cyclic guanosine 3'-5'-monophosphate (cyclic GMP), which leads to smooth muscle relaxation. Thus, NO synthase inhibitors, which decrease NO release, produce pulmonary vasoconstriction. The pulmonary vascular endothelium also produces vasoconstrictive substances, such as endothelin-1 (ET-1) and thromboxane A2 (TXA2).

Furthermore, it is possible that hypoxia itself may act directly on vascular smooth muscle by inhibiting potassium efflux from cells, which would cause depolarization, with the entry of calcium into the cells and subsequent muscle contraction. Just as hypoxia causes redistribution of circulation, the presence of low blood pH or high $PaCO_2$ also causes vasoconstriction, especially when associated with hypoxia. Hypoxic vasoconstriction is capable of redistributing blood flow, decreasing its delivery to hypoxic areas, thereby reducing the impact on gas exchange. This response seeks to prevent well-oxygenated pulmonary venous blood from mixing with blood that has not adequately participated in gas exchange, which would produce a lower PaO_2 and, in more severe conditions, even an increase in $PaCO_2$. Thus, blood flow is

redirected to better-ventilated areas of the lung. Due to the limited smooth muscle of the pulmonary blood vessels, this response is limited (55). For proper gas exchange, it is essential to keep the alveoli free of fluid. Fluid exchange across the endothelium obeys Starling's law, which states that the force tending to push fluid outward from the capillary is the capillary hydrostatic pressure minus the interstitial fluid hydrostatic pressure (Pc – Pi). The force tending to retain fluid inside the capillary is the colloid osmotic pressure of the blood proteins minus the pressure of the interstitial fluid proteins (πc - πi). This force depends on the reflection coefficient σ, which indicates the capillary wall's effectiveness in preventing proteins from passing through it.

$$\text{Fluid outflow} = K\,[(Pc - Pi) - \sigma\,(\pi c - \pi i)]$$

K is a constant called the filtration coefficient.

When fluid leaves the capillaries and exits the fluid then flows into the interstitium, reaching the perivascular and peri-bronchial spaces within the lung. Lymphatic vessels travel through the perivascular spaces and transport fluid to the hilar lymph nodes. The initial form of pulmonary oedema results from congestion of these peri bronchial and perivascular spaces, which constitutes interstitial edema. As it progresses, fluid can cross the alveolar epithelium into the alveolar spaces, producing alveolar edema and impaired gas exchange (56).

Ventilation/Perfusion Imbalance

$\dot{V}/\dot{Q}$ imbalance is the main pathophysiological cause of respiratory failure in upright humans, and the main cause of this disorder or imbalance is gravity. The lung bases are better perfused than the apices, and this is clearly because of gravity on hydrostatic pressure within the blood vessels (see perfusion). It should also be clear that ventilation is greater at the bases than at the apices. This is also due to the impact of gravity, but now on pleural pressure. As we descend from the apices to the bases, for every cm of length, gravity reduces pleural pressure by 0.3 cm H_2O, such that for a lung 30 cm long, the pleural pressure at the bases is 9 cm H_2O less negative (0.3 x 30 = 9). To illustrate, if the pressure at the apices is -12 cm H_2O, at the bases it will be -3 cm H2O. Therefore, the alveoli at the apices (which are fewer in number than at the bases) will be more dilated in the resting position than those at the bases, which will therefore be smaller. When there is a change in pleural pressure (for example, from FRC to TLC), the change will be smaller at the apices than at the bases, and ventilation will be greater at the bases than at the apices (it is easier to put more air into a very deflated balloon than a balloon that is already partially inflated). Therefore, ventilation is greater at the bases. Therefore, ventilation and perfusion are greater at the bases than at the apices. Ventilation per unit decreases towards the top of the lung, as does blood flow, but the rate of change of ventilation is much slower (approximately one-third of that of blood flow). This is due to the behavior of two different elements under gravity. The density of blood is about 1000 times greater than that of air (57).

At this point in the discussion, it is obvious that both ventilation and perfusion decrease towards the top of the lung in a vertical position. The change in ventilation is much less than that of the flow, which leads to alveoli at the base of the lung being better perfused than ventilated and those at the apex of the lung better ventilated than perfused. The index ventilation/perfusion is abnormally low at the base of the lung (around 0.6) and then increases

as we ascend in the lung, slowly at first, and then rapidly, until it reaches high values (greater than 3 at the apex). It is this relationship that determines the exchange of gases in any unit or region of the lung. Studies of healthy individuals using the MIGET (multiple inert gas elimination technique) show that the ventilation-perfusion ratio can range from 0.1 to 10, but that most of the blood flow and ventilation go toward units with a ventilation-perfusion ratio close to 1 (Figure 6). In fact, the average value for the entire lung is 0.85. This assumes an alveolar ventilation of 4 liters/minute and a blood flow of 5 liters per minute (58). At this point, it is important to briefly clarify two concepts: first, the inequality of the ventilation-perfusion ratio is because gravity has on air (ventilation) and blood (perfusion), which behave differently under Newton's law due to their different densities. Second, the inequality of this ratio is the pathophysiological mechanism most frequently involved in respiratory failure in patients who attend medical services in clinics and hospitals.

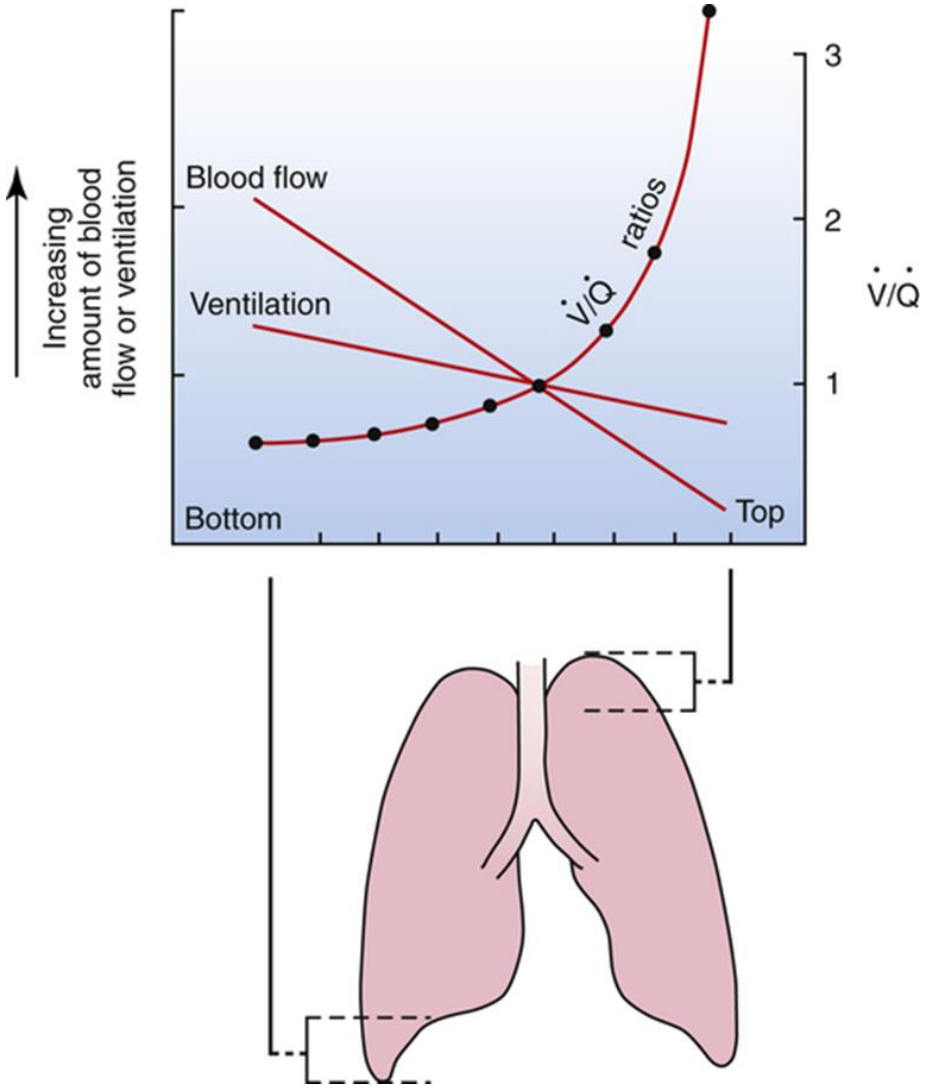

Figure 6: Ventilation-Perfusion ratio.

Legend. Although the lung bases are better perfused and ventilated than the lung apices, the slope of the ventilation curve is less steep than that of the perfusion curve. This is due to the lower density of air than that of blood. When estimating the ventilation-perfusion relationship, the index is > 1 at the apex and < 1 at the bases.

Under physiological conditions, this imbalance adds approximately 4 mm Hg to the alveolar-arterial O2 difference. Thus, normally, diffusion, the physiological right-to-left shunt, and the physiological ventilation/perfusion imbalance establish a normal alveolar-arterial gradient of approximately 10–15 mm Hg. Obviously, the gradient increases under pathological conditions.

Gas Transport

The blood gas transport system requires the integration of the respiratory and circulatory systems (blood and cardiovascular system) and refers to how O_2 reaches the tissues to maintain their metabolic processes, and how CO_2, the product of aerobic metabolism, is eliminated. Oxygen is transported physically dissolved in the blood and chemically combined with hemoglobin (Hb) within the erythrocyte. Under normal conditions, with a partial pressure of arterial oxygen (PaO_2) close to 100 mmHg, blood carries 0.3 ml of dissolved oxygen per 100 ml of blood (0.003 ml/100 ml for each mmHg of pressure, at a temperature of 37°C) (Henry's law). Dissolved oxygen is of considerable physiological importance, as its pressure determines both the degree of hemoglobin saturation (and the reversibility of oxygen binding) and the diffusion or movement of oxygen from the blood to the tissues (59). However, this amount is insufficient to satisfy cellular demands, even at rest. Clearly, an additional form is required to deliver oxygen to the cells, and this is Hg. Under normal conditions, each gram of Hb combines with 1.34 ml of O_2. A subject with 15 g of Hb/100 ml of blood has the capacity to transport 20.1 ml of O_2 per 100 ml of blood.

The erythrocyte has no nucleus, ribosomes, or mitochondria; therefore, it cannot divide, synthesize proteins, or perform oxidative phosphorylation. Its cell membrane allows it to be a very effective transporter of O_2: it is foldable, allowing it to pass through capillaries and, at the same time, is resistant to the turbulent flow of large vessels. The hemoglobin contained within the red blood cell molecule is responsible for transporting almost all the oxygen in the blood. It combines very quickly and reversibly with O_2, allowing it to be easily released. The Hb molecule, with notable properties, consists of four protein chains, each of which carries a HEM group (four pyrrole molecules with an Fe^{2+} at the center). The Fe^{2+} has a free bond to receive O_2. Both the alpha and beta chains are linked to the HEM group by a histidine. They have 141 and 146 amino acids, respectively. Their coiled shape is vitally important for the reaction with O_2 to occur. The shape is determined by weak bonds between amino acids of the same or different chains. This causes the HEM groups to be in the clefts formed by the weak bonds. The loop-like shape limits and controls the ease of access of O_2. One way to express the proportion of Hb bound to O_2 is its percentage of saturation (SpO_2). There is a relationship between plasma oxygen pressure (PO_2) and hemoglobin saturation, which is graphed in the Hb dissociation curve, which has a sigmoidal shape. This shape is due to the cooperative effect of Hb chains in binding O_2: the binding of a first O_2 to an HEM molecule in one of the four Hb subunits induces a local conformational change whose effect is transferred to the other subunits, facilitating the binding of more O_2 molecules to these subunits. The reverse occurs to release O_2. There are factors that shift the Hb dissociation curve in one direction or another. The mechanisms and factors involved in shifting the curve to the right, that is, leading to a lower affinity of Hb for O_2, are: 1- increased PCO_2; 2-decreased pH (increased hydrogen ions). This factor is related to the previous one since as pCO_2 increases, the action of carbonic anhydrase increases H^+, which binds to hemoglobin, decreasing its affinity by oxygen and oxygen is released into the tissues (*Bohr effect*); 3-increased temperature increased 2,3-diphosphoglycerate (2,3 DPG) (organic

phosphate presents erythrocytes). Its concentration increases with intense exercise, altitude, and chronic respiratory diseases. The first three factors facilitate oxygen delivery to the tissues, where PCO_2, H^+ concentration, and temperature are higher because of cellular metabolism. The shift of the curve to the left, which implies a greater affinity for O_2, is due to decreased pCO_2 and increased pH. This occurs in the pulmonary venous capillaries, increasing the affinity for O_2; fetal Hb binds more oxygen; inhalation of carbon monoxide (CO), which has 210 times greater affinity for hemoglobin than oxygen. This conformation prevents O_2 from binding to hemoglobin and, at the same time, prevents O_2 from being released (60).

CO_2 is a product of aerobic metabolism and is produced within mitochondria. In an adult, an average of 200-250 ml of CO_2 is produced per minute, which is transported from the cells to the blood and then reaches the lungs for elimination. Much of the CO_2 that reaches the blood diffuses into the red blood cells, where a portion combines with the amino groups of hemoglobin, and another portion reacts chemically with water to form bicarbonate and carbonate ions. Therefore, CO_2 is transported in the blood in three forms: dissolved in plasma; in the form of bicarbonate and carbonate ions; in combination with proteins (carbamino compounds). 5 to 10% of the CO_2 found in the blood is dissolved in plasma, and the amount of dissolved CO_2 is proportional to its partial pressure, following Henry's Law mentioned above. CO_2 is 24 times more soluble than oxygen. 60 to 90% of the CO_2 in the blood is transported as bicarbonate (HCO^{3-}), which is the main form of CO_2 transport. Bicarbonate is generated when CO_2 combines chemically with water, according to the following sequence of reactions:

$$CO_2 + H_2O \longrightarrow H_2CO_3 \longrightarrow HCO^{3-} + H^+$$

The first reaction is very rapid and occurs inside the red blood cell by the action of carbonic anhydrase (CA), generating carbonic acid (H_2CO_3). The second reaction, the ionic dissociation of carbonic acid, occurs without enzymatic action and generates bicarbonate (HCO^{3-}) and hydrogen protons (H^+). The H^+ binds to the imidazole groups of hemoglobin and other amino terminal groups of blood proteins by buffering the pH. (HCO^{3-}) leaves the red blood cell and is exchanged for chloride ions thanks to the action of a membrane transporter. 5–30% of total CO_2 is transported in the blood as carbamino compounds (61). Carbamino compounds are produced when CO_2 combines with the terminal amino groups of blood proteins, the most important of which is the globin in hemoglobin (carbaminohemoglobin). This reaction does not require enzymatic action and always generates a proton (H^+). Reduced Hb (or deoxyhemoglobin) can bind more CO_2 than oxyhemoglobin (HbO_2). Thus, the release of O_2 or its delivery into the capillaries facilitates CO_2 loading (*Haldane effect*) and vice versa; oxygenation (O_2 loading) in pulmonary capillaries then facilitates CO_2 discharge (5). Like what happens with O_2, there is a dissociation curve or equilibrium curve for CO_2, although its shape and meaning vary. The CO_2 dissociation curve is much more linear than the O_2 dissociation curve. This explains why the mixed arterial-venous O_2 (PO_2) difference is usually higher (approximately 60 mmHg) than that of CO_2 (PCO_2) (approximate difference of 5-7 mmHg).

Respiratory Mechanic

In physics, work is forcing times distance. In respiratory terms, it is the product of pressure times volume. In the ventilation segment, we discussed the volumes that enter and exit during

breathing, but for air to enter and exit, pressure changes are required. These changes are studied under the term respiratory mechanic. For air movement to occur, there must be a pressure gradient between the environment and the alveoli. It should be remembered that air moves from a location of higher pressure to a location of lower pressure, just as water moves from top to bottom. When the system is at rest (FRC), the pressure at the mouth is 0 cm H_2O and, in the alveoli, there is no airflow. At this moment, which is the resting expiratory position (and immediately before the next inspiration occurs), the expansion force of the rib cage generated by the respiratory muscles (primarily the diaphragm) is canceled out by the inward retraction of the thorax generated by the alveoli. These are two opposing forces or vectors that cancel each other out; there is no pressure gradient, and there is no airflow. During the following inspiration, the sequential contraction of the muscle bundles in the diaphragm generates greater outward expansive forces on the rib cage than exceeds the inward retraction of the alveoli. This exerts a kind of suction on the pleural space, generating negative pressure, which is transmitted to the alveoli (for example, if the pressure in the pleural space is -5 cm H_2O, in the alveoli it will be -1 or -2 cm H_2O). Since the mouth is 0 cm H_2O, there is a pressure gradient of 1 to 2 cm H_2O from the environment to the alveoli, and air will enter the system. At the end of inspiration, the entry of air generates an alveolar pressure greater than atmospheric pressure; the gradient reverses, and passive expiration occurs. The difference between pleural pressure (external to the alveoli) and alveolar pressure (internal to the alveoli) is known as transmural pressure. A pressure-volume curve is used to study the relationship between volume and pressure. Volume is measured with a spirometer attached to a mouthpiece in the patient's mouth, and pressure changes are measured with a pressure manometer attached to a nasogastric tube placed in the distal third of the esophagus. Changes in pressure in the distal third reflect changes in pleural pressure. Compliance (C) refers to how many ml of volume enter the airway for each cm of H_2O that the pressure in the pleural space becomes more negative (62). Normal C is 200 ml/cm H_2O. Evidently, compliance evaluates the system's capacity to distend through inspiration (it can also be measured during expiration, during which the volume will be greater than during inspiration for any pressure. This phenomenon is known as hysteresis and occurs due to changes in surfactant and recruitment/decruitment of alveolar units). Distensibility (compliance) is the ability of matter to stretch after being altered by a force. The ability to return to its resting point after stretching is known as elastance or elastic recoil (E). E is the ability of the lung to return to its resting point (the pulmonary hilum) and is given by the elastic tissue of the lungs. It would be a change in pressure per change in volume (5-7 cm H_2O/Liter). Note that the unit of volume is liters and not ml, since decimals would have to be used in the value (63). This property explains why when the lungs are removed from the thoracic cavity during an autopsy, they tend to empty their air and collapse. This does not occur under normal conditions because the lung, through the pleura, is attached to the thoracic wall, and this serves as support to prevent complete emptying. Therefore, there is a residual volume at the end of expiration (64).

In addition, there is normally a surfactant material that lines the alveoli on the inside, reducing surface tension and preventing collapse. The surface tension of the air-tissue of the alveolar membrane is because the molecules of liquid lining the alveoli generate forces of attraction between them. These forces are greater than those between the liquid and the alveolar air in the honeycomb’s structures, generating a centripetal pressure that tends to collapse the alveoli, particularly those having smaller (65). The surfactant material is formed primarily by

dipalmitoyl phosphatidylcholine and is amphipathic meaning that when it contacts the air-liquid interface, it directs his “hackbone” into the aqueous subphase and chains of hydrocarbons into the air. When this occurs, the surfactant material generates intermolecular repulsion forces opposing molecular forces responsible for the fluid surface tension. Therefore, the basic function of surfactant will reduce the surface tension in the alveoli. For the same surface tension, the alveoli with smaller radius generate a centripetal pressure inside them that exceeds the one of those with bigger radius. Therefore, small alveoli empty into large alveoli. The surfactant reduces this phenomenon. A third mechanism is to keep alveoli dry. Because the surface tension tends to collapse the alveoli, it tends to suck fluid into the alveolar space from the capillaries. By reducing the surface tension, the surfactant prevents transudation of fluid (66). At about 24 weeks of gestation of the human fetus, respiratory epithelial cells initiate synthesis of phosphatidylcholine, phosphatidylglycerol and surfactant apoprotein, but full production and function occur later, between weeks 34 and 36 (67). The components of the surfactant are synthesized and assembled into organelles called lamellar bodies and are secreted into the fluid delimiting extracellular alveolar surface (68). Resorption surfactants occur through alveolar type II cells, involving endosomes, and then are transported to the lamellar bodies to be recycled. Macrophages also take some surfactant in the liquid phase (10-20% of the clearing). Much less amount is absorbed by the interstice or removed by air (69).

To ensure airflow, not only is adequate pressure gradient sufficient, but it is also necessary to understand the other physiological phenomenon that opposes airflow, called airway resistance (R). R = pressure difference (cmH_2O) / flow (L/s), which means that R is significant only when there is airflow. The small airways are arranged in parallel, and therefore, the resistance to flow determined by thousands of small airways is extremely low. A significant portion of the R value to airflow is in the upper supraglottic airways, approximately 25 to 40% of the total R value. In an adult, airways <2 mm in diameter only account for 20% of total respiratory function and become the silent area of the lung. They will become symptomatic when their condition is very severe (e.g., COPD). The remainder of the R in normal circumstances in adult are found in medium-sized airways (70).

Airway diameter is the greatest determinant of R, but viscosity, length, and the type of flow generated are also important. This is well explained by Poiseuille's law (in physics for rigid tubes), where R is directly proportional to the tube length and viscosity (n), and inversely proportional to the radius to the 4^{th} power ($R = 8\ nl/P¶r^4$). (¶=3.14). Thus, a 50% decrease in radius will determine an increase in R of at least 16 times (which partly explains the high incidence of obstructive laryngitis in children under 5 years of age, until the larynx acquires a more significant diameter). Laminar, turbulent, and transitional flow coexist in the airways, with laminar flow occurring more frequently in smaller airways and turbulent flow occurring more frequently in larger airways. Finally, we will analyze how the flow is related to resistance and lung volumes. At high lung volumes, due to the larger diameter of the airways, the R is lower. Airway R is very high at low lung volumes. Closing volume, closing capacity and flow/volume curve allow us to study these concepts (71).

Respiratory Control

During the evolution of aerobic animal life on land, a respiratory control system was developed to regulate respiration according to metabolic and homeostatic demands.

Breathing is usually unconscious, automatic and involuntary, although in certain situations it can be influenced by higher brain centers such as the cerebral cortex. In its simplest form, respiratory control can be viewed as a three-component system. A group of receptors (chemoreceptors and pulmonary receptors) send impulses through afferent pathways to central controllers located in the brainstem. This controller processes the information and sends impulses through efferent pathways to the respiratory muscles (diaphragm, intercostal muscles, and abdominal muscles) to maintain normal, constant levels of PCO_2 and PO_2 (Figure 7).

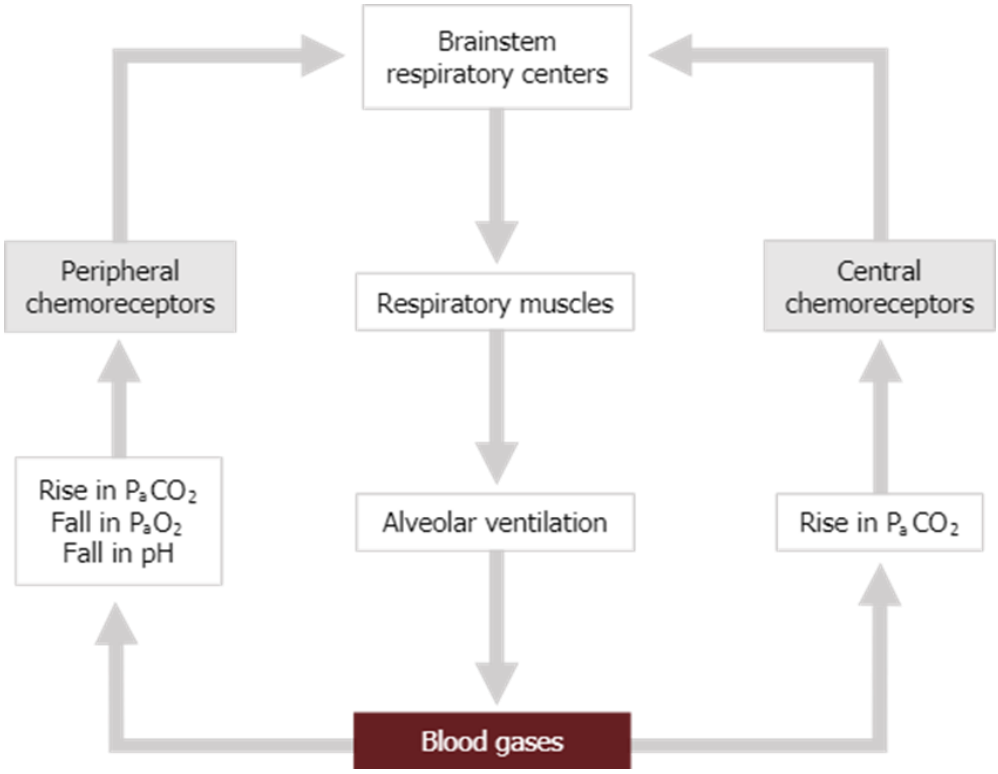

Figure 7: Respiratory control. A three-component system.

Legend. A group of receptors (chemoreceptors and pulmonary receptors) send impulses through afferent pathways to central controllers located in the brainstem. This controller processes the information and sends impulses through efferent pathways to the respiratory muscles (diaphragm, intercostal muscles, and abdominal muscles) to maintain normal, constant levels of PCO_2 and PO_2.

Central Controllers:

In the brainstem the controllers are in the medulla oblongata (MO) (spinal bulb) and the pons. Respiratory neurons in the MO are concentrated in two anatomical sites, both of which exhibit numerous interconnections (72) (Figure 8). The dorsal respiratory group (DRG), close to the nucleus of the solitary tract, composed primarily of inspiratory neurons, receives input from receptors via the glossopharyngeal nerve (CN IX) and the vagus nerve (CN X). They generate a response toward the inspiratory cells of the anterior horn on the opposite side of the spinal cord, which stimulate the diaphragm and internal intercostal muscles. The DRG is primarily responsible for synchronizing the respiratory cycle, adjusting the rhythm and frequency of breathing. Ventral respiratory group (VRG), located in the ventrolateral area of the MO, it sends impulses mainly to the diaphragm, external intercostal muscles, and abdominal muscles.

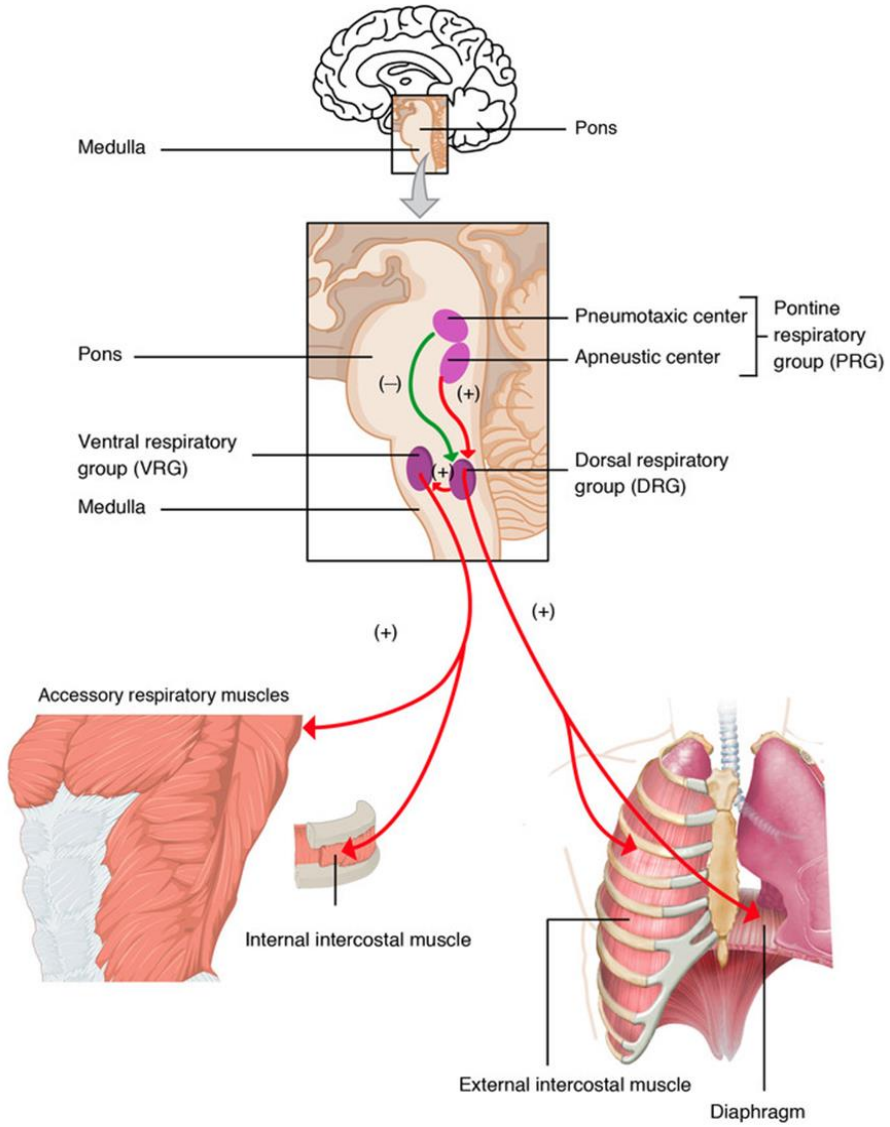

Figure 8: Central controllers in the brainsteam.

Legend. The location and interrelations of the neuronal centers located in the medulla oblongata and pons and the muscular effectors are shown.

It comprises a column of respiratory neurons, including (72):

1) Caudal ventral respiratory group (cVRG): contains the retroambigualis nucleus, which is predominantly expiratory, and the paraambigualis nucleus, which controls the force of contraction of the contralateral inspiratory muscles.
2) Rostral ventral respiratory group (rVRG) with a predominantly inspiratory function and is involved in the dilation of upper airway muscles.
3) Pre-Bötzinger complex (preBötC): located on each side of the MO, between the ambiguous nucleus and the lateral reticular nucleus, and is believed to be the anatomical location of the central pattern generator (CPG). It has predominantly inspiratory function, interacting with the respiratory centers to ensure a smooth transition between the different phases of breathing. The Bötzinger complex, located in the upper zone of

the RVG, participates in the expiratory process, playing an inhibitory role on the inspiratory cells of the DRG.

Pontine respiratory group or pneumotaxic center: It has a set of neurons in the upper portion of the pons, which discharge in synchrony with the different phases of respiration, sending inhibitory impulses to the respiratory neurons of the MO, via a Mult synaptic pathway. They thus modulate the intensity and frequency of medullary signals, contributing to the fine control of respiratory rhythm during eupneic breathing. Its stimulation causes the end of inspiratory effort with a decrease in inspiratory time. Kölliker–Fuse nucleus: main component of the pneumotaxic center, playing an essential role in the activation of the post-inspiratory phase, regulating the inspiratory-post inspiratory transition, and dynamically controlling upper airway patency during the respiratory cycle (73). Apneustic center: in the lower portion of the pons, it sends impulses that stimulate the inspiratory region of the MO, prolonging inhalation, and inhibitory impulses to expiratory neurons. It receives inhibitory signals from the pneumotaxic center at the end of inspiration and input from peripheral sensors through the vagus nerve, managing to stop inspiration and prevent overexpansion of the lung. The automatic inspiration-expiration process occurs synchronously, smoothly, finely controlled, and adaptively, thanks to the coordination of different neuronal groups.

Sensors or Receptors of the Control System:

1) Peripheral chemoreceptors (PCRs): the main ones are in carotid bodies, at the junction of the internal and external carotid arteries, and of lesser importance, in the aortic bodies, along the arch. They respond primarily to the decrease in pO2 and, to a lesser extent, changes in pCO_2 and pH (Figure 9).

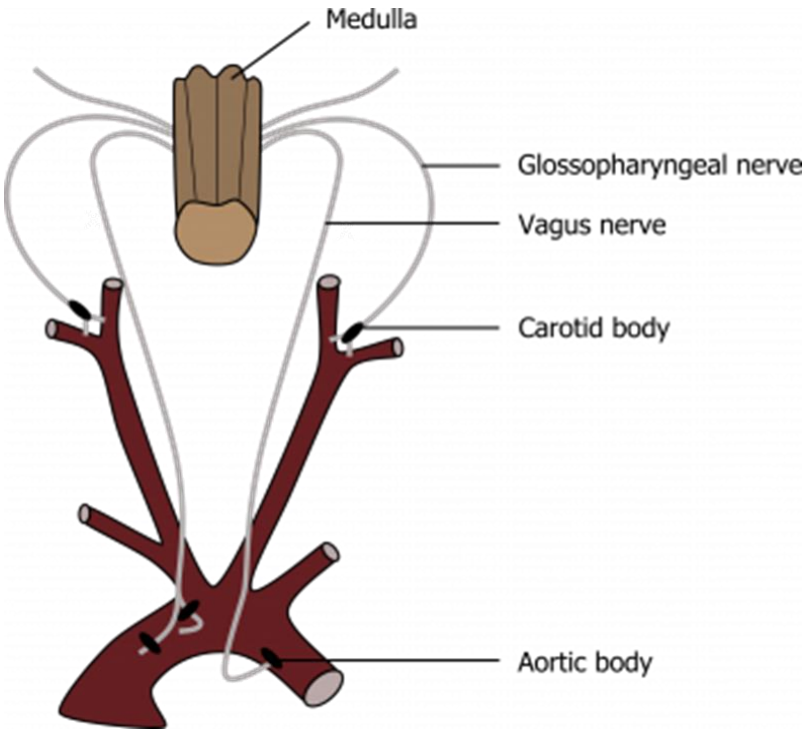

Figure 9: Peripheral chemoreceptors.

Legend. The location of the carotid and aortic receptors and their respective innervations are shown.

In both the carotid and aortic bodies, two types of cells have been identified: type I, or glomus cells, which under hypoxic conditions release catecholamines, primarily dopamine, as well as serotonin and acetylcholine, which possibly act as neurotransmitters; and type II, which would have a predominantly supportive function (74). Catecholamines released by type I cells stimulate the nerve endings of the carotid sinus nerve, conducting a signal through the glossopharyngeal nerve to the central nervous system, from which a response is emitted that increases ventilation, primarily by increasing tidal volume rather than respiratory rate. These sensors are very sensitive to a decrease in arterial pO_2 below 60 mmHg due to generous blood flow, generating a nonlinear response. In situations with normal PaO_2 but reduced O_2 content transported by Hb, as occurs in anemia and CO poisoning, the response is weaker. On the other hand, PCRs have a limited response to increased pCO_2 and decreased pH, contributing to less than 20% of the ventilatory response to these stimuluses. However, acidosis and hypercapnia can enhance the response to hypoxemia. Stimuli generated by the aortic bodies ascend through the vagus nerve.

2) Central chemoreceptors (CCRs): when the CCRs detect hypercapnia, ventilation increases proportionally within certain limits, since if hypercapnia worsens, it can cause narcosis and respiratory depression. Although the PCRs also generate stimuli that allows ventilation to be increased, their contribution in this regard is minor. In conditions of chronic hypercapnia, renal metabolic compensation increases bicarbonate, which diffuses across the blood-brain barrier and combines with hydrogen ions, reducing the stimulus on the CCRs, with a significant decrease in the ventilatory response. The mechanism that is usually believed to underlies is the reduction oi the ventilatory response to hypoxia and subsequent hypoventilation. Already since 1980s, Aubier and colleagues demonstrated, administering 100% oxygen to COPD patients, that this mechanism contributes only 22% to hypercapnia, and 30% is due to the reduced availability of hemoglobin to bind and transport CO_2, (oxyhemoglobin displaces the hemoglobin dissociation curve with CO_2 to the right by increasing the amount of CO_2 dissolved in blood, which determinates $PaCO_2$). The largest responsible for the increase of carbon dioxide is an increase in dead-space ventilation (48%) by release of hypoxic vasoconstriction in sub-ventilated areas, causing imbalance ventilation/perfusion and non-hypoventilation (75). Under conditions of central nervous system depression, for example because of depressant drugs, the CCRs may be depressed in their functioning, but not the PCRs, which acquire crucial importance under these circumstances.
3) Other non-chemical receptors: a) Stretch or slow-adapting receptors, located in the smooth muscles of the airway, primarily in the central airway. Their impulses reach the apneustic center via the vagus nerve and are responsible for the Hering-Breuer insufflation reflex, which is more prominent in newborns, causing interruption of inspiration, increased expiratory time, and a reduction in heart rate. b) Irritation or rapidly adapting receptors, located in the epithelial and submucosal lining of the airway, respond primarily to chemical irritants, including histamine, generating the cough reflex, reflex vasoconstriction, bronchoconstriction, and tachypnea. c) Muscle and joint mechanoreceptors of the chest wall detect changes in tension, movement, or elongation of these structures, contributing to the coordination of respiratory muscle contraction at rest and during exercise. They can limit the depth of the inspiration-expiration cycle and, in some cases, increase ventilation (73). d) Unmyelinated C fibers, which can be

found in the juxtacapillary position (J receptors) or at the bronchial level (bronchial C fibers), are sensitive to chemicals present in the pulmonary circulation and to increased interstitial volume, or pulmonary hyperinflation, and may play a role in the increase in interstitial space pressure, causing dyspnea or superficial tachypnea. e) Arterial baroreceptors, located in the aorta and carotid arteries, cause an increase or decrease in ventilation in response to hypotension tension or hypertension, respectively. f) Pain and temperature receptors, whose activation causes hyperventilation. g) Metaboreceptors, located in skeletal muscles, respond to different metabolic byproducts during exercise, with the goal of stimulating respiration.

Effectors:

The response from the control centers is directed at the muscles involved in inspiration, such as the diaphragm and internal intercostals; the dilator muscles of the upper airway; and other muscles such as the sternocleidomastoid, pectoralis major and minor, scalenus, trapezius, and serratus, known as accessory muscles, in addition to the abdominal muscles that participate in forced or voluntary expiration. For adequate ventilation control, integration and coordination between sensors, control centers, and effectors is necessary (75).

Mucociliary Clearance

Another important component of the structure of the respiratory system is mucociliary clearance. The mucus layer is rich in mucins, in addition to proteins, salt and water and is one that includes pathogens and foreign material (for example particles). Efficient clearance depends on ionic balance, water transport between mucus and epithelium, mucus secretion, and ciliary beat. There are approximately 200 cilia per cell, which beat 15-20 times per second and propel the gel at a speed of 1 mm/minute under normal condition (76). In major airways, mucins come from submucosal glands and from goblet cells on the epithelial surface, but Clara cells (Club cells) are the main mucus producers in small airways. The submucosal glands are positioned to produce abundant mucus in those regions of the airways (nasal cavities, upper airways, airway bifurcations) where there is an increased probability of large particle deposition (77). The submucosal glands are the simplest exocrine glands that exist. The mucins that form the gel are large, glycosylated proteins, which form polymers (78). Since the alveoli lack cilia, the particles deposited in them are engulfed by large cells with phagocytic activity such as macrophages and certain leukocytes, and thus the contaminating material leaves the lung through the lymphatics and/or with the blood.

CONCLUSION

Jean-Baptiste Pierre Antoine de Monet, chevalier de Lamarck, often known simply as Lamarck, was a French naturalist, biologist, academic, and soldier. Lamarck proposed that organisms develop traits based on their use or disuse of certain organs and, in the respiratory system, it is obvious that the structure is in function of the gas interchange. The objective is to give molecular oxygen to mitochondria for aerobic metabolism and obtain energy. So molecular oxygen is essential for life. The complex scaffolding of external respiration is designed to deliver oxygen to mitochondria, and the mitochondria are designed to perform the biochemical and molecular work of utilizing oxygen to obtain the energy needed for cellular life.

References

1. Herman JR, Newman PA, McPeters R, Krueger AJ, Bhartia PK (1995). Meter 3/total ozone mapping spectrometer observation of the 1993 ozone hole. J Geophys Res. 100:2973-2983.
2. Maina JN (2002). Fundamental structural aspects and features in the bioengineering of the gas exchangers: comparative perspectives. Adv Anat Embryol Cell Biol. 163: III-XII, 1-108.
3. Alvarado A, Arce I. (2016). Metabolic functions of the lung, disorders and associated pathologies. J Clin Med Res. 8:689-700.
4. Hamilton J. They Made Our World (1st ed). BBC World service and Broadside Books Ltd. 1995: London.
5. Priestley J. (1776). Experiments and observations on different kinds of air. Vol. II. London: J. Johnson
6. Wemple ML, Swenson KE, Swenson ER (2023). Oxygen therapy. Part 1-History, Physiology, and Evaluation. NEJM Evid. 2: April.
7. Wemple ML, Swenson KE, Swenson ER (2023). Oxygen therapy. Part 2- Indications and Toxicity. NEJM Evid. 2. June.
8. West JB. Respiratory Physiology: the essentials. (6th Ed). Lippincott Williams & Wilkins. 2000: USA.
9. Semenza GL, Wang GL (1992). A nuclear factor induced by hypoxia via de novo protein synthesis binds to the human erythropoietin gene enhancer at site required for transcriptional activation. Mol Cell Biol.12:5447-5454.
10. Semenza GL (2007). Life with oxygen. Science. 318:62-64.
11. Kaelin WG (2007). Von Hippel-Lindau disease. Annu Rev Pathol. 2:145-173.
12. Coleman ML, Ratcliffe PJ (2009). Signaling cross talk of the HIF system: involvement of the FIH protein. Curr Pharm Des. 15:3904-3907.
13. Patel SA, Simon MC (2008). Biology of hypoxia-inducible factor-2 alpha in development and disease. Cell Death Differ. 15:628-634.
14. Semenza GL (2010). Oxygen homeostasis. Wiley Interdiscip Rev Syst Biol Med. 2:336-361.
15. Taylor CT (2008). Interdependent roles for hypoxia inducible factor and nuclear factor-kβ in hypoxic inflammation. J Physiol. 586:4055-4059.
16. Eltzschig HK, Carmeliet P (2011). Hypoxia and inflammation. N Engl J Med. 364:656-665.
17. Alvarado A, Arce I (2016). Immune recognition in lung diseases: basic research and clinical application. Clin Infect Immunol. 1:31-40.
18. Semenza GL (2003). Targeting HIF-1 for cancer therapy. Nat Rev Cancer. 3:721-732.
19. De Bock K, De Smet F, Leite de Oliviera, Anthonis K, Carmeliet P (2009). Endothelial oxygen sensors regulate tumor vessels normalization by instructing phalanx endothelial cells. J Mol Med. 87:561-569.
20. Natarajan V, Parinandi NL. Mitochondrial functions in lung health and disease. New York, USA: Human Press; 2014.
21. Cloonan SM, Choi AM (2016). Mitochondria in lung disease. J Clin Invest. 126:809-820.
22. Gray MW, Burger G, Lang BF (1999). Mitochondrial evolution. Science. 283:1476-1481.
23. Chinnery PF, Zeviani M (2016). Mitochondrial matchmaking. N Engl J Med. 375:1894-1896.
24. Bialas AJ, Sitarek P, Milkowska-Dymanowska J, Protrowski WJ, Gorski P (2016). The role of mitochondrial and oxidative/ antioxidative imbalance in pathobiology of chronic obstructive pulmonary disease. Oxid Med Cel Longev. 2016:7808576.
25. Kang MJ, Shadel GS (2016). A mitochondrial perspective of chronic obstructive pulmonary disease pathogenesis. Tuberc Respir Dis (Seoul). 79:207-213.

26. Seth RB, Sun L, Ea CK, Chen ZJ (2005). Identification and characterization of MAVS, a mitochondrial antiviral signaling protein that activates NF-kappa β and IRF 3. Cell. 122:669-682.
27. Falk MJ, Decherney A, Kahn JP (2016). Mitochondrial replacement techniques - implications for the clinical community. N Engl J Med. 374:1103-1106.
28. Phimister EG. Mitochondrial donation clearing the final regulatory huddle in the United Kingdom. N Engl J Med. 376:171-173.
29. Picard M, Wallace DC, Burelle Y (2016). The rise of mitochondria in medicine. Mitochondrion. 30:105-116.
30. West BJ. Pulmonary Pathophysiology (2nd Ed). Williams & Wilkins. 1982: Baltimore/London.
31. West JB (2017). Physiology effects of chronic hypoxia. N Engl J Med. 376:1965-1971.
32. Semenza GL (2011). Oxygen sensing, homeostasis, and disease. N Engl J Med. 365:537-547.
33. Halliwell B (1996) The Radical View: Free radicals, health and disease. Odyssey 2:10-15.
34. Bryan CL and Jenkinson SG (1988) Oxygen toxicity. Clin Chest Med 9: 141-152.
35. Tobin MJ (1986) Update on strategies in mechanical ventilation. Hosp Pract 21: 69-84.
36. Gerschman R, Gilbert DL, Nye SW, Dwyer P, Fenn Wo (1954) Oxygen poisoning and x-irradiation: a mechanism in common. Science 119: 623-626.
37. Chapman DJ, Schopf JW (1983) Biological and biochemical effects of the development of an aerobic environment. In: Earths Earliest Biosphere: Its origin and Evolution. Schopf JW (Ed). Princeton Univ. Press pp: 302-320.
38. Reeves JT, Groves BM, Cymerman A, Sutton Wagner PD, Turkevich DJR, et al. (1990) Operation Everts II: cardiac filling pressure during cycle exercise at sea level. Respir Physiol 80: 147-154.
39. Ryan US, Ryan JW, Crutchley DJ (1985). The pulmonary endothelial surface. Fed Proc. 44:2306–2309.
40. Weibel ER. In: Handbook of Physiology, sect 3: The Respiratory System, vol 1: Circulation and non-respiratory Functions. Fishman AP, Fisher AB, (eds). Bethesda, MD: American Physiological Society; 1985. Lung cell biology; pp. 47–91.
41. Alvarado A (2023). Ion channels and respiratory channelopathies. Clin Res Trial. 9:1-17.
42. Powers KA, Dhamoon AS. Physiology, Pulmonary Ventilation and Perfusion. In Stat Pearls. Treasure Island (FL): Stat Pearls Publishing; 2021 Jan-: https://www.ncbi.nlm.nih.gov/books/NBK539907/.
43. West J B. Pulmonary Physiology. The essentials. Williams and Wilkins Co. Baltimore, USA, 2016.
44. Dejours P. Principles of Comparative Respiratory Physiology (2nd Ed). Amsterdam, Elsevier North-Holland, 1981.
45. Levitzky MG. Diffusion of Gases and Interpretation of Pulmonary Function Tests. In Pulmonary Physiology. Mc Graw-Hill Education. (9th Ed). USA 2017, pag 1-11.
46. Bashir M, Garg N, Muzaffar M, Nyiem M, Jaan I, et al (2024). A comprehensive guide to pulmonary function tests for 1st-year medical students – Simplifying PFTS and their interpretation. Asian J Med Science. 15:151.
47. Graham B, Brusasco V, Burgos F, Cooper B, Jensen R, et al (2017). ERS/ATS standards for single-breath carbon monoxide uptake in the lung. Eur Respir J. 49: 16E0016.
48. Suresh K (2016). Lung Circulation. Compr Physiol. 6:897-943.
49. Murthy R (2018). Pulmonary vascular pathophysiology. Cardiovasc Diagn Ther 8:208-213.
50. Bonnet S, Michelakis ED, Porter CJ, Andrade-Navarro MA, Thebaud B, et al (2008). An abnormal mitochondrial-hypoxia inducible factor-1α-Kv channel pathway disrupts oxygen sensing and triggers pulmonary arterial hypertension in fawn hooded rats: similarities to human pulmonary arterial hypertension. Circulation. 113:2630-2641.

51. Fijalkowska I, Xu W, Comhair SA, Janocha AJ, Mavrakis LA, et al (2010). Hypoxia-inducible factor-1α1 regulates the metabolic shift of pulmonary hypertensive endothelial cells. Am J Pathol. 176;1130-1138.
52. Archer SL, Marsboom G, Kim GH, Zhan HJ, Thot PT, et al (2010). Epigenetic attenuation of mitochondrial superoxide dismutase 2 in pulmonary arterial hypertension: a basis for excessive cell proliferation and new therapeutic target. Circulation. 121:2661-2671.
53. Beall CM (2007). Two routes to functional adaptation: Tibetan and Andean high-altitude natives. Proc Natl Acad Sci USA. 104(Supl 1):8655-8660.
54. Simonson TS, Yang Y, Huff CD, Yun H, Quin G, et al (2010). Genetic evidence for high-altitude adaptation in Tibet. Science. 329:72-75.
55. Lan SHN, Massam BD, Kulkarni SK, Lang CC (2018). Pulmonary Arterial Hypertension: Pathophysiology and Treatment. Diseases. 6:38.
56. Barile M (2020). Pulmonary Edema: A Pictorial Review of Imaging Manifestations and Current Understanding of Mechanisms of Disease, Eur J Radiol Open. 7:100274.
57. Levitsky M. Pulmonary Physiology. McGraw-Hill Education. (9th Ed), USA, 2018.
58. Kibble J, Halsey CR: The Big Picture, Medical Physiology. McGraw-Hill, USA, 2009.
59. West, JB (2016). Oxygen conditioning: a new technique for improving living and working at high altitude. Physiology (Bethesda). 31:216-222.
60. Shimoda, LA, Semenza, GL (2011). HIF and the lung: role of hypoxia-inducible factors in pulmonary development and disease. Am J Respir Crit Care Med. 183:152-156.
61. Saavedra BM, Escobar AP, Caussade L (2022). Respiratory physiology: transport of oxygen and carbon dioxide in the blood. Neumol Pediatr 2022. 17: 72 – 75.
62. Altose MD. Pulmonary mechanics. In: Fishman AP (editor). Pulmonary Diseases and Disorders. New York, McGraw-Hill Book (1st Ed). 1980:359-372.
63. Murray JF. Respiration. In: Smith LH and Their SO (eds). Pathophysiology. The biological principles of disease. Philadelphia, WB Saunders (2nd Ed). 1985: 753-856.
64. Rahman NM, Wang N-S†. Anatomy of the pleura. In: Light RW, Lee YCG (Eds). Textbook of Pleural Diseases. London, Hooder Arnold (2nd Ed). 2008:13-26.
65. King RJ, Clements JA. Lipid Synthesis and Surfactant Turnover in the Lungs. Compr Physiol 2011, Supplement 10: Handbook of Physiology, The Respiratory System, Circulation and Nonrespiratory Functions. p. 309-336. First published in print 1985.
66. Haagsman HP, van Golde LM (1991). Synthesis and assembly of lung surfactants. Annu Rev Physiol. 53:441-464.
67. Whitsett JA, Stahlman MT (1998). Impact of advances in physiology, biochemistry, and molecular biology on pulmonary disease in neonates. Am J Respir Crit Care Med.157(4 Pt 2): S67-71.
68. Clements JA, Avery ME (1998). Lung surfactant and neonatal respiratory distress syndrome. Am J Respir Crit Care Med. 157(4 Pt 2): S59-66.
69. Mason RJ, Crystal RG (1998). Pulmonary cell biology. Am J Respir Crit Care Med.157(4 Pt 2): S72-81.
70. He Z, Wang C, Tian, H (2025). Dynamic nature of airway resistance in ARDS: methodological concerns in MPR calculations. *Intensive Care Med*. 51:450–451.
71. Chen Y, Yuan Y, Chang Q. (2024). Continuous estimation of respiratory system compliance and airway resistance during pressure-controlled ventilation without end-inspiration occlusion. BMC Pulm Med. 24:1-8.
72. Hansel TT, Barnes PJ. An atlas of chronic obstructive pulmonary diseases: COPD. A resource for teaching and lecture (1st ed). Taylor & Francis, 2003, London.

73. Alvarado A, Arce I (2015). Molecular biology of chronic obstructive pulmonary disease from the bases to the therapeutic decision: a review. Br J Med Medic Res. 10:1-14.

74. Abara S, Cepeda J (2022). Respiratory physiology: breath control. Neumol Pediatr. 17:117-121.

75. Aubier M, Murciano D, Milic-Emili J, Toutay E, Daghflus J, et al (1980). Effects of the administration pf O_2 on ventilation and blood gas in patients with chronic obstructive pulmonary disease during acute respiratory failure. Am Rev Respir Dis. 122:747-754.

76. Button B, Goodell HP, Atieh E, Chen YC, Shenoy SW, et al (2018). Roles of mucus adhesion and cohesion in cough clearance. Proc Antl Acad Sci USA. 115:12501-12506.

77. Widdicombe JH, Wine JJ (2015). Airway gland structure and function. Physiol Rev. 95:1241-1249.

78. Fahy JV, Dickey BF (2010). Airway mucus function and dysfunction. N Engl J Med.363:2233-2247.