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Research Article

Are environmental toxins responsible for biochemical and physiological changes in emphysema?

Aditya Banerjee[1], Imamul Haque Mansoori, Kishore Kumar Soni[1*]

[1]Department of Epidemiology, National Institute for Research in Environmental Health, Indian Council of Medical Research, Bhopal (M.P.), India.

Abstract: Emphysema is a chronic, progressive form of a lung disease. Emphysema and chronic bronchitis both are grouped within the same disease state called as COPD, i.e. chronic obstructive pulmonary disease. It is one of the prevailing cause of morbidity and mortality in both developing and industrialized countries. There are several risk factors associated with emphysema, but, cigarette smoking is predominant factor leading to pathological variations in lung function. However, significant published literature also indicates that about 15% of all the cases of emphysema is environment-related with developing countries at highest risk. Although, there are many published literature regarding the risk factors, epidemiological evidences, diagnosis, management and prevention of emphysema, but very few explains the biochemical and physiological changes associated with environmental carcinogens. This review will help in further understanding the mechanism underlying the changes.

Keywords: Emphysema, COPD, cigarette smoking, environmental carcinogens.

Background:

Emphysema is an obstructive disease of the lung because the normal airflow gets lowed due to the over-inflation and perforation of the lung tissue. It is characterised by dyspnea leading to obstructions in and out of the lungs influenced by host factors such as environmental surrounding, genetic mark-up and exogenous factors like both active and passive cigarette smoking. (Hogg and Senior, 2002a, Postma et al., 2015) According to the health statistics by the National Health Interview Survey, prevalence of emphysema is seen in 18 out of 1000 persons in the United States of America. (Adams et al., 2008) Burden of Obstructive Lung Disease study indicates the worldwide incidence of emphysema at 10.1% with higher prevalence seen in men compared to women at 11.8% and 8.5% respectively. (Buist et al., 2007) Globally, an estimate of 3 million deaths have been reported by WHO in 2015. ("WHO- Chronic Respiratory Diseases," n.d.)

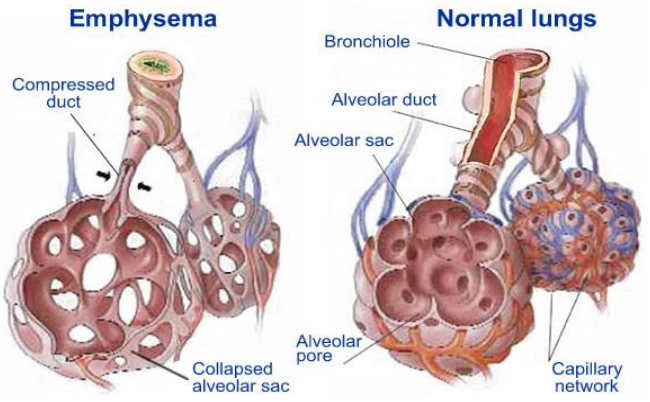


Figure 1: A comparative difference between morphology of normal lungs and emphysema. The collapsed alveoli turns into swollen air sac, also known as bullae, results in less oxygen transportation causing dyspnea. (Courtesy: Umstead, n.d.)

There are several reasons which could lead to destruction of lung tissues. One of the primary cause is cigarette smoking which directly distresses the cilia (helps in clearing up the mucus and other secretions) present on the epidermis of the cells in the thoracic cavity. Due to the constant exposure to smoke, the cilia gets depleted leading to build up mucus providing a favourable environment for the growth of opportunistic bacteria's among others leading to infections. ("What Is Emphysema, and What Causes It?" n.d.) This persistent inflammation leads to release of certain enzymes called alpha-1-antiprotease which decreases the elasticity nd further destructs the alveoli leading to progressing decrease in the lung function. (Umstead, n.d.)

This essay will emphasis on the biochemical and physiological changes that occur during emphysema.

Biochemical and Physiological Manifestation of Emphysema:

Emphysematous tissue has a diverse type of inflammatory cells which give rise to a range of proteinases leading to the destruction of lung tissue. The hypothesis of protease-antiprotease concept states that, pulmonary emphysema is the manifestation of uncontrolled digestion by the elastolytic proteinases of interstitial elastin. The elastin which is

produced by polymorphonuclear neutrophils and human neutrophil elastase (HNE) acts as a key factor during the degradation of lung tissue. (Grassi et al., 2013a) Traditionally, alpha-1-antitrypsin deficiency is associated with emphysema, in which HNE acts as a crucial proteinase. This was first identified by Laurell and Eriksson in 1963 and named it as circulating deficiency. (Laurell and Eriksson, 1963) However, the exclusive enzymes linked to emphysema pathogenesis is yet to be identified. However, several studies have been published were MMPs and neutrophil elastase are important proteinase mostly linked with emphysema. (Hogg and Senior, 2002a)

The probability that NE is significant in emphysema even amongst smokers with standard levels of α_1-antitrypsin has substantial support. For example, level of NE in BAL fluid is increased upon smoking and CT scan of smokers is an indication of emphysema with high levels of neutrophil specific proteinases together with NE in their BAL fluid compared to that of smokers without emphysema. (Betsuyaku et al., 2000, 1999; Fera et al., 1986) NE plays an important role in causing emphysema by degrading the elastin of the elastic fibres with other mechanisms operating simultaneously. In one of the study, rodents lacking NE (achieved through gene targeting) shown to have protection against emphysema with decreased alveolar organization of monocytes and neutrophils; caused by cigarette smoking. The non-NE mice also shown deprivation of TIMP-1 which is an inhibitor of the macrophage elastase. (Leberl et al., 2013; Shapiro et al., 2003)

Matrix metalloproteinases (a type of proteinase involved in destruction of alveolar tissues in emphysema) has been associated with pathological and physiological alteration of several tissues, including lungs. (Parks and Shapiro, 2001) These group of enzymes are usually untraceable in normal lung biopsy, but are easily detectable during any lung disease. During emphysema, the alveoli tissue produces two types of MMP's- neutrophil collagenase (MMP-8) and gelatinase B (MMP-9). These MMP's and alpha-1-antitrypsin together implicate the biochemical pathogenesis of the emphysema. (Shapiro and Senior, 1999) The MMP-1 produces fibroblasts and MMP-8 elevates the level of neutrophils during emphysema. It was studied in guinea pigs that upon exposure to cigarette smoke, together MMP-1 and MMP-8 gets elevated which not only causes alveolar septal destruction but also leads to the destruction of alveolar interstitial and epithelial cells compared to the normal lungs in control animals. (Selman et al., 1996) MMP-2 and MMP-9 proteinases are responsible for degradation of several ECM components, including elastin and type IV collagen. During exogenous exposure, the alveolar cells gets stimulated and releases MMP-9 which acts as a promoter and seen mostly in smokers with emphysema. (Minematsu et al., 2001) (Gooptu et al., 2014)

In emphysema, active protein synthesis lead to the misfolding and accumulation of polypeptide chains (alpha-1-antitrypsin) in high concentration within the cells. This misfolded protein evades the cellular control mechanism and effects the normal functioning of the lungs. (Goldberg, 2003; Helles, 2008) This accumulation causes distortion to the ER architecture of the lungs leading to the formation of NF- kappa beta complex which either helps in pro survival or functions in apoptosis based on the inflammatory response of the protein. (Hidvegi et al., 2005) The precise pathway which helps in the activation of the cellular toxicity of NF- kappa beta complex in alpha-1-antitrypsin deficiency implies the expression of mutant cells leads to the cell death and dysfunction of pulmonary system, exacerbating the development of chronic emphysema. (Lawless et al., 2004) (Gooptu et al., 2009)

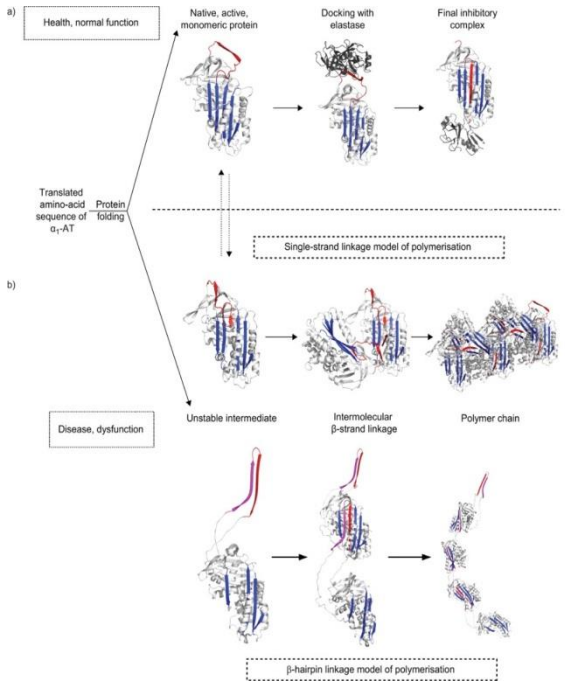


Figure 2: Representation of folding, misfolding and dysfunction during alpha-1-antitrypsin deficiency. A) Non mutated cells normally expresses the alpha-1-antitrypsin showing inhibition of neutrophil elastase. The reactive site loop (red) and enzyme substrate (dark grey) allows insertion to β-sheets (blue). B) The unstable intermediate state leads to the pathogenic mutations following the folding. This forms a β-hairpin linkage which inhibits the activity of alpha-1-antitrypsin. (Courtesy: Gooptu et all., 2009)

Figure 3: This is a representation of cellular and biochemical basis of alpha-1-antitrypsin deficiency emphysema stimulated by cigarette smoke. This exogenous inflammatory stimuli increases the levels of interlukin-8, elastin and interlukin-B4 creating a permeable gradient through which neutrophils migrate into airspace through circulation. (Courtesy: Gooptu et all., 2009)

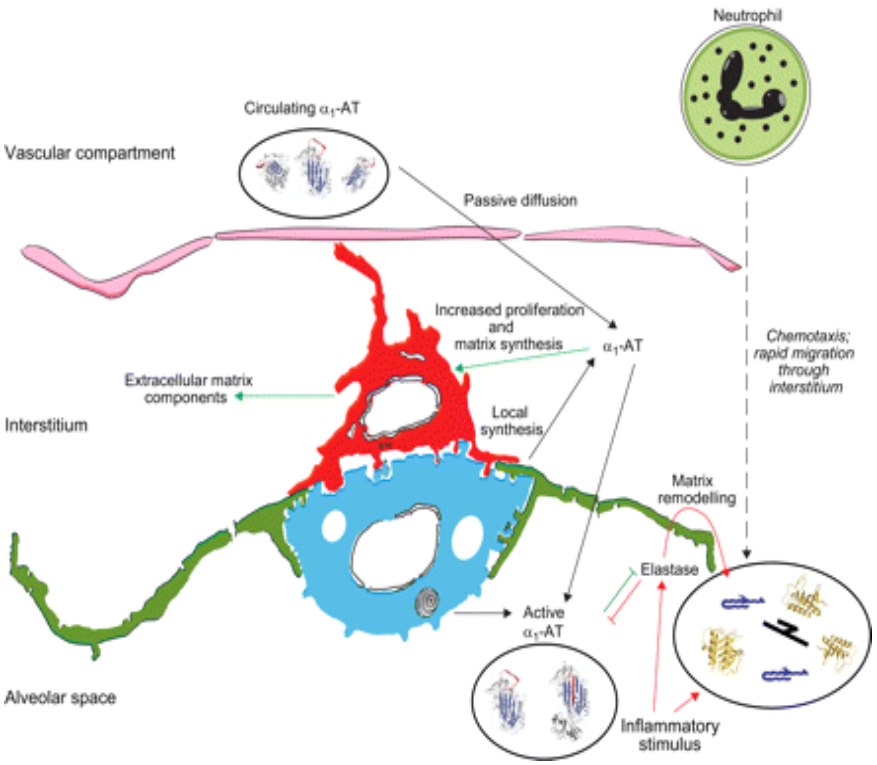
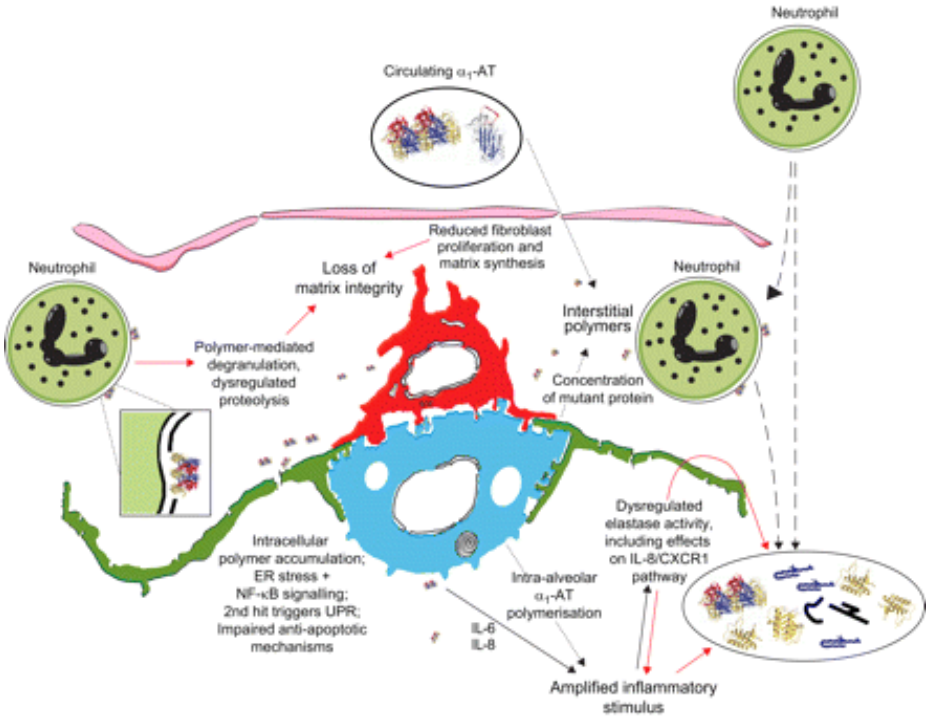


Figure 4: The presence of pathogenic mutagens results in the deficiency of alpha-1-antitrypsin which reduces the level of protein in the circulation and increases the level of type II pneumocytes. The loss of elasticity accelerates the pathogenesis and the ability to kill bacteria in decreased due to excessive elastase. This proteolysis leads to destruction of tissue causing dyspnea. (Courtesy: Gooptu et all., 2009)



Pathologically, emphysema is has characteristic enlarged airspaces distal to the bronchioles declining the surface area of the alveolar sack resulting in hindered gaseous exchange. Loss of alveolar walls and supporting structures effects the elastic recoil limiting the airflow. (Hogg, 2004) Centriacinar emphysema is the predominant type of pulmonary emphysema mostly restricted to the proximal respiratory bronchioles which are predominantly present in the upper lung zones with focal destruction. The adjacent lung parenchyma is frequently untouched with distal alveolar ducts and sacs present. It is also known as centrilobular emphysema, this unit is linked with and closely-related to prolonged cigarette smoking and inhalation of dusts. (Finkelstein et al., 1995)

Figure 5: Centrilobular emphysema with fibroid formation due to chronic smoke exposure. Courtesy: Radiopaedia.org

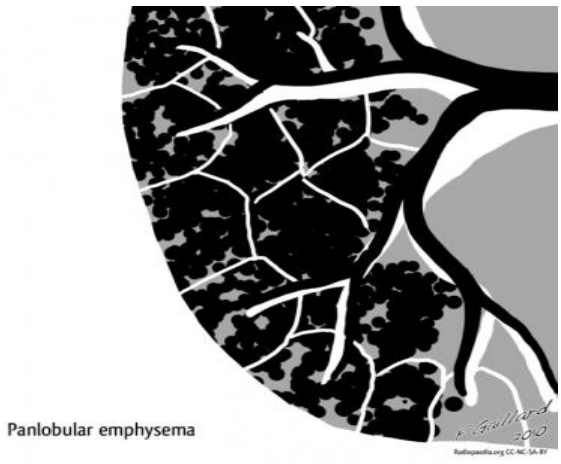


Figure 6: Panacinar emphysema is characterised by the entire destruction of alveolus. This form is predominant in patients with alpha-1-antitrypsin deficiency. Courtesy: Radiopaedia.org

Expiratory flow limitation i.e. EFL is a hallmark of COPD. This arises due to the parenchymal destruction i.e. emphysema and also because of airway dysfunction. Emphysema effects in condensed lung elastic recoil pressure that leads to a decreased driving pressure for expiratory flow through contracted and ailing airways in which airflow resistance is considerably augmented. (Hyatt, 1983) There are several factors involved in the progression of COPD. The most prominent is smoking followed by environmental surroundings. The chronic exposure invokes a series of inflammatory pathological changes which includes emphysema and chronic bronchitis. (Hogg et al., 2004) Expiratory limitations to airflow is the prime physiological defect in emphysema followed by intrinsic factors such as inflammation and remodelling of the bronchial wall, increased mucosal secretions and inflammation. Extrinsic factors includes loss of elasticity in tissues which support the small airways with its dynamic expiratory compression. (Barnes et al., 2009) The dysfunction in the respiratory muscles leads to increased respiratory rate which progressively increases functional residual capacity (FRC). This is known was dynamic hyperinflation. (BC Medical Journal," n.d.) (O'Donnell, 2006)

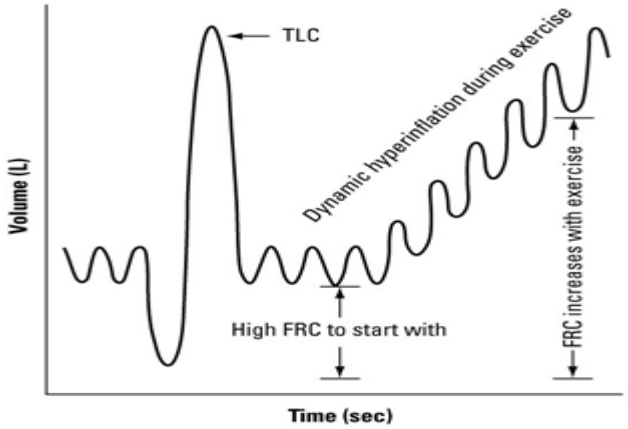


Figure 7: Dynamic hyperinflation in patients with chronic emphysema and exercise limitations in COPD. (Courtesy: O'Donnell, 2006)

Hyperinflation in emphysema is also characterised by dysfunctioning of ventilatory muscles which limits the endurance and force generation by the lungs. (Mergoni and Rossi, 2001) Another common characteristics is cardio logical disturbances triggered by smoking. Pulmonary hypertension worsen this condition and further adds to the mortality of this disease. Emphysema is diagnosed based on the FEV1/FVC ratio, which should be less than 0.7L. (Vestbo et al., 2013) and a reduction of FEV1 to less

than 80%.

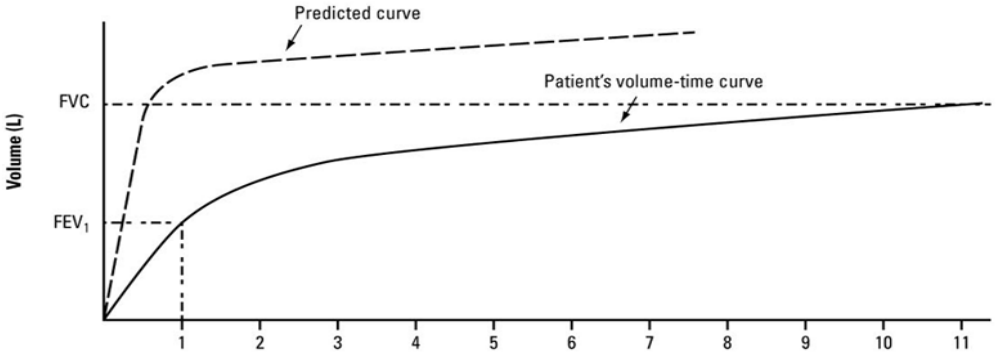


Figure 8: Volume/Time curve of an emphysematic patient. The straight line indicates airway obstruction compared to the predicted curve. (Courtesy: O'Donnell, 2006)

In typical chronic case of emphysema/COPD, the expiratory flow/volume curve is concave. This implies collapse of airway including forced exhalation.

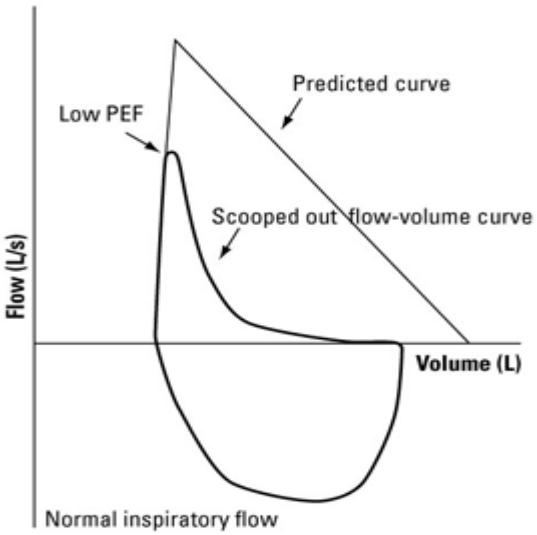


Figure 9: Representation of maximum inspiratory and expiratory flow/volume curve. In emphysema, due to the loss of supportive tissue, airways tends to collapse with forced exhalation giving a characteristic concave appearance. (Courtesy: O'Donnell, 2006)

Conclusion and Remarks:

Scientific knowledge acquired over the course of recent years establishes that emphysema is a result of proteolytic injury to alveolar septa due to various environmental and exogenous factors. (Umstead, n.d.; "What Is Emphysema, and What Causes It?," n.d.) The assumption based on the imbalance of protease-antiprotease have also been hypothesized, agreeing to which a sporadic or systematic release of proteinase that occurs in the pulmonary tissue, digests the proteins which is sustained by the pulmonary structure. In general, the lung structure is protected by harmful effects of protease inhibitors especially those circulating in the blood, which can be produced locally as well. Emphysema is the consequence of this imbalance of protease-antiprotease in support of protease. (Grassi et al., 2013b) The repair mechanism present in the pulmonary system is deficient and insufficient to reverse this imbalance followed by functional and physiological changes. The identified risk factors responsible for the early onset of oxidative stress and cellular inflammatory process has already been established. ("Biochemical Changes Induced by Emphysema in Children," n.d.) Upon the association of these risk factors with genetic predisposition, they lead to the improper functioning of inflammatory cells likewise T lymphocytes, CD8 and macrophages. These inflammatory responses leads to progressive destruction of the lung parenchyma and eventually lead to COPD. (Hogg and Senior, 2002b) The traditional treatment for patients with emphysema includes administration of bronchodilators such as salmeterol, salbutamol, and fluticasone etc., oral steroids like prednisone, surgeries to reduce lung volume among others. Alternative therapy which includes sulphur, coenzyme Q10, herbs (ginkgo biloba), N-acetyl-cysteine helps not only in reducing inflammation and mucus formation, but also boosts immune response. (Diaz et al., 2008) A recent medical invention using metal coils has helped in easing the suffering of emphysema patients. This is achieved by inserting slinky like metal coils to the damaged sections of the lung, restoring the elasticity and resulting in normal respiration. ("Doctors turning to metal coils for new emphysema treatment | CTV News," n.d.) (Ries et al., 2008) Regenerative therapy is has given hope in development of damaged alveoli's. Matthew Hind and Malcolm Maden has envisaged the future application of embryonic stem cells for emphysema. This has been achieved

in rodents where endogenous embryonic stem cells have not only proliferated but also differentiate into the damaged tissues *in situ*. However, this could also lead to development of sarcomas and initiate fibrosis. In future it can be rectified by generating patient's own induced pluripotent stem cells. (Hind and Maden, 2011)

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