

Metabolic Functions of the Lung, Disorders and Associated Pathologies

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Abstract

The primary function of the lungs is gas exchange. Approximately 400 million years ago, the Earth's atmosphere gained enough oxygen in the gas phase for the animals that emerged from the sea to breathe air. The first lungs were merely primitive air sacs with a few vessels in the walls that served as accessory organs of gas exchange to supplement the gills. Eons later, as animals grew accustomed to a solely terrestrial life, the lungs became highly compartmentalized to provide the vast air-blood surface necessary for O₂ uptake and CO₂ elimination, and a respiratory control system was developed to regulate breathing in accordance with metabolic demands and other needs. With the evolution and phylogenetic development, lungs were taking a variety of other specialized functions to maintain homeostasis, which we will call the non-respiratory functions of the lung and that often, and by mistake, are believed to have little or no connection with the replacement gas. In this review, we focus on the metabolic functions of the lung, perhaps the least known, and mainly, in the lipid metabolism and blood-adult lung vascular endothelium interaction. When these functions are altered, respiratory disorders or diseases appear, which are discussed concisely, emphasizing how they impact the most important function of the lungs: external respiration.

Keywords: Metabolic functions; Lung; Lipid and pulmonary surfactant; Blood-endothelial interactions

Introduction

Respiratory function of the lung is critical and of immediate importance for the survival of organisms, and molecular oxygen is vital for energy that is essential for life [1]. Relevant to this primary role, the physiological model of the lung consists

of conducting airways to transport the gas in and out of the lungs and the alveolar membranes where gas exchange occurs by diffusion from the alveoli to capillaries. Within the lung, oxygen diffuses freely through the cells that form the alveolar septa to the pulmonary capillaries for eventual distribution by the systemic blood flow [2]. Due to the availability of O₂ from the alveolar space, the alveolar cells do not rely on pulmonary perfusion for oxygen delivery. For this reason in the adult, O₂ consumption of the lungs only represents 0.5-4% of the total oxygen consumption [3].

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 O₂ 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 [4].

Non-respiratory lung functions are many and varied. Active roles include active defense mechanisms, heme fluency, lipid metabolism and biological interactions with plasma [5]. The last two are the subject of this review. The objective was to discuss the metabolic role of the lung and how it generates various disorders or pathologies that interfere with gas exchange.

Lipid Metabolism and Pulmonary Surfactant

Overview

The lung plays an important series of functions in connection with lipids such as *de novo* synthesis of fatty acids and oxidation, lipid esterification, acid-ester bonds hydrolysis, hydrolysis of lipoproteins, synthesis of phosphatidylcholine, synthesis and secretion of prostaglandins and other eicosanoids from arachidonic acid precursors [6].

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 honeycombs structures, generating a centripetal pressure that tends to collapse the alveoli, particularly those having smaller [7]. The surfactant material is formed primarily by dipalmitoyl phosphatidylcholine and is amphipathic meaning that when it makes contact with the air-liquid interface, it directs his "hick-bone" into the aqueous subphase and chains of hydrocarbons into the air. When this occurs, the surfactant material generates intermolecular repulsion forces opposing molecular forces

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responsible for the fluid surface tension [7, 8]. 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, also it tends to suck fluid into the alveolar space from the capillaries. By reducing the surface tension, the surfactant prevents transudation of fluid [9].

At about 24 weeks of gestation of the human fetus, respiratory epithelial cells initiate synthesis of phosphatidylcholine, phosphatidylglycerol and surfactant apoprotein, but really full production and function occurs later, between weeks 34 and 36 [10]. The components of the surfactant are synthesized and assembled into organelles called lamellar bodies and are secreted into the fluid delimiting extracellular alveolar surface [6, 11].

Four distinct surfactant associated proteins have been identified: SP-A, SP-B, SP-C and SP-D; they are synthesized on polyribosomes and extensively modified in the endoplasmic reticulum and Golgi apparatus [12, 13].

Increased evidence supports the concept that proteins play a role as components of the innate immune system of host defense [14, 15].

Resorption surfactant occurs through alveolar type II cells, involving endosomes, and then is 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 [16].

Neonatal respiratory distress syndrome (RDS)

RDS is caused by a deficiency of pulmonary surfactant in the lungs of newborns, more common in those born before 37 weeks of gestation. In the United States (US), it is estimated that 20,000 - 30,000 RDSs occur in newborn infants each year [17]. There are hereditary rare cases, caused by mutations in the genes encoding the surfactant protein [18-23].

Due to the deficiency of the surfactant, great pressure would be required to open the alveoli. As this level of pressure cannot be generated, the surface tension collapses the alveoli and lung becomes diffusely atelectatic [7]. The presence of a disorder ventilation/perfusion and right-left shunt takes the infant to hypoxemia and hypercapnia. The gases also show respiratory and metabolic acidosis that causes pulmonary vasoconstriction and alters the epithelial and endothelial integrity, leading to exudation of proteinaceous material and formation of hyaline membrane [24, 25].

Arterial blood gases show hypercapnia, hypoxia and acidosis. A newborn is affected by RDS if you have a $\text{PaO}_2 < 50$ mm Hg (< 6.6 kPa), central cyanosis in room air or require supplemental oxygen to maintain $\text{PaO}_2 > 50$ mm Hg (> 6.6 kPa) and typical radiographic abnormalities: the "reticulogranular" texture of the lung opacities, decreased lung expansion, symmetrical generalized consolidation of variable severity, ef-

acement of normal pulmonary vessels, air bronchograms up to dense and ground-glass opacities [26, 27].

The treatment is based on surfactant, supplemental oxygen and mechanical ventilation when necessary. The prognosis with treatment is excellent; mortality is $< 10\%$. With only adequate ventilatory support, surfactant production starts, and once this happens, the RDS resolves within 4 - 5 days. However, at that time, if hypoxemia is severe, it can lead to multiorgan failure and death [28]. The surfactant, preferably natural, must be given to all newborns less than 24 weeks of gestational age requiring $\text{FIO}_2 > 0.3$ or higher 24 weeks with $\text{FIO}_2 > 0.4$ [29].

Regular dosages are multiples of 100 mg/kg. Ideally (by clinical and pharmacokinetic) it is 200 mg/kg [30-32]. Options for replacement surfactant are beractant, calfactant, poractant, and lucinactant [33-36].

There are two preventive strategies. When a fetus must be delivery between 24 and 34 weeks, the mother was given two doses of betamethasone 12 mg IM 24 h apart or four doses of dexamethasone 6 mg IV or IM q 12 h at least 48 h before delivery. This induces fetal surfactant production and reduces the risk of RDS or decreases its severity [37].

Prophylactic intra-tracheal surfactant therapy giving to neonates that are at high risk of developing RDS (infant < 30 weeks completed gestation especially in absence of antenatal corticosteroid exposure) has been shown to decrease risk of neonatal death and certain forms of pulmonary morbidity (e.g., pneumothorax) [38-44].

RDS can be anticipated prenatally using tests of fetal maturity, which are done on amniotic fluid obtained by amniocentesis or collected from the vagina (if membranes have ruptured).

Amniotic fluid tests include the lecithin/sphingomyelin ratio, foam stability index test (the more surfactant in amniotic fluid, the greater stability of the foam that forms when the fluid is combined with ethanol and shaken), and surfactant/albumin ratio [10].

Risk of RDS is low when lecithin/sphingomyelin ratio is > 2 , phosphatidylglycerol is present, foam stability index is > 47 , or surfactant/albumin is > 55 mg/g.

Pulmonary alveolar proteinosis (PAP)

PAP is a rare disease [45, 46]. Of unknown etiology, it is characterized by alveolar filling with granular eosinophilic material that stains positive with periodic acid-Schiff (PAS) method and is derived from the phospholipids and the surfactant proteins.

PAP is classified into two main categories: congenital (neonatal) or acquired [47-51]. The mortality rate associated with conventional therapy is close to 100% [49].

Iatrogenic secondary lung damage can occur in the congenital form as a result of high levels of ventilatory support and high FIO_2 [52, 53].

Acquired PAP is subdivided into an autoimmune form (previously termed idiopathic/primary) and secondary form (i.e., due to an underlying disease) [54]. Approximately 90% of patients with PAP have the autoimmune/idiopathic form of

PAP [55]. Secondary PAP is associated with various underlying diseases [56-67]. This variant occurs without antibodies against GM-CSF.

Autoimmune PAP is characterized by the presence of such antibodies. GM-CSF is a key cytokine for the growth of granulocytes and monocytes. Neutralizing anti-GM-CSF antibody is an IgG type immunoglobulin [68, 69]. The antibody hinders signaling GM-CSF and its receptor, and this molecular process is vital for the macrophage to clarify the surfactant. This obstacle occurs because the antibody sequesters GM-CSF, leaving without ligand the receptor, thereby inhibiting the late maturation processes of the alveolar macrophages, limiting their ability to catabolize the surfactant, and causing their accumulation in the alveolar spaces [70-72].

Dyspnea is present in 39% of cases and cough, productive or not, at 21%. Chest pain, weight loss, fatigue and fever are frequently. Hemoptysis is rare. The physical examination is usually normal. Cyanosis and digital clubbing may be present in up to 30% of cases, and auscultation may reveal crackles [73].

The chest radiograph shows bilateral and symmetrical areas of airspace consolidation. The pattern resembles acute pulmonary edema [74]. With high-resolution CT (HRCT), the characteristic finding is the presence of ground-glass opacities associated with thickening of the interlobular septa, giving the "crazy paving" pattern [75-77].

In patients with autoimmune PAP, measurement of the autoantibody level against granulocyte-macrophage colony-stimulating factor (GMAB) has been used to identify this disease. Uchida and colleagues were able to determine a serum level of 5 µg/mL as the optimal cutoff value for distinguishing autoimmune PAP from normal serum [78]. Other method is latex agglutination in serum. A concentration of > 19 µg/mL is specific to autoimmune PAP, and a concentration of < 10 µg/mL has a good negative predictor value [79]. Previously, an open biopsy was considered the criterion to establish the diagnosis of PAP. However, transbronchial biopsies or cytologic evaluation of bronchoalveolar lavage (BAL) samples are now routinely used to diagnose this disease [80].

Since the widespread use of whole-lung lavage, 5-year survival period is 95% [73].

It is lung lavage with saline serum (1 L infusions of warm saline at 37 °C, each time for a total of 15 L). Wash one lung and 24 - 48 h after wash the other, using general anesthesia and selective intubation [81, 82].

The patient's respiratory function improved due to the removal of proteinaceous material and local anti-GM-CSF antibodies [83, 84]. For patients with secondary PAP, in addition to whole-lung lavage, treatment of the underlying condition should be instituted.

The administration of exogenous GM-CSF or suppression of anti-GM-CSF antibodies has been used to treat those patients with autoimmune PAP [85-88].

Novel forms of therapy are currently being explored. These include plasmapheresis, which could be effective to reduce the concentration of anti-GM-CSF, and rituximab, which is a monoclonal antibody directed against the CD20 antigen on B lymphocytes and could attenuate PAP by reducing the concentration of anti-GM-CSF [89-95].

Lipoid pneumonia

The lipoid pneumonia is a specific form of lung inflammation that develops when lipids enter the bronchial tree. The gross appearance is a poorly defined area, pale yellow which has led to colloquial term, pneumonia "gold" [96, 97]. The lipid source may be exogenous or endogenous. In the exogenous, lipids enter the respiratory tract from the outside and can be acute or chronic. For example, nasal drops inhaled with an oil base in a long time, or accidental inhalation of cosmetic oil in a short time [98]. The mineral oil is used in children with partial small bowel obstruction by *Ascaris lumbricoides* [99]. It must be remembered that infants and children usually object in a vigorous way to ingesting oil, resulting in vomiting that precipitates aspiration [100].

Different substances called pyrofluids are used by the "fire-eaters" (performers who "spit fire"). The most common is the kerdan derived oil. After flame blowing, the "fire-eater" takes a deep breath, and can aspirate the kerdan remaining in the mouth. Pneumonia is acute, with symptoms appearing in the first 12 h after aspiration [101].

Other less common causes range from the use of antiarrhythmic amiodarone, aspiration of milk, oil poppy seed and egg yolks until occupational exposure to inhaled paraffin droplets released by the machines in tableware cardboard factories and suicide attempt [102, 103].

Factors that increase the risk include extremes of age; anatomical and structural abnormalities of the nasopharynx and esophagus, psychiatric disorders; episodes of loss of consciousness, and neuromuscular disorders, and digestive form of Chagas disease [104-107].

In endogenous lipids from the same patient's body, for example when an airway is obstructed, distal to the obstruction lipid-laden macrophages and giant cells fill the lumen of the excluded airspace [108].

Cough, dyspnea, usually fever and hemoptysis have also been reported, usually mild. It may be dullness to percussion, wheezing and crackles. The diagnosis lies in the history of exposure to oil, compatible radiological finding and the presence of lipid-laden macrophages in sputum or BAL [109, 110].

The diagnostic performance of chest radiography in diseases aspiration is low. Confluent consolidations and diffuse, ill-defined bilateral opacities, mass-like lesions, symmetrical and bilateral reticulo-nodular pattern, alveolar and interstitial mixed patterns, and unilateral or bilateral nodules have been described [111]. HRCT gives the best image for radiological diagnosis of the entity. The most common findings are airspace consolidation, ground-glass opacity, crazy paving pattern, interlobular septal thickening, nodules, airspace and mass-like lesions. Consolidation is more common in children, and adult crazy paving pattern [112]. The most characteristic feature is the presence of consolidation with areas of fat attenuation, i.e., a negative value of attenuation. Negative densities values between -150 and -30 HU inside areas of consolidation are highly suggestive of intrapulmonary fat and consistent with lipoid pneumonia [108].

With respect to treatment it is obvious that to identify and discontinue offending agent is essential, but sometimes the

oil is only a minor component of the commercial preparation [113, 114]. The use of corticosteroids to reduce the inflammatory response is controversial, and is reserved for severe cases [115].

Repeated aspiration can cause severe fibrosis, and hypoxia can lead to cor pulmonale [116]. Hypercalcemia is another possible complication, probably by inflammatory cells producing calcitriol [117].

While acute and fatal cases are described, most have an indolent course. Scar fibrosis with volume loss can occur. By suspending exposure symptoms, radiological abnormalities improve within months, but expectoration of oil may continue for years [104, 115, 117].

Other disorders and significant associations

Sphingolipids are mediators of signals. Altered metabolism of these lipids in the alveolar compartment is related to increase in ceramides and hyperinflammation, for example, in acute lung injury, cystic fibrosis and COPD [118, 119]. Cigarette smoke is an oily surface to enter the cells and hijacks the surfactant to alveolar macrophages. In addition, tar snuff inactivates the surfactant, decreasing its protective role and creating a toxic damage that perpetuates and promotes the development of COPD [120].

The accumulation of lipids in the lung worsens the gas exchange during microbial infections. The clearance of these lipids could improve lung function during these processes and could, therefore, be future therapeutic targets [121].

Endogenous lipid pneumonia and non-specific interstitial pneumonitis have been predated the development of PAP in humans [122, 123].

In extrinsic allergic alveolitis, it has been postulated that inflammatory reactions in the lung can be influenced by the local environment of the lipid [124].

In the presence of liver non-alcoholic hepatic steatosis (NASH), it is related to lipid dysfunction and in fact is considered, by some authors, as part of the metabolic syndrome [125-127]. In contrast, in lungs, the lipemia does not significantly impact the biology and biochemistry of lung lipids.

Pulmonary drug delivery lipid-mediated

The lungs are an attractive target for delivery of pharmacologically active ingredients (APIs) [128-131]. The most difficult aspect to develop a colloidal system for fogging is maintaining the critical physicochemical parameters for fogging to be successful [132].

Particles greater than 5 μm are deposited in the oropharynx and upper airways by impaction. Gravitational forces are predominantly responsible for the sedimentation deposited particles with a diameter of 1 - 5 μm , which happens in small airways and bronchioles way. Slow breathing provides sufficient time for the sedimentation [133]. Particles smaller than 0.5 μm are deposited in the deep alveolar regions but due to their small size many are exhaled [134]. Therefore, for drug delivery system for nanoparticles, sedimentation is the most

attractive deposit method.

Mucociliary movement clears particles from trachea till the tertiary bronchi and ejecting them by coughing or swallowing. In the alveolar region, the transport mechanism is more complex [135]. Actually there is a gap in knowledge regarding the exact mechanisms of uptake, transport and clearance of particles in the alveolar epithelium and as APIs enter the systemic circulation [132].

There are several systems for pulmonary application based on nanoparticles. Solid lipid nanoparticles (SLNs) are aqueous suspensions nanoscale prepared mainly from phospholipids and triglycerides physiological tolerability [136]. Solid lipid microparticles (SLMs) have also been used for delivery of antioxidants and anti-inflammatory drugs in asthma. Flavonoid quercetin can be delivered by SLM, like the antioxidant curcumin by SLN, both for asthma [137, 138]. There have also been studies of SLN with sildenafil for pulmonary arterial hypertension [135] with amikacin for lung infections [139] and doxorubicin for cancer [140].

Polymeric nanoparticles have gained rapid importance for pulmonary drug delivery. Proteins, genes, low molecular weight heparin, antineoplastic (paclitaxel), antioxidants to asthma and other inflammatory diseases of the airways have been studied with this system [132].

Liposomes are prepared primarily of phospholipids. They have a sustained release which maximizes the effect of the drug over an extended period of time. Surfactant, antibiotics (ciprofloxacin, amikacin, and amphotericin), and antioxidants (n-acetylcysteine, vitamin E, and glutathione) have been investigated in various models [141].

Blood-Endothelial Interactions

Endothelium

Pulmonary endothelium to perform its respiratory and non-respiratory functions requires a large area. Calculated surface of 70 m^2 is possibly underestimated due to the presence of pinocytotic vesicles and glycocalyx that serve as a gateway to the receptors, the enzymatic domains, transport molecules on the endothelial surface and act as a matrix for surface reactions [4].

Leukocytes, respiratory gases, water, electrolytes, nutrients and other molecules move endlessly in one direction or another, through the alveolar-capillary barrier. The pulmonary capillary endothelium is part of an elaborate mechanism to monitor systemic blood pressure.

Angiogenesis

This growth of new capillaries depends largely on the activity of endothelial cells.

In COPD, exposure to cigarette smoke and pollutants/biomass fuels initiates an inflammatory response at different anatomical sites [142]. In this process, pulmonary vascular remodeling, activation of endothelial cells and angiogenesis are involved [143].

In bronchial asthma, about 100 inflammatory mediators are released, which are growth factors and adhesion molecules [144, 145]. In addition, pro-inflammatory factors activated Th2 cytokines, apoptosis, necrosis, bronchial hyperreactivity and increased vascular permeability, angiogenesis and vascular remodeling [146].

There are a considerable number of patients over 50 years of age who have obstructive airway disease with features of a dual diagnosis of asthma and COPD [147]. The debate continues as to whether the COPD develops from asthma (Dutch hypothesis) or if both entities are completely independent (British hypothesis) [148]. Recently, a joint effort between GOLD and GINA tried to characterize an overlap syndrome (ACOS), which has characteristics of both diseases [149]. If the Dutch hypothesis is true, remodeling and angiogenesis, together with fibroblast activation, are vital in the development of asthma to chronic obstruction irreversible airflow.

All nucleated cells in the body sense and respond to hypoxia. Under reduced oxygen availability, hypoxia-inducible factor 1 (HIF-1) regulates the expression of genes that mediate adaptive response [150-153]. HIF-1 was first identified in human cells as a regulator of erythropoietin, a vascular-endothelial growth factor (VEGF) which stimulates angiogenesis and glycolytic enzymes [154].

Hypoxic pulmonary hypertension is a progressive and fatal complication of chronic lung disease. The pulmonary hypertension leads to right heart failure and progressive hypoxemia. The HIFs regulate target genes that play a role in the pathogenesis of pulmonary hypertension [155-157]. The alveolar hypoxia induces HIF-1 that activates the vascular smooth muscle cells leading to decreased expression of voltage-gated potassium channels, increased expression of transient calcium channels receptors-potential and increased expression of sodium-hydrogen exchanger. The resulting changes in intracellular concentrations of potassium, calcium and hydrogen trigger hypertrophy of smooth muscle cells, proliferation, depolarization and contraction, which leads to increased pulmonary vascular resistance. From a physiological point of view, the ultimate goal of treatment of chronic lung diseases is to improve alveolar oxygenation and relieve the hypoxemia [1].

HIF-1 therefore mediates alterations in energy metabolism in smooth muscle cells and endothelial cells play an important pathogenic role in hypoxic pulmonary hypertension (World Health Organization (WHO) group III) and in idiopathic pulmonary hypertension (WHO group I) [158-160].

Endogenous amines

Since 1925, when Starling and Verney showed that the lungs should be included in the circuit to continue defibrinated blood circulation through the isolated kidney, lungs are known to participate in the detoxification [161].

Histamine

The lung is rich in histamine. It originates from glucogenic amino acid histidine by histidine decarboxylase enzyme. Re-

ceptors are H1, H2, H3 and H4. It is degraded enzymatically by methylation or oxidative deamination [162].

It is released during immune reaction, particularly in type 1 allergic reaction. At the respiratory level, it produces bronchoconstriction that can be critical in asthmatic patients, induces vasodilation of arterioles and precapillary sphincters, decreases peripheral resistance with reduced systolic and diastolic blood pressure, and increases vascular permeability generating urticaria and laryngeal edema. It can also act in cardiac pacemaker, increasing heart rate and through the stimulation of H₂ receptors stimulate the secretion of hydrochloric acid. In pregnant woman it results in uterine contraction and also in the gastrointestinal smooth muscle. At the level of the central nervous system it has a role as a neurotransmitter and neuro-modulator. In anaphylactic shock, it is released into the lungs by degranulation of mast cells [163].

Serotonin (5-hydroxytryptamine (5-HT))

In the pulmonary circulation, there exists an effective system to remove 5-HT. The 5-HT, such as norepinephrine, is removed from the blood by a system-dependent sodium transport and a carrier [5].

Carcinoid tumor is a type of cancer that arises from the cells of the diffuse endocrine system and is mainly located in the gastrointestinal tract [164]. Carcinoid syndrome refers to a set of symptoms and signs that occur secondary to carcinoid tumor and include flushing, diarrhea, and, less commonly, heart failure and bronchospasm, mainly by the endogenous secretion of serotonin and kallikrein [165]. The syndrome occurs in approximately 5% of carcinoid tumors and occurs when vasoactive substances (such as serotonin) from the tumor enter the systemic circulation and hepatic metabolism escape [166].

The significant association between serotonin and pulmonary arterial hypertension (PAH) is of vigorous research. The serotonin transporter protein (SERT) and the serotonin receptor are vital to understanding this association [167]. The aminorex and dexfenfluramine anorectic behave like SERTs and indirect serotonergic agonists and have been associated as a cause of PAH. Serotonin then acts on the 5-HT receptor (1B) mediating constriction and proliferation of smooth muscle cells of the artery pulmonary [168].

Agents capable of selectively blocking the proliferation of smooth muscle cells by SERT require investigation as potential treatments in human PAH [169, 170].

Vasoactive polypeptides

The lungs are involved in activation and inactivation of circulating peptide release. Bradykinin is an inflammatory norepineptide generated by proteolytic cleavage of its precursor kininogen by the enzyme kallikrein. It exerts its action through two receptors, B1 and B2 and is degraded by three kininases. It is a potent vasodilator resulting in a reduction in blood pressure, also stimulates contraction of not vascular smooth muscle bronchus and intestine and is involved in the pain mechanism, cell growth and respiratory allergic reactions [171]. Brady-

kinin also causes natriuresis, contributing to the drop in blood pressure [172].

Angiotensin I, a decapeptide, is produced by action of renin, an enzyme present in the juxtaglomerular apparatus of the kidney, on angiotensinogen. ACE separates turn dipeptide His-Leu to form the octapeptide angiotensin II, one of the most potent vasopressors known. ACE is located in the pulmonary capillary endothelial surface, so you have easy access to blood flow. It is obvious that the ACE is involved in the metabolism of the two peptides (angiotensin and bradykinin) [5].

Inhibiting ACE is a well consolidated hypertension treatment by reducing the genesis of a vasoconstrictor peptide [173, 174]. Increased levels of bradykinin are considered responsible for the dry cough that occurs in some patients using ACE inhibitors, to cause sensitization of afferent sensory nerves in the airways to increase the reflection [175, 176].

Angiotensin II has pro-inflammatory effects. It has been postulated that angiotensin II may contribute to the FEV1 decline in persistent smokers [177]. ACE inhibitors might therefore reduce the FEV1 declining phenomenon. Patients with COPD show microalbuminuria, an indicator of systemic vascular endothelial dysfunction. It is possible that ACE inhibitors could have an effect on endothelial dysfunction and on vascular and parenchymal destruction. The protective effect of ACE inhibition also appears to be greater in patients with associated cardiovascular disease, hypertension and diabetes [178].

Prostaglandins

They are a group of substances of lipid nature derived from fatty acids. They are synthesized from essential fatty acids by the action of cyclooxygenases, lipoxygenase, and cytochrome P-450. The most important precursor of PGs is arachidonic acid. The group of enzymes involved are known as PG-synthetase.

As mentioned above, in bronchial asthma, approximately 100 inflammatory mediators are released, within which they are lipid mediators [145].

The leukotriene receptor antagonists (LTRAs) are less effective than inhaled steroids in asthma (ICS). They can be used as controller initial therapy for patients who are unable to learn or use inhaled steroids, for patients experiencing intolerable side effects with ICS, or for patients with concomitant allergic rhinitis (step 2) (GINA) [179]. They can be added to low doses of steroids in step 3 as another option to regular moderate doses of ICS plus SABA (as needed), but are less effective than adding an LABA (beta-2 agonists, long-acting); and in step 4 they can be added as a third controller drug to regular medium doses of ICS more LABA. This alternative is valid in children and adults [180].

Since prostaglandins involved in inflammatory stimulating nerve endings of pain responses, non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, work by inhibiting cyclooxygenase (COX) and thus, the production of prostaglandins. In patients with the triad of asthma, nasal polyposis and aspirin intolerance, it is believed that inhibiting COX, the arachidonic acid metabolism is biased toward the lipoxygenase pathway, generating more lipid mediators such as leukotrienes

favoring bronchospasm.

Conclusions

External respiration is the primal and the most important function of the lungs but not the only one.

Specific alterations of passive and active non-respiratory functions generate functional or anatomical disorders that compromise breathing later.

In these disorders, lipid metabolism and blood-endothelium interaction are prominently.

The basic scientific and clinical research of various diseases generated by alterations of these functions can produce knowledge on the pathophysiology, biochemistry, genetics and immunology. These studies allow us to understand the mechanisms leading to dysfunction pharmacology to advance the design of therapeutic strategies that impact. This will result in better control of them and respiratory function.

Source of Economic Support

None.

Conflicts of Interest

None.

Author Contributions

This work was carried out in collaboration between both authors. Authors AA and IA contributed equally in the planning, data collection, data analysis, writing and critical review. Both authors read and approved the final manuscript.

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