Chapter

Emphysema

Tomislav M. Jelic

Abstract

Emphysema (Greek word meaning to inflate/to blow) is an increase in the size of airspace distal to the terminal bronchiolus, that is, hyperinflation of the alveoli due to the destruction of the gas-exchanging structures: alveolar walls, alveolar ducts, and respiratory bronchioles with coalescence of airspaces into the abnormal, much larger airspaces. The main consequences are the reduction of alveolar surface for gas exchange and the chronic obstructive pulmonary disease due to the destruction and disappearance of respiratory bronchioles with decreased total small airway diameter sum. Both decreased alveolar surface for gas exchange and chronic obstructive pulmonary disease lead to difficulty in breathing with dyspnea varying from mild to very severe. Two main pathohistologic types of emphysema are centriacinar and panacinar. Centriacinar emphysema involves the central portion of the acinus, and inflation mainly involves respiratory bronchioles and adjacent alveoli, and not all alveoli inside the acinus are involved. Panacinar (panlobular) emphysema is characterized by uniform enlargement and destruction of alveoli throughout the entire acinus. The panacinar emphysema is rare and its most common cause is hereditary alpha-1 antitrypsin deficiency. The centriacinar emphysema is the most frequent emphysema. It is mainly caused by smoking but also by coal dust exposure and advanced age.

Keywords: emphysema, chronic obstructive pulmonary disease, smoking, coal dust, alpha-1 antitrypsin deficiency, oxidative radicals, telomeres

1. Introduction

Emphysema, enlarged airspaces due to destruction of alveolar walls, respiratory bronchioles, and alveolar ducts, is a well-defined disease. However, in the medical practice, it is mainly encountered as an essential component of the chronic obstructive pulmonary disease syndrome. Other components are chronic bronchitis, small airway disease, small airway hyperactivity, and inflammation. Chronic obstructive pulmonary disease presents with cough, sputum production, and exertional dyspnea. In advanced cases, patients are breathless while doing even simple daily activities and may develop resting hypoxemia (blue cyanotic lips and finger nails) that requires continuous application of supplemental oxygen. Chronic obstructive pulmonary disease during its course is complicated by viral, bacterial, and fungal infections, and pneumonias and chronic obstructive pulmonary disease are the fourth leading cause of death in the USA. Urban air pollution and industrial air pollution are contributory factors in the genesis of chronic obstructive pulmonary disease, and with increase in cigarette smoking in developing countries, an estimate is that the chronic obstructive pulmonary disease will rise from the sixth to the third most common cause of death worldwide by the year 2020 [1].

2. Heading

2.1 Morphologic and histologic features of the normal lung

A normal lung consists of airways and alveoli. Airways are tubes (pipes) that conduct air to alveoli where gas exchange occurs. Oxygen (O_2) through alveolar wall enters into red blood cells in the alveolar capillaries and binds to hemoglobin, while carbon dioxide (CO_2) goes in opposite direction being released from hemoglobin, enters alveoli, and is being exhaled.

The trachea beyond the carina undergoes to about 23 generations of dichotomous branching. Airway tubes with diameter of more than 1 mm are called bronchi. With each division the diameter of the bronchus becomes smaller, but the sum of the two diameters exceeds diameter of the parent bronchus meaning that with divisions resistance to air flow becomes smaller. The bronchus consists of the lumen, mucosa, submucosa, muscularis, cartilage, and adventitia that is composed of connective tissue and contains lymphatics (**Figure 1**).

Bronchi are accompanied by branches of the pulmonary artery that have a diameter of similar size to the diameter of the bronchus they follow. The mucosa is mainly lined by columnar respiratory epithelium with cilia. All columnar cells lie on a basement membrane, but since columnar cells differ in their length, nuclei differ in their position regarding basal membrane, and respiratory epithelium appears stratified, but in fact it is pseudostratified. The mucosa also contains small number of mucinous cells that contain apical mucin, small number of basal cells, and rare neuroendocrine cells. Basal cells are precursors of ciliated cells and of mucinous goblet cells. Cilia arise from the apices of the respiratory cells and serve as escalator pushing mucin upstream to the throat and nose. Neuroendocrine cells are scattered singly and form small groups, neuroepithelial bodies near the airway bifurcations. The functional significance of the neuroendocrine cells is largely unknown. Beneath the pseudostratified ciliated mucosa is the submucosa that consists of loose connective tissue harboring bronchial mucous (seromucinous) glands, lymphoid tissue aggregates, and plasma cells. Mucinous glands secrete mucus composed of glycoprotein, proteoglycans, lipids, IgA (secretory) immunoglobulins, lysozyme peroxidase, and other substances to inactivate invading microorganisms, and trap air pollution particles. Cartilage plate and muscle bundles lie beneath the submucosa. The cartilage prevents collapse of the bronchial lumen. There are about 9–12 generations of bronchi. The smallest bronchi are 1 mm in diameter. Bronchi branch into the bronchiole. Bronchioles are less than 1 mm in diameter and they lack cartilage and

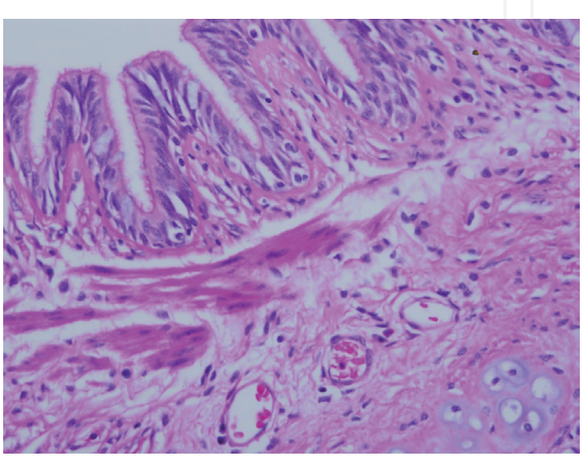

Figure 1.
Portion of the wall of the bronchus with respiratory epithelium with cilia, smooth muscle layer, and cartilage.

exocrine mucinous glands in their walls. The larger bronchioles are called terminal bronchioles and measure on average 0.5–1 mm. Since terminal bronchioles do not contain cartilage, they are also called membranous bronchioles (**Figure 2**).

Terminal bronchioles consist of respiratory mucosa composed of one layer of cuboidal ciliated respiratory cells and occasional Clara cells. Clara cells are non-ciliated columnar epithelial cells with protuberant apical cytoplasm that contains granules of surfactant and protease inhibitors. Clara cells are also precursors of bronchiolar epithelial cells. Goblet cells are generally not present or rare in the mucosa of the terminal bronchioles. Beneath the mucosa of the terminal bronchiolus is a layer of smooth muscle and connective tissue adventitia. Terminal bronchioles branch into the respiratory bronchioles. One side of the airway wall of the respiratory bronchiolus is lined by simple columnar to cuboidal bronchiolar epithelium without cilia. The opposite wall is lined by alveoli, that is, the wall consists of openings of the alveolar sacs. The average diameter of respiratory bronchioles is 0.15–0.2 mm. The respiratory bronchioles branch into about two more generations of respiratory bronchioles. Respiratory bronchioles branch into alveolar ducts, straight tubular spaces bounded entirely by alveoli (**Figure 3**).

In fact all alveoli (alveolar sacs) open into the alveolar ducts. Thus alveoli have incomplete wall and alveolar sacs are outpockets of alveolar ducts. Alveoli that appear lined with alveolar walls on all sides are in fact artifact of cut section. Alveolar ducts are not accompanied by the artery. The acinus is a functional unit of the lungs that consists of terminal bronchiolus with its respiratory bronchioles, alveolar ducts, and alveoli forming tridimensional spherical space with average

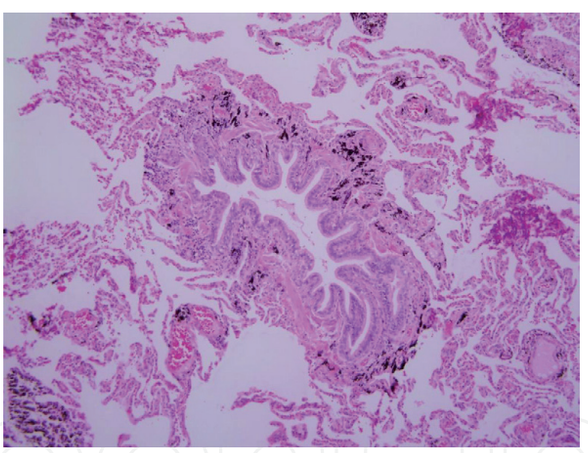

Figure 2.
Terminal bronchiolus, lined by respiratory epithelium, with no cartilage and no exocrine glands.

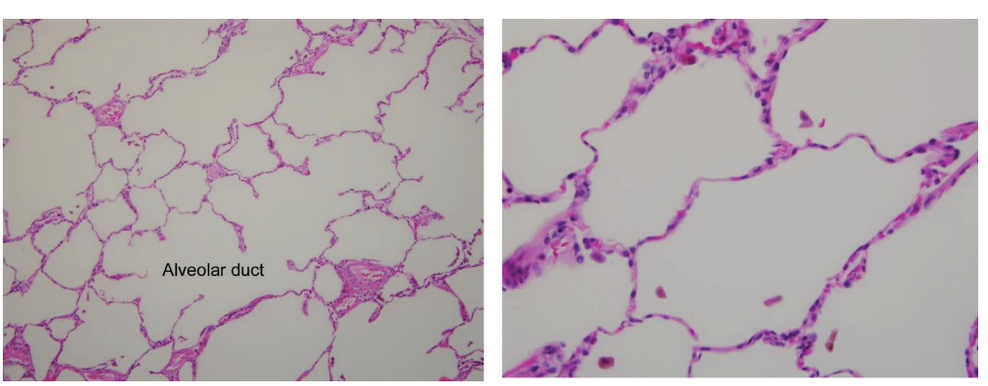

Figure 3.
Alveolar duct and alveoli (original magnification × 100) and alveolar septa with alveoli (original magnification × 400). Courtesy of Dr. Nadia N. Naumova.

diameter of 7.5 mm. There are about three generations of respiratory bronchioles inside the acinus and approximately 25,000 acini in normal adult male lungs with a volume of 5.25 liters [2]. Cluster of three to five terminal bronchioles, that is, acini, form pulmonary lobule. The pulmonary lobule is an anatomic unit, polygonal in shape, and bound by complete or incomplete connective tissue interlobular septa and measures about 1.5–3 cm.

Gas exchange starts in respiratory bronchioles and mainly occurs in alveoli. The alveolar wall (also called alveolar septum) is very thin in order to permit efficient gas exchange (**Figure 3**). It consists only of one layer of epithelial cells called pneumocytes. Pneumocytes type 1 are very thin, flat, large epithelial cells that cover 90% of the alveolar surface and are not capable of mitosis. Pneumocytes type 2 are cuboidal cell with large basal nucleus and prominent nucleolus. Pneumocytes type 2 secrete surfactant, are able to divide and participate in repair, and may become hyperplastic in response to alveolar damage. Pneumocytes type 2 are also precursors of pneumocytes type 1. Pneumocytes lie on the basal membrane that is fused with the basal membrane of the capillary endothelial cell. Thus the alveolar wall (septum) consists only of capillary sandwiched between the two layers of pneumocytes from two adjacent alveoli (**Figure 3**). An occasional myofibroblast may be present in the alveolar wall as well as rare scattered small lymphocytes, rare mesenchymal cells, and rare macrophages. Hematoxylin and eosin-stained sections of the normal lung on high magnification show delicate alveolar walls (septa) containing inconspicuous capillaries, occasional cuboidal cells of pneumocytes type 2, and nuclei of pneumocytes type 1, endothelial cell nuclei, and nuclei of rare scattered lymphocytes, mesenchymal cells, and macrophages. The cytoplasm of pneumocytes type 1 is too thin to be visible without special immunoperoxidase stains. Alveolar macrophages egress from capillaries, are increased in number in chronic inflammatory settings, and are involved in phagocytosis of foreign material as well in the inflammatory and immune responses.

The interstitium provides the connective tissue framework of the lungs and is composed of collagen fibers, elastic fibers, mesenchymal cells, and few inflammatory cells. In normal lungs the interstitium is generally inconspicuous and can be recognized only along bronchovascular bundles, around veins, and where it forms interlobular septa. In the children up to 4 years of age, the interstitium is more apparent and presents as thickening of the alveolar walls [3]. The term "small airways" includes airways with diameter of 2 mm and smaller and thus includes small bronchi, terminal bronchioles, and respiratory bronchioles.

2.2 Morphologic and histologic features of emphysema

Emphysema is permanent enlargement of airspaces distal to the terminal bronchiole (acinus) due to the destruction of the walls of the alveoli, alveolar ducts, and the respiratory bronchioles. Grossly, the lung is hyperinflated and spongy.

According to the location of the hyperinflated alveoli inside the acinus, there are four types of emphysema: centriacinar (centrilobular, proximal), panacinar (panlobular), distal acinar (paraseptal), and irregular (associated with scar). Each of the emphysema type has characteristic microscopic morphology and characteristic etiology.

The most frequent is centriacinar emphysema which comprises more than 95% of all emphysemas. **Centriacinar emphysema** involves proximal respiratory bronchiolus and adjacent alveoli, which is in the center of the acinus, hence the name centriacinar emphysema (**Figure 4**).

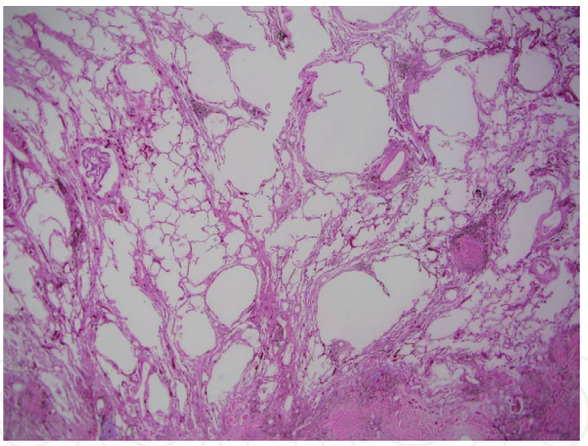

Figure 4.
Centriacinar emphysema caused by coal mine dust. Some alveoli are normal, some emphysematous. Hematoxylin and eosin stain, original magnification 20×.

Inhaled cigarette smoke or mineral dust, most frequently coal mine dust, reach respiratory bronchioles. There are no cilia in the respiratory bronchioles; cigarette smoke particles and coal dust particles (silica particles in the coal dust are the most toxic ones) stick there and initiate processes of inflammation and destruction. The first damaged structure is thus respiratory bronchiolus with its dilatation or disappearance. In the beginning, alveolar ducts and alveoli are spared. Soon their destruction and coalescence into the larger air space follows. In the acinus, which contains several (about 14) respiratory bronchioles, some bronchioles and alveoli are damaged, enlarged, and emphysematous, and some are not damaged and are normal in size. Thus characteristic microscopic feature with low power magnification of centroacinar emphysema is that some alveoli are normal and some emphysematous (**Figures 4** and **5**).

Cigarette smoke produces similar damage, and in fact the most frequent cause of centriacinar emphysema is cigarette smoking. Centriacinar emphysema predominantly involves the upper and posterior portions of the lungs and upper parts of the individual lobes. In severe emphysema, emphysematous spaces may coalesce and form bullae which may reach several centimeters in diameters. By definition bulla is at least 1 cm in diameter. Bullae are usually located in the lung apices and subpleurally but can occur anywhere in the emphysematous lungs.

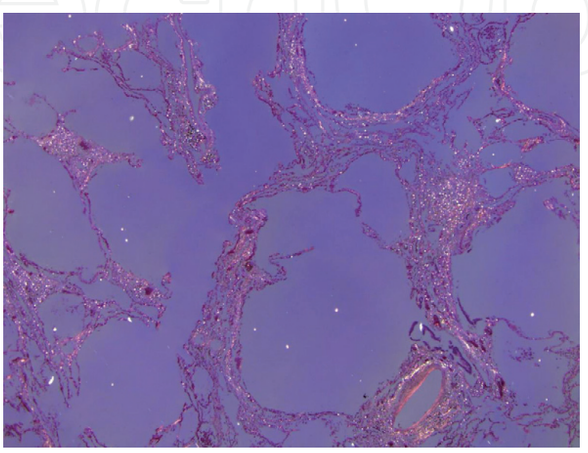

Figure 5.
Centriacinar emphysema and interstitial fibrosis caused by birefringent silica/silicate particles from coal mine dust. This is the same area as in **Figure 4**, *but with original magnification × 400 and photographed under polarized light to highlight birefringent silica/silicate particles; small white dots in the interstitium and silvery collagen fibers of interstitial (septal alveolar) fibrosis.*

Panacinar emphysema (panlobular emphysema) comprises 1% of emphysemas. It involves the entire acinus, that is, all alveoli in the acinus are about equally dilated, and all acini in the lobule are involved by panacinar (panlobular) emphysema (**Figure 6**). In centriacinar emphysema, some alveoli are enlarged and some are normal.

Panacinar emphysema is associated with alpha-1-antitrypsin deficiency, an autosomal codominant genetic disorder. Since defect is present in the gene (chromosome 14, segment q32.1), every cell, in which this gene is active and its product anti-protease alpha-1 antitrypsin enzyme pertinent, is affected. Thus all respiratory bronchioles, alveolar ducts, and alveoli are affected and about equally damaged and equally hyperinflated. The lungs are diffusely affected by panacinar emphysema, and histologically there is diffuse enlargement of the alveoli affecting the entire acinus. Normal level of alpha-1 antitrypsin in the serum is 20–48 μM/L . P atients with emphysema have concentration of serum alpha-1 antitrypsin 2.5–7 μM/L, and they are homozygous for PI*ZZ allele (PI* denotes protein inhibitor gene). There are more than 90 different alleles of PI* gene, and some variants cause a change in conformation of the alpha-1-antitrypsin molecule leading to polymerization and retention of misshaped protein in hepatocytes (major site of synthesis of alpha-1 antitrypsin) that might lead in children as well in adults to cirrhosis of the liver. If there is absence of protein inhibitor gene, serum level of alpha-1 antitrypsin is zero. Panacinar emphysema might also occur in intravenous drug abusers and then is accompanied with talc granulomas and interstitial fibrosis [3, 4]. Birefringent particles of talk could be seen under polarized light in the granulomas and in the fibrotic interstitium (**Figure 7**).

Distal acinar emphysema (paraseptal emphysema) involves distal part of the acinus including alveolar ducts and alveoli. It is rare. Distal acinar emphysema is most often present in the upper lobes beneath the pleura and along septa between lobules and also is called paraseptal, subpleural, or localized emphysema. The pathogenesis of distal acinar emphysema is unknown. Distal acinar emphysema produces apical bullae which may cause spontaneous pneumothorax in young adults.

Irregular emphysema is airspace enlargement due to lung destruction associated with scarring, also termed scar emphysema, paracicatrical emphysema, and perifocal emphysema. Foci of irregular emphysema are asymptomatic and clinically insignificant. The National Heart, Lung, and Blood Institute does not regard irregular emphysema as a form of emphysema but as "airspace enlargement with fibrosis" [5].

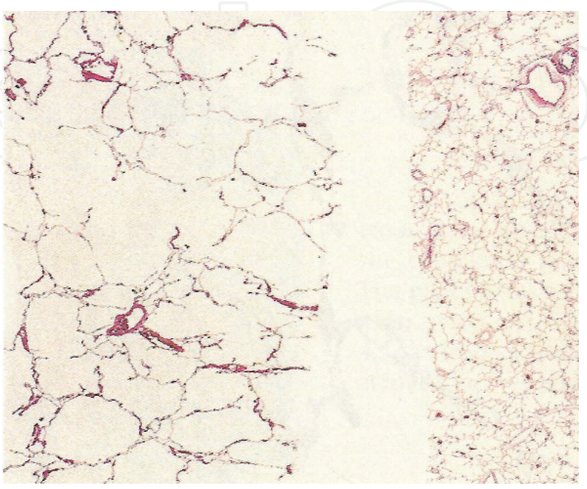

Figure 6.
Panacinar emphysema (left) and normal lung (right). In panacinar emphysema, all alveoli are enlarged. Figure 6, is reproduced with permission from the American Registry of Pathology from the Atlas of Nontumor Pathology Series; Non-Neoplastic Disorders of the Lower Respiratory Tract by William D. Travis et al published by the American Registry of Pathology and the Armed Forces Institute of Pathology Washington DC, USA, Copyright© 2002.

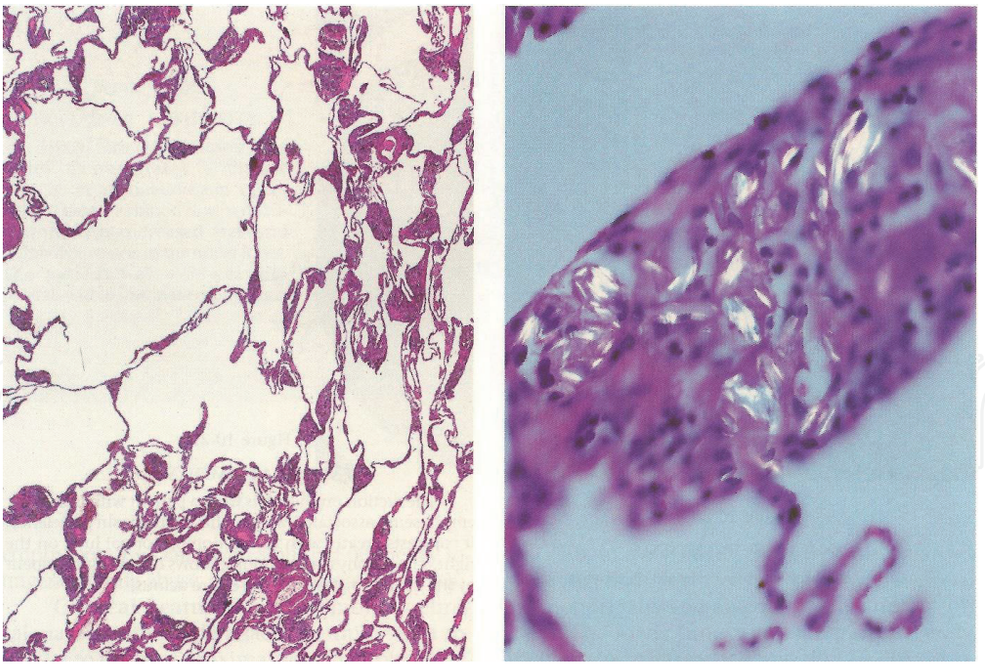

Figure 7.
Panacinar emphysema caused by drug abuse. Mild interstitial fibrosis is present as well as birefringent deposits of talc in the interstitium. Figure 7 is reproduced with permission from the American Registry of Pathology from the Atlas of Nontumor Pathology Series; Non-Neoplastic Disorders of the Lower Respiratory Tract by William D. Travis et al published by the American Registry of Pathology and the Armed Forces Institute of Pathology Washington DC, USA, Copyright© 2002.

The pathogenesis of centriacinar and panacinar emphysema is conceptually similar and based on proteinase-antiproteinase imbalance, that is, inequity between enzymes that degrade the extracellular matrix and proteins that oppose this proteolytic activity [6]. The first clue appeared in 1963 when Laurell and Eriksson identified patients with alpha-1 antitrypsin (more appropriate name is alpha-1 antiproteinase) deficiency on serum electrophoresis who had severe emphysema of early onset and in 1964 when Gross and coworkers demonstrated that proteolytic enzyme papain can produce emphysema in rats [7, 8]. Alpha-1 antitrypsin is a proteinase inhibitor that inhibits proteolytic enzymes, primarily neutrophil elastase. Elastase is an enzyme that destroys elastin fibers, and if it is not adequately inhibited by alpha-1 antitrypsin, destruction of acinar tissue follows leading to emphysema. Imbalance between other proteolytic enzymes (metalloproteinases including interstitial collagenase-1, interstitial collagenase-3, metalloelastase, matrilysin, gelatinase A and gelatinase B, cathepsins) and their inhibitors (tissue inhibitors of matrix metalloproteinases, elafin, epithelium-derived secretory leukoprotease inhibitor) also contributes to emphysema and chronic obstructive pulmonary disease [3, 6].

Cigarette smoking is the most frequent cause of emphysema and accounts to 80–90% of chronic obstructive pulmonary disease cases in the USA [9]. Cigarette smoke and coal mine dust cause emphysema by a similar pathophysiologic pathway. Inhaled cigarette smoke as well as coal mining dust particles travel by airflow to respiratory bronchioles and alveoli where they interfere with epithelial cells, alveolar macrophages, and neutrophils. Cigarette smoke contains per puff an estimated 10^{15}–10^{17} oxidants/free radicals and about 4700 different chemical compounds, including reactive aldehydes and quinones [10, 11]. Toxic oxidant compounds in cigarette smoke induce DNA damage and peroxidation of lipids, harm proteins, fold proteins, and cause them to aggregate in the cytoplasm of the respiratory cells and alveolar cells [12]. Alveolar epithelial cells and macrophages damaged by cigarette smoke release cytokines which invite inside alveoli

inflammatory cells mainly macrophages but also T cells (T8 more than T4) and small number of neutrophils. Characteristic histologic findings in cigarette smokers are tobacco-associated respiratory bronchiolitis with the presence of macrophages containing smoker granules (yellow-brown) inside alveoli (**Figure 8**). Macrophages and neutrophils activated by cigarette smoke or silica (quartz) [13] particles in coal mine dust release abovementioned proteolytic enzymes that destroy collagen and elastic alveolar tissue causing connective tissue breakdown and alveolar tissue destruction, that is, emphysema [14]. Oxidative radicals in the cigarette smoke as well as quartz-generated hydrogen peroxide not only damage intracellular proteins but also inactivate alpha-1 antitrypsin by oxidizing the SH group of methionine to methionine sulfoxide [14]. Other proteins, for example, proteasome with caspase-like activity, are also impaired by this oxidation. The final effect of cigarette smoke and inhalation of coal mine dust is unopposed (or insufficiently inhibited) action of proteolytic enzymes that destroy lung parenchyma and cause emphysema.

Macrophages also produce transforming growth factor-beta, platelet-derived growth factor, and tumor necrosis-alpha, which all stimulate fibroblast growth, collagen production and repair with associated fibrosis [15]. Repair may not be perfect and interstitial fibrosis may occur. Bronchioles and small bronchi can be involved by fibrosis and contribute to the chronic obstructive pulmonary disease. Tobacco-caused respiratory bronchiolitis-associated interstitial lung disease with fibrosis (**Figure 9**) is now a plausible and established term [16, 17].

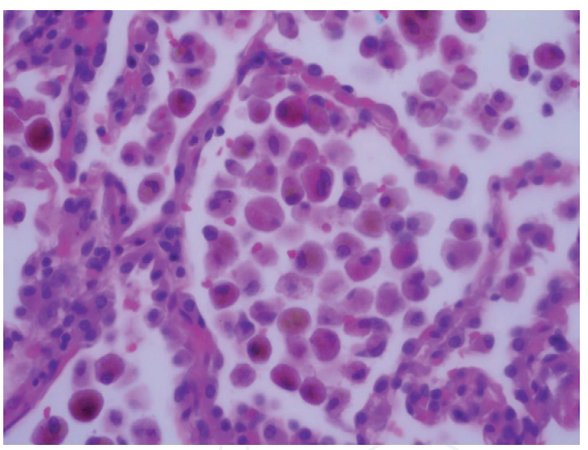

Figure 8.
Tobacco-associated respiratory bronchiolitis. Macrophages with smoker granules inside alveoli. Hematoxylin and eosin stain, original magnification 400×.

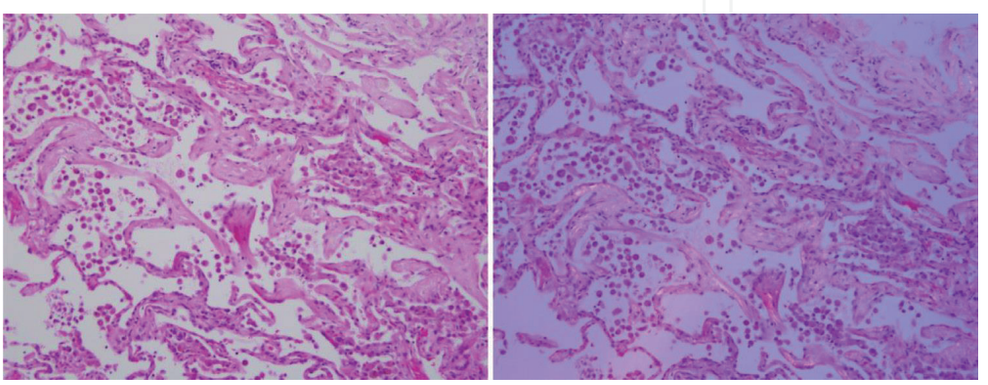

Figure 9.
Tobacco-associated respiratory bronchiolitis with interstitial fibrosis. Hematoxylin and eosin stain, original magnification 200×. Right, same picture under polarized light to demonstrate collagen (silvery shine) fibers in thickened fibrotic alveolar septa.

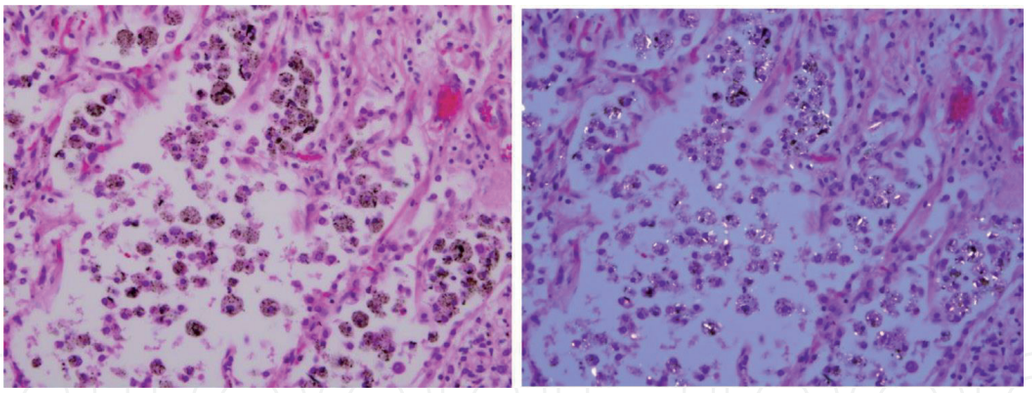

Figure 10.
Initial event in development of emphysema and interstitial fibrosis in coal miners is appearance of macrophages laden with silica and silicate particles and anthracotic pigment inside alveoli. Hematoxylin and eosin stain, original magnification 400×. Right side, same picture under polarized light to demonstrate birefringent silica and silicate particles in the cytoplasm of macrophages. Very small and faint white dots are silica particles, and small bright dots are silicate particles.

It is obvious that tobacco-associated emphysema and tobacco-associated interstitial fibrosis are related and that the first step in their genesis is accumulation of macrophages with smoker granules in the alveoli. The similar process can be elicited by silica and silicates from coal mine dust. The first sign of exposure to coal mine dust is accumulation of silica/silicate particles and anthracotic pigment in the alveolar macrophages (**Figure 10**) [18].

In coal miners with complicated coal worker's pneumoconiosis, the role of smoking in causing fibrosis is insignificant in comparison with that of silica/silicate particles from coal mine dust [18]. Since smoking and coal mine dust simultaneously may cause pulmonary fibrosis and emphysema by destruction of lung tissue and healing by fibrosis, it is plausible that in some patients emphysema is dominant, in others interstitial fibrosis, and in some others combined pulmonary fibrosis and emphysema syndrome (**Figure 11**) may occur [18, 19].

Alpha-1 antitrypsin deficiency is not the only one known genetic cause of emphysema. Telomere length is also associated with emphysema [20]. Both tips (ends) of the chromosomes are capped (protected) by telomeres composed of tandemly repeated DNA sequences. Telomeres are highly conserved and practically identical from protozoa to vertebrates. In humans, the TTAGGG repeat region is 10–15 kilobytes long. With each mitosis terminal nucleotides at the tail of telomeres are lost, and telomeres become shorter with each cell division. When telomere becomes critically short, the cell cannot

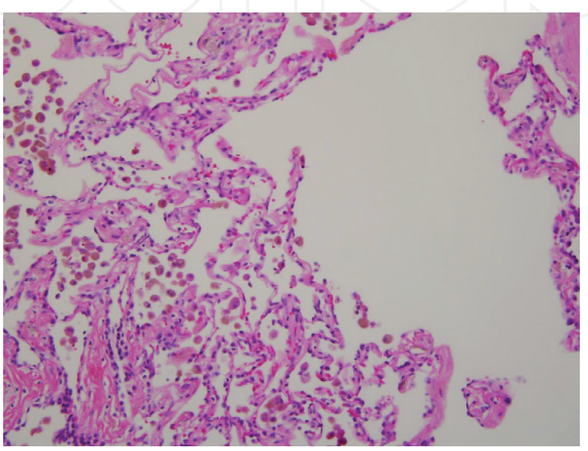

Figure 11.
Tobacco caused emphysema and tobacco caused respiratory bronchiolitis-associated interstitial lung disease with fibrosis, called combined pulmonary fibrosis and emphysema syndrome. Courtesy of Dr. Nadia N. Naumova.

divide anymore and thus becomes an old cell that will finally end up in apoptosis. Telomerase is an enzyme that synthesizes telomeres. Mutations in telomerase gene and telomere genes cause short telomere length for cell age and disease spectrum called short telomere syndrome/accelerated aging syndrome. The main presentation (90%) of short telomere syndromes are idiopathic pulmonary (interstitial) fibrosis and emphysema. They may be associated with other features of premature aging including early graying, osteoporosis, liver disease, predisposition to bone marrow failure, infertility, as well as myelodysplastic syndrome and acute myeloid leukemia [21]. Reduced telomere length may be identified in 25% of patients with sporadic idiopathic pulmonary fibrosis and half of those cases with family aggregation [22]. Telomerase deficiency and telomere shortening are responsible for only 1% of all emphysemas but are conceptually important as a link between interstitial fibrosis, emphysema, combined emphysema and interstitial fibrosis, and effect of environment on phenotypic presentation of genetic defect [21]. Pathogenic mechanism is premature senescence of alveolar epithelial stem cells, their apoptosis, disappearance of alveoli (emphysema), and abnormal repair with excessive interstitial fibrosis. The same genetic change, germline deletion in the Box H domain of the RNA telomerase, can cause in the father idiopathic pulmonary fibrosis, in one daughter emphysema, and in the other daughter combined pulmonary fibrosis and emphysema syndrome [20]. Interaction between the gene and environment determines lung disease. Never-smokers develop pulmonary interstitial fibrosis, while smokers develop an early onset emphysema alone or combined emphysema and pulmonary interstitial fibrosis [20, 21]. Cigarette smoke causes additive DNA damage to telomere function, and genetic defect in this setting expresses as emphysema [20].

In short, the main causes of emphysema and interstitial fibrosis are cigarette smoking and in coal miners silica and silicate particles from coal dust. Hereditary emphysemas caused by alpha-1 antitrypsin deficiency and short telomere length are epidemiologically insignificant but can help to elucidate pathogenesis of emphysema and interstitial fibrosis. Not all smokers develop emphysema and chronic obstructive pulmonary disease. Only 10–20% of the smokers develop chronic obstructive pulmonary disease pointing at an additional risk factor such as genetic susceptibility reflected in polymorphisms in genes coding for various antiproteases, a disintegrin, and metalloproteinase 33 or antioxidant superoxide dismutase and proinflammatory mediators including tumor necrosis factor-alpha [10] and possibly genes associated with telomeres. Combined pulmonary fibrosis and emphysema are also in the vast majority of cases caused by cigarette smoking or in coal miners by coal dust, and the above mentioned genetic factors might contribute to a now unknown degree of susceptibility.

Patients with emphysema only are extremely rare, and in practice emphysema is component of the chronic obstructive pulmonary disease which affects about 24 million people in the USA. Chronic bronchitis is chronic mucous hypersecretion syndrome and is clinically defined as productive cough for at least 3 months in 2 successive years. Its pathohistological features (**Figure 12**) include enlargement of the mucus-secreting glands in the bronchial wall, goblet cell metaplasia of the respiratory epithelium, infiltration of the bronchial mucosa with lymphocytes, squamous metaplasia and dysplasia in the bronchial epithelium, increased bronchial smooth muscle, as well as mucous plugging, inflammation, and fibrosis of the bronchioles.

Chronic bronchitis becomes chronic obstructive bronchitis when airflow obstruction occurs. It can be detected by spirometry or expiratory wheezing can be heard by auscultation. Bronchial airways are being compressed during expiration, and expiration is in chronic obstructive bronchitis difficult and prolonged. Auscultation reveals diminished breath sounds, prolonged expiratory phase, and expiratory wheezing. The main airflow obstruction occurs in small airways, with diameter less than 2 mm. Obstruction is caused by mucosal thickening, due to lymphocytic infiltration, fibrosis, edema, mucous plugging, and smooth muscle hypertrophy. **Figure 13** demonstrates

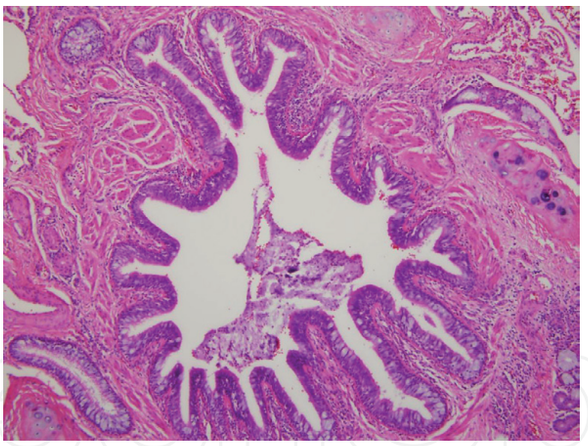

Figure 12.
Chronic bronchitis presenting with mucus in the lumen of the bronchus, partial goblet cell metaplasia of the respiratory epithelium, predominance of the mucinous cells in the bronchial exocrine gland, infiltration the bronchial wall by small lymphocytes and plasma cells, hypertrophy of the muscle layer, and peribronchial fibrosis.

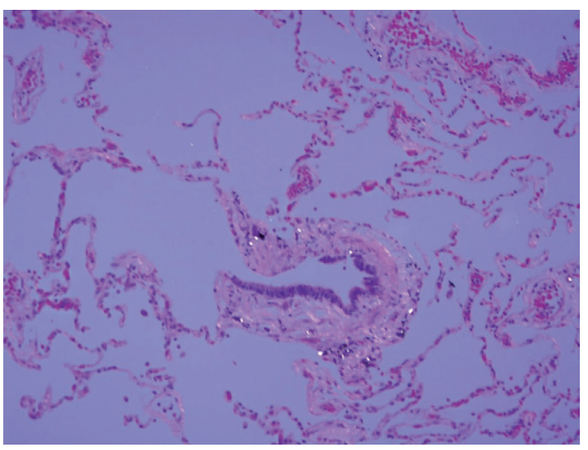

Figure 13.
The wall of the terminal bronchiolus is thickened by fibrosis and smooth muscle hypertrophy and this is one of the essential pathologic bases for obstructive pulmonary disease. Birefringent silica and silicate particles are etiological factor. Hematoxylin and eosin stain, original magnification 200×, polarized light.

thickening of the wall of the terminal bronchiolus by fibrous tissue and smooth muscle hypertrophy caused by birefringent silica/silicate particles from coal mine dust.

Clara cells that secrete surfactant are replaced by goblet cells, and decrease of surfactant increases surface tension at the air-tissue interface, and small bronchi and bronchiole are prone to collapse. Emphysema also contributes to airflow obstruction. Destruction and disappearance of respiratory bronchiole and alveolar ducts decrease total airway diameter. Destruction of acinar tissue with disappearance of elastic fibers decreases lung recoil and decreases expiratory air force. The net effect of chronic obstructive pulmonary disease is difficulty in breathing, prolonged expiration with expiratory wheezing, air trapping in the lungs with hyperinflation of lungs, increased residual volume, decreased vital capacity, and dyspnea.

Three cardinal features of chronic obstructive pulmonary disease are cough, sputum production, and exertional dyspnea. Dyspnea during physical activity may start insidiously, and patients complain of difficult breathing, gasping and air hunger, heaviness in chest in the beginning only during rather heavy physical work and later during light daily physical activity. Patients with chronic obstructive pulmonary disease poorly tolerate physical activity with arms but tolerate better physical work like pushing shopping cart when arms are fixed and enable the use of accessory respiratory muscles [1]. Acute exacerbations of chronic obstructive pulmonary

disease are prominent feature of its natural history and are characterized by cough, increase in amount and character (color) of sputum, and dyspnea and may or may not be accompanied with fever, myalgia, and sore throat. The health-related quality of life of patients with chronic obstructive pulmonary disease better correlates (inverse correlation) with frequency of acute exacerbations than with the degree of airflow obstruction (Reilly-Harrison). Patients with advanced emphysema due to hyperinflation of lungs have barrel chest with poor diaphragmatic excursion as assessed by percussion and dramatic decrease in breath sounds and are sitting in the characteristic tripod position with stretched fixed arms to enable the use of accessory respiratory muscles including sternocleidomastoid, scalene, and intercostal ones [1]. Patients with predominant emphysema are called "pink puffers" because they breathe through pursed lips with the help of accessory respiratory muscles. When small airway obstruction ensues, patients become hypoxic and cyanotic in the lips and nail beds, and when fluid retains due to right heart decompensation, they become "blue bloaters." However the majority of chronic obstructive pulmonary disease patients have some signs of both, "pink puffers" and "blue bloaters." Advanced chronic obstructive lung disease is accompanied by systemic wasting due to high energy expenditure for increased work of breathing muscles including accessory breathing muscles and elevated levels of inflammatory cytokines including tumor necrosis factor-alpha. Such patients have a significant weight loss and diffuse loss of subcutaneous fatty tissue. Some patients with advanced chronic obstructive pulmonary disease have paradoxical inward movement of the lower rib cage (Hoover sign) due to diaphragmatic contraction in a setting of permanently hyperinflated lungs [1]. Advanced chronic obstructive pulmonary disease, especially during acute exacerbation, can be accompanied by right heart failure. Signs include right ventricular heave, third heart sound, distended jugular veins, congested liver, ascites, and edema of legs.

2.3 Radiologic findings

Cardinal features of emphysema, hyperinflation of the lungs, and lung tissue destruction can be visualized by radiologic means. On the chest roentgenogram hyperinflation presents with increased lucency, increased retrosternal air space, depression and flattening of the diaphragm. Lung destruction presents in focal lucencies and areas of decreased vascularity. Mild emphysema is usually missed by standard chest X-rays.

High-resolution computerized tomography is superior to the chest X-ray in detecting emphysema. High-resolution computerized tomography can visualize focal areas of decreased attenuation sharply circumscribed without visible walls and with small centrilobular vessel in the areas of emphysema [3]. Several studies showed good correlation between the degree of pathologic findings and high-resolution computerized tomography findings [23]. However, mild focal areas might not be detected, and high-resolution computerized tomography cannot be used to rule out emphysema [24].

2.4 Tests of pulmonary function

Spirometry and pulse oximetry are basic simple pulmonary function tests that can be performed in the ambulatory settings. The patient exhales in the spirometry instrument as completely as possible, then forcibly inhales as much as possible, and then forcibly exhales as much as possible. Forced vital capacity is the maximum amount of air forcibly expired after maximum inspiration. Residual volume is amount of air retained in the lungs after maximal and forceful exhalation, and it can be calculated after using gas dilution technique or body-box plethysmography. In the emphysema due to the destruction of respiratory bronchioles, spirometry

will demonstrate obstructive pattern. Forced expiratory volume in 1 second will be decreased. Alveolar destruction in emphysema decreases amount of lung parenchyma, and thus forced vital capacity will decrease. Essentially emphysema is a mixed lung disorder, both obstructive and restrictive.

Transcutaneous pulse oximetry estimates oxygen (O_2) saturation of capillary blood using instrument in shape of clip positioned on a finger. Estimation is accurate and correlates to 5% of measured atrial O_2 saturation obtained by invasive procedure.

2.5 Therapy

Centriacinar emphysema is a progressive disabling disease for which there are no good therapeutic options. Large bullae that compress functional lung tissue can be surgically removed. Patients with severe, predominantly upper lung emphysema, and low baseline exercise capacity may benefit from lung volume reduction by resection, including bronchoscopic lung volume reduction, of non-functioning emphysematous areas. Dyspnea decreases because of reduced hyperinflation and residual volume and because forced expiration volume in the first second is increased [25]. Exercise tolerance and 2-year mortality rate are improved supposedly to decreased residual lung volume, enhanced lung recoil, and improved diaphragmatic function. Long-term effects of the lung volume reduction surgery are unknown. Improvement after lung transplantation is better than after the lung volume reduction surgery. Candidates for lung transplantation are younger than 60 years, with an FEV_1 less than 25% predicted or pulmonary artery hypertension. The 5-year survival after transplantation for emphysema is 45–60%. Lifelong immunosuppression brings risk of opportunistic infections.

Conflicts of interest

None declared.

Author details

Tomislav M. Jelic
Department of Pathology and Laboratory Medicine, Charleston Area Medical Center, Charleston, West Virginia, USA

*Address all correspondence to: tomsilav.jelic@camc.org

References

[1] Reilly J, Silverman E, Shapiro S. Chronic obstructive pulmonary disease. In: Kasper D, Fauci A, Longo D, Braunwald E, Hauser S, Jameson LJ, editors. Harrison's Principles of Internal Medicine. 16th ed. New York: McGraw-Hill; 2005. pp. 1547-1554

[2] Sorokin SP. The respiratory system. In: Weiss L, editor. Cell and Tissue Biology. 6th ed. Baltimore: Urban & Schwarzenberg; 1988. pp. 753-814

[3] Travis W, Colby T, Koss M, de Christenson R, Muller N, King T Jr. Non-Neoplastic Disorders of the Lower Respiratory Tract. Atlas of Nontumor Pathology. AFIP, ARP. pp. 435-471

[4] Schmidt RA, Glenny RW, Godwin JD, Hampson NB, Cantino ME, Reichenbach DD. Panlobular emphysema in young intravenous Ritalin abusers. The American Review of Respiratory Disease. 1991;**143**:649-646

[5] Snider GL, Kleinerman J, Thurlbeck WM, Bengali ZH. The definition of emphysema. Report of a National Heart , Lung, and Blood Institute, Division of Lung Diseases workshop. The American Review of Respiratory Disease. 1985;**132**:182-185

[6] Pardo A, Selman M. Proteinase-antiproteinase imbalance in the pathogenesis of Emphysema: The role of metalloproteinases in lung damage. Histology and Histopathology. 1999;**14**:227-233

[7] Laurell CB, Eriksson S. The electrophoretical alpha1-globulin pattern of serum alpha1-antitrypsin deficiency. Scandinavian Journal of Clinical and Laboratory Investigation. 1963;**15**:132-140

[8] Gross P, Pfitzer EA, Tolker E, Babyok MA, Kaschak M. Experimental emphysema, its production with papain in normal and silicotic rats. Archives of Environmental Health. 1965;**11**:50-58

[9] Sethi S, Rochesert CL. Smoking and chronic obstructive pulmonary disease. Clinics in Chest Medicine. 2000;**21**:67-86

[10] Hongwei Y, Rahman I. Current concepts on oxidative/carbonyl stress, inflammation and epigenetics in pathogenesis of chronic obstructive pulmonary disease. Toxicology and Applied Pharmacology. 2011;**254**(2):72-85

[11] Church DF, Pryor WA. Free-radical chemistry of cigarette smoke and its toxicological implications. Environmental Health Perspectives. 1985;**64**:111-126

[12] Tran I, Ji C, Ni I, Min T, Tang D, Vij N. Role of cigarette smoke-induced aggresome formation in chronic obstructive pulmonary disease-emphysema pathogenesis. American Journal of Respiratory Cell and Molecular Biology. 2015;**53**(2):159-173

[13] Cohen RA, Petsonk EL, Rose C, et al. Lung pathology in U.S. coal workers with rapidly progressive pneumoconiosis implicates silica and silicates. American Journal of Respiratory and Critical Care Medicine. 1964;(6):673-680

[14] Churg A, Zay K, Li K. Mechanisms of mineral dust-induced emphysema. Environmental Health Perspectives. 1997;**105**(Suppl 5):1215-1218

[15] Schns RP, Borm PJ. Mechanisms and mediators in coal dust induced toxicity: a review. The Annals of Occupational Hygiene. 1999;**43**(1):7-33

[16] Vassalllo R, Ryu JH. Tobacco smoke-related diffuse lung diseases. Seminars in Respiratory and Critical Care Medicine. 2008;**29**(6):643-650

[17] Yousem SA. Respiratory bronchiolitis-associated interstitial lung disease with fibrosis is a lesion distinct from fibrotic nonspecific interstitial pneumonia: a proposal. Modern Pathology. 2006;(11):1474-1479

[18] Jelic TM, Estalilla OC, Sawyer-Kaplan PR, Plata MJ, Powers JT, Emmett M, et al. Coal mine dust desquamative chronic interstitial pneumonia: A precursor of dust-related diffuse fibrosis and of emphysema. International Journal of Occupational and Environmental Medicine. 2017;**8**(3):153-165

[19] Jankowich MD, Rounds SI. Combined pulmonary fibrosis and emphysema syndrome: a review. Chest. 2012;**141**:222-231

[20] Alder JK, Guo N, Parry EM, Anderson CJ, Gorgy AI, Walshg MF, et al. Telomere length is a determinant of emphysema susceptibility. American Journal of Respiratory and Critical Care Medicine. 2011;**184**:904-912

[21] Stanley SE, Merck SJ, Armanios M. Telomerase and genetics of emphysema susceptibility. Implications for pathogenesis paradigms and patient care. Annals of the American Thoracic Society. 2016;**13**(Suppl 5):S447-S451

[22] Molina-Molina M, Borie R. Clinical implications of telomere dysfunction in lung fibrosis. Current Opinion in Pulmonary Medicine. 2018;**24**(5):440-444

[23] Hruban RH, Meziane MA, Zerhouni EA, et al. High resolution computerized tomography of inflation-fixed lungs. Pathologic-radiologic correlation of centrilobular emphysema. The American Review of Respiratory Disease. 1987;**136**:935-940

[24] Miller RR, Muller NL, Vedal S, Morrison NJ, Staples CA. Limitations of computed tomography in the assessment of emphysema. The American Review of Respiratory Disease. 1989;**139**:980-983

[25] Gulsen A. Bronchoscopic lung volume reduction: A 2018 review and update. Turkish Thoracic Journal. 2018;**19**(3):141-149