

## Pulmonary Emphysema: An Inflammatory Lung Disease

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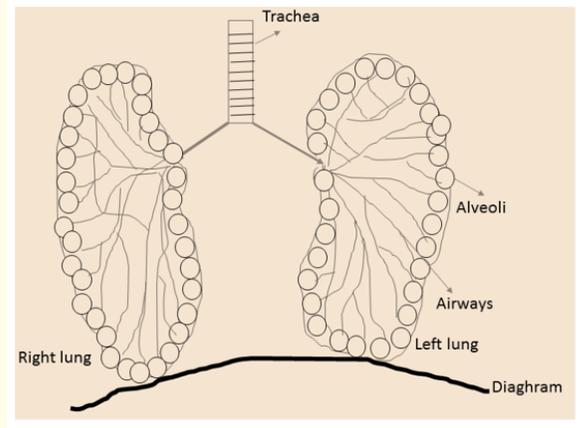
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### Introduction to the Human Lung

The lungs are one of the chief organs of the respiratory system of mammals like in humans and many other animals. In humans, the lungs are situated in the thoracic cavity at the middle position of the chest and are resting on the diaphragm. As shown in figure 1, humans and other animals have two lungs, a right lung and a left lung on either side of the heart. It has been observed that the right lung is slightly bigger than the left lung, the reason is unknown. The tentative weight of lung is 1.3 kilograms and it is spongy and sticky in nature and texture. Each lung is enclosed within a pleural sac, this sac contains a special fluid which is called as pleural fluid. This pleural fluid allows the inner and outer walls of the lung to slide over each other and hence reduces friction amid breathing time.

The major function of the lung is to deliver oxygen to cells from the atmosphere into the blood-stream, delivers oxygen to cells and removes waste gas that is carbon dioxide from blood-stream to the atmosphere, in a process of oxygen and carbon-dioxide exchange. The trachea or in more commonly called as wind pipe, conducts inhaled air into the lungs through its tubular branches, called bronchi. The bronchi thereafter then divide into smaller branches which are called as bronchioles, which are so microscopic. The bronchioles ultimately divide into alveolar ducts that give rise to the alveolar sacs which contain the alveoli, where gas exchange takes place. Between the alveoli is a thin layer of cells called the interstitium, which contains blood vessels and cells that help sup-



**Figure 1:** Human lung structure. Two lungs i.e. right and left lung. Lung is made up of tiny structure that is called as alveoli.

port the alveoli. There are about 300 to 500 million alveoli which are present in the human respiratory system.

### Chronic obstructive pulmonary disease

There are so many diseases which have been associated with the human lung. In comparison to the other human organs, lung diseases are some of the most common medical conditions in the world nowadays. It is estimated that tens of millions of people have lung disease in the United States alone. The possible reasons

of most lung diseases are thought to be smoking, infections, and genetics reasons. In accordance to the World Health Organization (WHO), globally, about 2 billion individuals are exposed to the toxic smoke of biomass fuel, one billion individuals inhale polluted air and nearly one billion individuals are exposed to tobacco smoke. Respiratory diseases execute an immense worldwide health burden. Five of these diseases are among most common causes of severe illness and death worldwide [1]. Nevertheless, here, these diseases are categories in the following three different types:

**Pulmonary tissue remodeling diseases:** all those lung diseases, in which the structure of the lung tissue gets affected or tissue remodeling due to the persistent inflammation that makes the lungs unable to expand fully. Pulmonary fibrosis and sarcoidosis are typical examples of such type of lung tissue disease.

**Pulmonary circulation diseases:** pulmonary hypertension is the typical example of disease under this category. In this disease, the blood vessels of the lungs are being affected. The reasons for the development of diseases are thought to be caused by clotting and inflammation of the blood vessels.

**Pulmonary airway diseases:** in this category, generally the airways conducting tubes that carry oxygen and other gases into and out of the lungs are being affected. Diseases under this category are usually due to a narrowing or blockage of the airways. Airway diseases include pulmonary asthma and asthma and Chronic Obstructive Pulmonary Disease (COPD).

However, patients with any above mentioned type of category may often have a shortness of breathing.

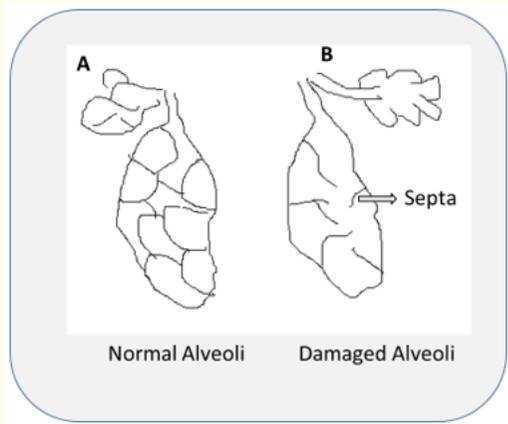
In this chapter, the prime focus of the author would be in the pulmonary airway diseases, specially the COPD. COPD is a chronic inflammatory lung disease that causes obstructed airflow from the lungs. It is seemly by slowly progressive development of airflow limitation. Nowadays, COPD has become one of the major and increasing global health problem. The WHO predicted COPD to be become the third most common cause of death and the fifth most common cause of disability in the world by 2022 [2]. Indeed, in the United States, COPD is already the fourth most common cause of death and the only common cause of death that has increased during the past 30 years [3]. However, India also contributes a significant and growing percentage of COPD mortality, which is esti-

mated to be amongst the highest in the world that is about 64.7 estimated age standardized death rate per 100,000 as reported by the WHO [3]. It has been seen that cigarette smoking is by far the most common cause of COPD, but only a fraction of the smoking population develops this complication. Exposure to air pollutants, occupational exposure to dust and fumes, and, in the developing world, exposure to biomass fuel used for cooking also are believed to be etiologic agents of COPD [4]. In addition, genetic susceptibility factors must contribute to the development of the disease [5]. A existing description of COPD is comprised mainly of two associated diseases: chronic bronchitis and pulmonary emphysema.

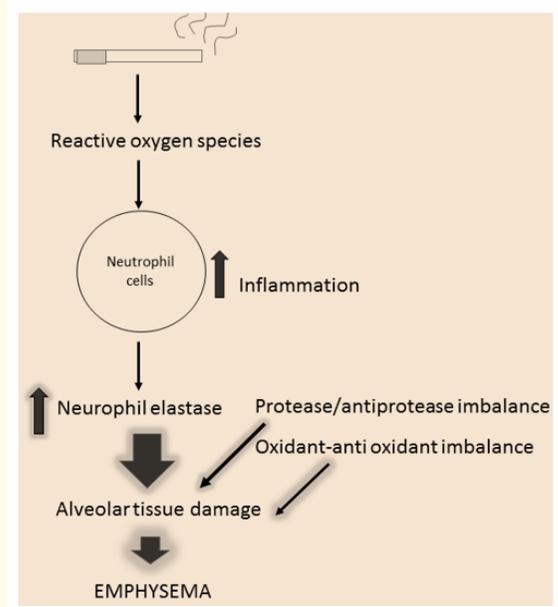
### What is pulmonary emphysema and its types?

Pulmonary emphysema is mentioned to as a pulmonary inflammatory disease in which destruction of the lung's gas-exchange structures generally take place that leads to insufficient oxygenation, disability, and frequently death. Such injury to the alveoli results in permanent "holes" in the tissues of the lower lungs and is thought to be irreversible (Figure 2). Emphysematous lung destruction reduces maximal expiratory airflow by decreasing the elastic recoil force that drives air out of the lungs. Symptoms include breathing difficulty, cough, mucus (sputum) production and wheezing. It's typically caused by long-term exposure to irritating gases or particulate matter, most often from cigarette smoke. When emphysema matures, the alveoli and alveolar ducts are demolished. With this impairment, the alveoli cannot sustenance the respiratory bronchial tubes and they gets collapse and cause an "obstruction" that results in trapping air inside the lungs. People with COPD are at increased risk of developing heart disease, lung cancer and a variety of other conditions.

As far now, there are three different types of pulmonary emphysema, which are known worldwide, i.e. a) centriacinar emphysema: in this type of emphysema, the alveoli and airways in the central acinus are generally affected. Destruction in the walls alveoli and alveolar ducts of the respiratory system are normally seen. b) The next type is known as panacinar emphysema. In panacinar emphysema the absolute acinus are usually gets affected. c) While the last third one is known as paraseptal emphysema. Paraseptal emphysema refers to a morphological subtype of pulmonary emphysema situated adjacent to the pleura and septal lines with a marginal distribution within the secondary pulmonary lobule [6].



**Figure 2:** Normal lung’s alveoli versus emphysema alveoli. In normal lung an intact alveoli with define alveolar septa is seen (a), however, in emphysema alveoli a damaged alveoli is visible with no define septa (b).



**Figure 3:** Pathogenesis of pulmonary emphysema. Cigarette smoke activates reactive oxygen species that further activates neutrophils and releases neutrophil elastase, imbalance of proteases/anti-proteases and oxidants/anti-oxidants imbalance that causes alveolar tissue damage.

**Pathophysiology and symptoms of pulmonary emphysema**

Pulmonary emphysema is mainly characterized by inflammation of lung parenchyma and pulmonary airways. Both types of involvement and activation of innate and acquired inflammatory processes are evidently noticed in the emphysema. Such activation of inflammatory processes may further lead to accumulate inflammatory mediators, including tissue proteases and cytokines, in the lung that ultimately causes injury to the lung and thereby contribute to tissue remodeling and destruction (Figure 3). Some genetic association in development of emphysema has also been reported, wherein,  $\alpha 1$ -antitrypsin deficiency has been well-described genetic risk factor for emphysema [7]. Additionally, involvement of oxidative stress and suppression of anti-oxidants due to the cigarette smoke inhalation, imbalance of proteases and anti-proteases [8] and apoptosis of epithelial and endothelial cells [9,10] are also been found to have a significant role in generating emphysema.

There are several symptoms which have been found to be associated with the emphysema, this may include coughing, wheezing, shortness of breath amid walking, tiredness (fatigue) chest tightness, and a hyper-secretion of mucus. Patients who gets emphysema, they may have an increased risk of pneumonia, bronchitis, and other lung infections.

**Management and treatment options for pulmonary emphysema**

Until today, there is no active treatment option has been available to re-establish normal gas exchanging lung parenchyma after emphysematous changes have been established. Even the available surgical treatments, such as volume reduction surgery and lung transplantation, are suitable only for a very limited subgroup of patients.

However, there are few options as discussed below are there which may provide some relief and it is temporary only. Moreover, the type of treatment will be contingent on the severity of the emphysema.

- **Abandoning cigarette smoking:** This is foremost option for management of emphysema. by quitting cigarette smoking one can able to reduce the ongoing inflammation in the lung due to smoke and thus one protect his/her lungs.

- **Use of Bronchodilator:** Bronchodilator is a medication that relaxes the muscles around the airways and opens the airways duct in the lungs. Normally, bronchodilators are used to treat respiratory diseases, such as asthma and COPD. They are able to relax the narrowed airways, which gets constricted or narrowed due to hyper-secretion of mucus of the airways.
- **Use of anti-inflammatory drug:** There are several steroid which are being used to reduce inflammation in the airways ducts. The exact doses of the same is still one of the greatest challenge, moreover its long-term side effects may also develop diseases like osteoporosis, hypertension, diabetes and weekend immunity.
- **Oxygen therapy:** Oxygen therapy is an option for emphysema patients whose lungs are not getting sufficient enough oxygen and whose blood oxygen saturation (<94%). Such patients needs to be provided oxygen, so that their blood oxygen saturation level can be maintained and should be >95%.
- **All trans-retinoic acid role:** Nevertheless, a decade ago, Massaro and Massaro reported that normal lung structure can be restored in emphysematous rat lungs by therapeutic supplementation with all-trans-retinoic acid [11]. This report brought much attention and considerable interest to retinoic acid. All trans-retinoic acid is a metabolite of retinol (vitamin A) that has been reported to implicate in the process of differentiation of many types of cells, tissues, and organs, including the lungs [12]. Beside this, there are several more reports in which authors have claimed that growth factors can also be one of the potential game changer candidate in the treatment of emphysema. Much talked growth factor in treatment of emphysema is keratinocyte growth factor (KGF). KGF also known as fibroblast growth factor-7 (FGF-7), is a potent mitogen for different types of epithelial cells and is a member of the FGF family of proteins which binds to a splice variant of FGFR2 termed FGFR2-IIIb or KGFR. KGF acts as a potent mitogen for alveolar type 2 cells.

In lung repair, exogenous supplementation of recombinant human KGF has been demonstrated, as assessed by *in vitro* and *in vivo* studies [13]. Plantier and colleagues recently demonstrated the protective effects of rHuKGF pretreatment in elastase-induced emphysema in mice [14]. Whereas, study performed by Yildirim., et

al. [15] suggests that therapeutic application of exogenous rHuKGF into emphysematous lungs is able to induce alveolar maintenance programs in the emphysematous mouse lung. Similar findings have also been reported by Moyal., et al. also [16].

Certainly, research into pulmonary stem cells has yielded obliging information concerning the origins and functions of stem cells at several anatomical locations. Stem cells have the exclusive ability to change into any cell type in the body by a process called cell differentiation. It is thought that stem cells may hold the key to new treatments, possibly even a treatment for emphysema. The application of exogenous stem cells to inspire the regeneration by endogenous lung stem/progenitor cells. Recently exogenous mesenchymal stem cells (MSCs) have been reported to repair the structure and improve the function of the injured alveoli in COPD models [17]. However, for implication of this method certainly needs a safe clinical trials procedure's optimization and greater effort is to be required towards a curing solution to emphysema patients.

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