THE RELATIONSHIP BETWEEN ATHEROSCLEROSIS AND PULMONARY EMPHYSEMA

POVEZANOST ATEROSKLEROZE I EMFIZEMA PLUĆA

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Introduction

Atherosclerosis (AS) (a metabolic, chronic, inflammatory, immune-mediated disease of the arterial walls) is a global health problem. In developed countries, AS and its complications (thrombosis, bleeding, ulceration, rupture, calcification, and aneurysms) account for 50% of all deaths [1]. Huge amounts of data have been collected about this disease of civilization: experimental, clinical, functional and ultrastructural, including those that point to common pathogenic mechanisms in the development of AS and pulmonary emphysema (PE), which is also widespread [2-5]. Pulmonary emphysema (abnormal and permanent enlargement of the airspaces distal to the terminal bronchioles accompanied by destruction of the alveolar wall) is also a common condition in chronic obstructive pulmonary disease (COPD) patients, which is one of the leading causes of death worldwide [6].

Summary

Introduction. The etiopathogenesis of atherosclerosis and subsequent pulmonary emphysema has not been fully elucidated. Experimental Studies. Foam cells are of great importance in the development of these diseases. It is known that local cytokine secretion and modification of native lipoprotein particles, which are internalized by the vascular and alveolar macrophages via the scavenger receptors on the surfaces of these cells, lead to the formation of foam cells. Thus, the exacerbation of local inflammatory process in the vascular and lung tissue ensues due to a generation of reactive oxygen species, resulting in further lipoprotein modification and cytokine production. Accumulating evidence suggests that oxidants may facilitate the inflammatory response by impairing antiprotease function, directly attacking vascular and lung matrix proteins and by inactivating enzymes involved in elastin synthesis and vascular and lung repair. Clinical Studies. Cigarette smoke is recognized as a rich source of oxidants. Nearly 90% of all patients with chronic obstructive pulmonary disease are smokers. The process of atherogenesis is also influenced by tobacco smoke. Conclusion. The role of vascular and alveolar macrophages has become increasingly important in understanding the development of atherosclerosis and resulting pulmonary emphysema.

Key words: Atherosclerosis; Pulmonary Emphysema; Smoking; Macrophages; Foam Cells; Cytokines; Lipoproteins; Oxidants; Hypercholesterolemia; Risk Factors

Sažetak


Ključne reči: Ateroskleroza; Plućni emfizem; Pušenje; Makrofagi; Penaste ćelije; Citokini; Lipoproteini; Oksidanti; Hipereholesterolimija; Faktori rizika

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Rabbits are particularly sensitive to dietary cholesterol. In rabbits, a cholesterol rich atherogenic diet increases the concentration of triglycerides (TG) and low density lipoproteins (LDL), but decreases the concentration of high density lipoproteins (HDL) [9]. In addition, the serum of rabbits, primates, rats, guinea pigs, and birds fed with high cholesterol diet, exhibits cholesterol-rich lipoproteins with β-electrophoretic mobility, the so-called very low density lipoproteins (VLDL) [8].

Foam Cells
Experimental AS induced by high-cholesterol diet is often associated with PE [4, 5, 10–12], increased levels of TG and high concentrations of free fatty acids in the lung tissue [4]. In rabbits, after a month of hypercholesterolemic diet, aortic lesions become microscopically visible. They are characterized by the accumulation of foam cells in the internal elastic membrane, while the endothelial surface is intact. Foam cells are a characteristic feature in the tissue response associated with bronchial obstruction [4, 5, 10–12].

In an experimental model of AS induced by a high-cholesterol diet, monocytes are the first cells adjacent to the endothelium. Then they migrate into the subendothelial space, swallow the oxidized cholesterol, and transform it into foam cells [13]. These cells are believed to play a major role in the pathogenesis of AS and subsequent PE [4, 5, 10–12].

Hypercholesterolemia associated with elevated levels of atherogenic lipoproteins (LDL and VLDL) in the blood leads to chronic presence of LDL in the arterial wall [9]. This condition enhances fatty streaks formation because lipid migration into the subendothelial space is greater than its removal from the arterial wall. It is known that local cytokine secretion and modification of native lipoprotein particles, which are internalized by vascular and alveolar macrophages via the scavenger receptors class A (SRA) on the surfaces of these cells, lead to the formation of foam cells. Thus, the exacerbation of local inflammatory process in the vascular and lung tissue ensues due to a generation of reactive oxygen species (ROS), resulting in further lipoprotein modification and cytokine production [13]. It has been shown that mononuclear phagocytic blood cells take part in the phagocytosis of native particles and of modified LDL particles to a lesser i.e. greater extent, respectively after their binding to the SRA. However, these particles may directly migrate into the subendothelium, being subject to phagocytosis, whereas SRA play an important role in the process. These receptors, which mediate the delivery and degradation of modified LDL particles, do not operate on the principle of negative feedback, so even when a large amount of lipid particles is accumulated in the cell, the intake continues, which leads to the formation of foam cells [14]. In a state of continuous inflammation, the concentration of LDL particles in blood in-
creases and through the process of passive diffusion they penetrate the arterial intima, where they are trapped by glycosaminoglycans, and ROS are affected as well. LDL particles become highly sensitive to different stimuli, and may be modified by oxidation, glycosylation, or by incorporation into immune complexes. In addition, LDL particles interact with proteoglycans (biglycan and decorin) and form aggregates, with a catalytic activity of sphinngomyelinase, cathepsin D, cathepsin F, and lysosomal acid lipase [15].

The ability of oxidized LDL molecules (oxLDL) to induce accumulation of cholesterol in macrophages was their first described proatherogenic property. Other proatherogenic effects of oxLDL particles, referring to endothelial cells, include expression of growth factors affecting smooth muscle cells, generation of superoxide anion (O2·−), and endothelial cells apoptosis [14]. The human endothelial receptor that mediates uptake of oxLDL belongs to C-type lectin family and is referred to as LOX-1 (lectin-like oxLDL receptor-1) [16].

Foam cell formation is also induced by receptors involved in oxLDL uptake (CD34, macrosialin/CD68+ and HDL receptor, which is referred to as SB-1 [16].

It is believed that macrophage-colony stimulating factor (M-CSF), interleukin-3 (IL-3) and granulocyte monocyte colony stimulating factor (GM-CSF) play a key role in the process of foam cell formation [17].

Apart from macrophages, foam cell formation is also promoted by vascular smooth muscle cells with properties of lipophages [13].

**Inflammatory Response of the Vessel Wall and the Lung Tissue**

Numerous animal studies have shown that activation of endothelial cells and expression of specific molecules, responsible for adhesion, migration and accumulation of monocytes and T-lymphocytes, play a crucial role in AS [8].

There is evidence that a high cholesterol diet soon results in the focal expression of vascular cell adhesion molecule-1 (VCAM-1) at the predilection sites. In addition, lysophosphatidylcholine, a component of modified lipoprotein, activates VCAM-1 gene transcription in endothelial cells. Lipoprotein(a), however, induces a dose-dependent expression of intercellular adhesion molecule-1 (ICAM-1) on endothelial cells, but it does not affect the expression of VCAM-1 and E-selectin. Furthermore, native LDL molecules, binding to the LDL receptors, increase the concentrations of VCAM-1 and E-selectin in human vascular endothelial cells [13]. On the other hand, the expression of these molecules is induced and enhanced by tumor necrosis factor alpha (TNFα) and interleukin-1 beta (IL-1β), which originate from either the circulating blood or the vascular wall. These molecules, which are part of the existing local or systemic inflammatory reaction, apart from stimulating the expression of adhesion molecules, lead to changes in procoagulant and fibrinolytic endothelial cells, and the surface of the endothelium becomes thrombogenic. By modifying the properties of endothelial morphology, these cytokines affect the production of nitric oxide (NO) and prostacyclin, inducing endothelium to synthesize other cytokines, which enhances their proinflammatory activity. IL-1 and TNFα, endothelial cell activators, induce synthesis of specific membrane glycoproteins, redistributing the cytoskeleton of endothelial cells and increasing the synthesis of platelet-activating factor (PAF). PAF is a phospholipid with potential proinflammatory and thrombogenic properties. Its specific significance in AS is indicated by the fact that components similar to this phospholipid are present in oxLDL, and that blockade of PAF receptors blocks the effects of oxLDL molecules on the peripheral mononuclear cells completely, which refers to the secretion of interferon-γ (IFN-γ) and partly to the secretion of TNFα. IL-1 and TNFα also stimulate endothelial cells to produce interleukin-8 (IL-8) that strongly attracts and activates leukocytes. Migration of leukocytes through the morphologically intact endothelium involves direct migration as a response to other cytokines, so-called chemo-kines. In the early phase of atherogenesis these are monocyte chemotactic protein-1 (MCP-1), localized in atherosclerotic lesions, IL-8, interleukin-16 (IL-16), and C5a-receptor fragment peptide, released in hypercholesterolemia [18].

Inflammatory response has been confirmed to affect the accumulation of lipoproteins in the arterial wall. Inflammatory mediators (TNFα, IL-1 and M-CSF) increase the binding of LDL to the endothelium and smooth muscle cells. After binding to SRA in vitro, modified LDL particles initiate a series of intracellular events, among which the activation of urokinase and inflammatory cytokines plays an important role. In this way, due to the presence of lipids, a vicious cycle of inflammation is maintained in the arteries, as well as modification of lipoproteins and continuous inflammation [13, 14]. Thus, LDL molecules enhance the expression of SRA on macrophages and, in synergy with inflammation, facilitate the formation of foam cells [13]. It should also be noted that a large number of activated macrophages undergo apoptosis, after which they release the lipid content into the matrix and form the lipid nucleus of atheromas [17].

Under physiological conditions, human alveolar macrophages (AM) act as a dynamic system composed of phenotypically and functionally diverse subpopulations, whose delicate balance participates in immune regulation. In contrast, the function of AM during the afferent phase of cellular immunity (phagocytosis) is particularly emphasized within the inflammatory and immune response in the lungs, whereas the efferent phase of macrophages is responsible for the activity of
other immune and inflammatory cells through the secretion of soluble mediators, such as prosta-
glandins, chemotactic factors, PAF, complement components, various enzymes, and others [19]. The activated inflammatory cells in the lungs then stimulate the release of IL-8 from AM, alveolar epithelial cells, and other lung cells, which, afterwards, attracts polymorphonuclear leukocytes (PMN) due to its chemotactic properties. Similar activities are also exhibited by leukotriene B$_4$ (LTB$_4$) [20].

Small blood vessels of the lungs, especially capillaries of intra-alveolar septa, in some animal species exhibit pulmonary intravascular macrophages (PIM). During inflammation, their number increases with inhomogeneous distribution. Studies of the metabolic characteristics of PIM have shown that these cells are much more active than PM [21].

**Lysosomal Enzymes of Inflammatory Cells**

Alveolar macrophages differ from other tissue macrophages in having a markedly hypertrophic lysosomal apparatus [22]. In contrast to other macrophages, AMs depend on aerobic glycolysis, which is explained by high partial oxygen pressure in the lungs. It has been shown that the activity of AM can be suppressed by the inhibition of oxidative phosphorylation [23], while the suppression of tissue respiration is one of the features of AS. Moreover, AS is associated with a reduced oxygen uptake in the lung tissue and other parenchymal organs [7]. Thus, in AS, PE impairs blood oxygenation, although frequent microembolism in hypercholesterolemia, as well as a decreased oxygen binding capacity due to a cholesterol layer around the red blood cells may contribute to this impairment [23, 24].

Over the last few decades, great importance is given to the role of proteolytic enzymes in the development of PE (Table 1). Proteases are constituents of PMN and AM. Phagocytosis increases the release of these enzymes. It is assumed that inflammatory reactions associated with infections and air pollutants may cause the same effect. The release of elastase from neutrophil lysosomes is believed to be mainly responsible for elastin degradation, ultimately resulting in the development of pathological processes in PE. Under normal circumstances, these unwanted events are prevented by anti-proteinase inhibitor enzymes, such as alpha-1 proteinase inhibitor (αPI), secretory leucoprotease inhibitor (SLPI), tissue inhibitors of matrix metalloproteinases (TIMPs), and others, found in serum, tissues, and bronchial secretions [25].

Various studies demonstrate the involvement of immune factors in the etiology of AS, possibly being etiopathogenic mechanisms of AS and PE [2–5, 7, 10–12, 17, 22, 23, 26]. Apart from antigens responsible for immune responses leading to AS, special attention is paid to vascular wall antigens. For example, aging causes the loss of elastin natural properties, and thus it becomes susceptible to deposition of calcium and elastolysis. Enhanced decomposition of insoluble elastin in the vascular wall leads to the appearance of peptides in the blood stream, whereas anti-elastin antibodies are created in response to them [17]. Rabbits with experimental AS and subsequent PE exhibit a progressive titer increase of these antibodies, as well as abnormal accumulation of microfibrils in the elastic tissue, which is closely associated with excessive elasto-lys of preformed or newly formed elastic fibers during elastic tissue remodeling. Enhanced synthesis of microfibrils may occur in response to elastolysis as a reparative phenomenon, but it also represents a response of the blood vessel wall and pulmonary tissue to elastolysis [27].

Histochemical methods showed an increased non-specific esterase activity of macrophages in the arterial walls during atherogenesis induced by hypercholesterolemic diet. It has also been observed that the amount of esterase is directly proportional to the degree of saturation of the intima with lipoproteins and other macromolecules [28].

Apart from lysosomal non-specific esterases, non-specific esterases have been found on the outer cell membrane of AM. These esterases, also known as ectoenzymes or ectoesterases, play a mediating role in regulation of AM response to various external and internal agents [22]. Some nonspecific esterases exert their activity in the glycosylax and on the outer side of the macrophage membranes. The most important enzyme with these properties is α-naphthyl acetate esterase (ANAE). The examination of ANAE activities in guinea pig Kurloff cells (mononuclear cells obtained from guinea pigs) showed a membranous and cytoplasmic distribution of its activity [29].

Human AM are reported to have a series of esterases with elastase-like activities. During maturation of these phagocytic cells, the amount of hydrolytic enzymes increases in their lysosomes [22]. In addition, the degree of esterase activity in mononuclear cells correlates with the cell viability and mitotic capacity [28]. It has been established that different local stimuli (immune complexes, antigens, lymphokines, bacterial components, etc.) may trigger the release of hydrolytic lysosomal enzymes into the extracellular space with autodestructive consequences [26].

Extracellular matrix is the principal component of the fibrous plaque. Extracellular matrix degradation is promoted by monocyte-macrophages which release matrix-degrading metalloproteinases (MMP). The activated MMP (gelatase, collagenase, stromelysin) can degrade all components of extracellular matrix [30]. Apart from MMP, matrix and fibrous cap degradation is also activated by cathepsins and other elastolytic enzymes (Table 1) [6]. It should be noted that the imbalance between factors of synthesis and degradation of extracellular matrix plays a major role in the rupture of atherosclerotic plaque and its subsequent consequences [30].
Clinical Studies

Smoking

Epidemiological studies have shown that smoking plays a principal role in the development of emphysema. It is generally believed that smoking is the most important extrapulmonary etiopathogenic factor of this disease. The development of centriacinar emphysema is believed to be closely related to cigarette smoking [25]. Approximately 90% of patients with chronic obstructive pulmonary disease (COPD) are smokers or former smokers who suffer from frequent bronchopulmonary infections. Chronic airflow limitation, characteristic for these patients, is caused by a mixture of small airway diseases known as obstructive bronchiolitis and parenchymal destruction consistent with emphysema, but the proportion of these components varies from a person to a person. It has been established that an early decrease in lung function in COPD patients correlates with the inflammatory response in peripheral airways, which is similar to inflammatory changes in the central airways (exudation into the airway lumen, goblet and squamous cell metaplasia, inflammatory airway mucosal edema, and increased airway mucosa due to goblet cell metaplasia). However, peripheral airway obstruction is the most common pathological finding in COPD. Cigarette smoke-induced inflammation leads to repeated cycles of repair and damage of the walls of the peripheral airways, which may result in airway wall remodeling (an increase in collagen content, and scar tissue formation). This results in luminal narrowing and permanent airway obstruction [3]. It has been shown that tobacco smoke stimulates epithelial cells and macrophages to produce TNFα, and other mediators of inflammation. Long-term smoking causes mucous gland hyperplasia and hypertrophy [2]. It is believed that tobacco smoke inhibits antiproteases and stimulates macrophages and PMN to release proteolytic enzymes [20]. Components of tobacco smoke are largely retained in the so-called “transitional zone” (respiratory bronchioles) due to airflow cessation in the respiratory tree. This results in modification of the local microenvironment, whereas respiratory bronchioles of smokers and smokers suffering from AS are sites where large amounts of non-specific lysosomal esterases enter the extracellular space [23]. Then, non-specific esterase, in conjunction with acid phosphatases, elastase, hyaluronidase, cathepsin, collagenases and plasminogen activators, may damage the surrounding tissue [3]. Moreover, the activity of esterase, lysosome, and lactate dehydrogenase was found to be five times higher in AM of smokers than in normal AM. It is assumed that AM and vascular wall macrophages in smokers can upload, modify, and activate PMN-released elastase [28]. Alveolar macrophages of smokers with AS also show accumulation of free fatty acids, phospholipids, and TG [3].

Tobacco smoke is an important source of oxidants. The gas phase of cigarette smoke contains abundant free radicals including nitric oxide [2] that induce oxidative damage to the vascular tissues of smokers, exacerbate the existing inflammatory process and accelerate the progression of atherosclerotic lesions (Scheme 1) [19].

Table 1. Inflammatory cell-derived proteases in atherogenesis and pulmonary emphysema

<table>
<thead>
<tr>
<th>Protease</th>
<th>Type of active site</th>
<th>Site of synthesis</th>
<th>Elastolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elastase</td>
<td>Serine</td>
<td>Neutrophil, macrophage</td>
<td>+</td>
</tr>
<tr>
<td>Elastase</td>
<td>Serine</td>
<td>Neutrophil, makrofag</td>
<td>+</td>
</tr>
<tr>
<td>Proteinase 3/Proteinaza 3</td>
<td>Serine/Serine</td>
<td>Neutrophil/Makrofag</td>
<td>+</td>
</tr>
<tr>
<td>Cathepsin G</td>
<td>Serine</td>
<td>Neutrophil, makrofag</td>
<td>+/-</td>
</tr>
<tr>
<td>Katepsin G</td>
<td>Serine</td>
<td>Neutrophil, makrofag</td>
<td>+/-</td>
</tr>
<tr>
<td>Trypase/Triptaza</td>
<td>Serine/Serine</td>
<td>Mastocyte/Mastocit</td>
<td>/</td>
</tr>
<tr>
<td>Chymase/Himaza</td>
<td>Serine/Serine</td>
<td>Mastocyte/Mastocit</td>
<td>/</td>
</tr>
<tr>
<td>Plasminogen activator</td>
<td>Serine</td>
<td>Macrophage</td>
<td>?</td>
</tr>
<tr>
<td>Aktivator plazminogena</td>
<td>Serine</td>
<td>Makrofag</td>
<td>?</td>
</tr>
<tr>
<td>Procollagenase</td>
<td>Metal</td>
<td>Neutrophil</td>
<td>/</td>
</tr>
<tr>
<td>Prokolagenaza</td>
<td>Metalo</td>
<td>Makrofag</td>
<td>/</td>
</tr>
<tr>
<td>Gelatinase/Želatinaza</td>
<td>Metal/Metalo</td>
<td>Neutrophil/Makrofag</td>
<td>/</td>
</tr>
<tr>
<td>72 kDa collagenase</td>
<td>Metal</td>
<td>Macrophage</td>
<td>+</td>
</tr>
<tr>
<td>72 kDa kolagenaza</td>
<td>Metalo</td>
<td>Makrofag</td>
<td>+</td>
</tr>
<tr>
<td>92 kDa collagenase</td>
<td>Metal</td>
<td>Macrophage</td>
<td>+</td>
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<tr>
<td>92 kDa kolagenaza</td>
<td>Metalo</td>
<td>Makrofag</td>
<td>+</td>
</tr>
<tr>
<td>Stromelysin/Stromelizin</td>
<td>Metal/Metalo</td>
<td>Macrophage/Makrofag</td>
<td>/</td>
</tr>
<tr>
<td>Cathepsin B/Kathepsin B</td>
<td>Cistein/Cisteine</td>
<td>Macrophage/Makrofag</td>
<td>/</td>
</tr>
<tr>
<td>Cathepsin L/Kathepsin L</td>
<td>Cysteine/Cisteine</td>
<td>Macrophage/Makrofag</td>
<td>/</td>
</tr>
</tbody>
</table>
smoking stimulates phagocytic activity of lung macrophages and macrophages in COPD patients [2, 20]. An increased number of AM, epithelial cells, lymphocytes, mast cells and other metabolically active lung cells which use oxygen and thereby release ROS, contribute to altering the balance between oxidants and antioxidants in the lungs of patients with COPD (Scheme 1) [2, 3, 15, 19, 20].

Comorbidities in Patients with COPD

The first symptoms of COPD include chronic cough and shortness of breath. With the progression of disease, a number of additional symptoms may develop due to multiple organ system damage, which is why comorbidities are quite common in patients having COPD. Since COPD affects long-term smokers and middle-aged people, most patients with COPD may have other diseases associated with smoking (cardiovascular disease, and lung cancer) and with aging (prostate cancer, depression, diabetes mellitus, Parkinson’s disease, dementia, arthritis). In addition, COPD may coexist with respiratory tract infections, asthma, osteoporosis and bone fractures, sleep disorders, cataract, glaucoma, gastroesophageal reflux, gastritis, anemia, anxiety disorders and cognitive impairment. Consequently, some coexisting diseases may result from COPD (cardiovascular disease, lung cancer, and osteoporosis). Furthermore, many patients with COPD have multiple comorbid conditions, among which the most common are hypertension, diabetes mellitus, and coronary heart disease [31]. COPD is also associated with systemic (extrapulmonary) conditions, such as systemic inflammation and skeletal muscle dysfunction, which limit physical activities and impair overall health of COPD patients [3].

Lung cancer and cardiovascular diseases (ischemic heart disease, cardiac arrhythmias and heart failure) are reported to be the most common causes of fatal outcome in patients with mild to moderate COPD, while, respiratory failure is the leading cause of death in its advanced stage [32].

COPD is an independent risk factor for the development of cardiovascular diseases. The mechanisms associating COPD with AS, ischemic heart disease and stroke are not fully understood. It is believed that chronic systemic inflammation plays a key role in atherosclerotic plaque formation. There is increasing evidence that endothelial function, which is significantly impaired in patients with COPD, may increase the risk of cardiovascular disease [33]. Namely, endothelial dysfunction of pulmonary arteries occurs early in COPD patients, directly induced by tobacco smoke components or indirectly by inflammatory mediators (C-reactive protein (CRP), fibrinogen, IL-1, TNFα, etc.). Thickening of the intima is the first structural change, followed by proliferation of vascular smooth muscle cells and infiltration of the vessel wall by inflammatory cells. These structural changes are correlated with an increase in pulmonary vascular pressure that develops first with exercise and then at rest. As COPD progresses the amount of proteoglycan and collagen increases, which leads to further thickening of the vessel walls. In advanced stages of the disease, changes in the muscular arteries may be associated with emphysematous destruction of the pulmonary capillary bed. Moreover, it was found that thickening of the arterial walls in the systemic circulation correlates with the development of emphysema [7].

Pulmonary hypertension, which develops in severe COPD, is a major cardiovascular complication of the disease. It has been associated with the development of pulmonary heart disease (cor pulmonale), and has a poor prognosis. Pulmonary hypertension and reduction of the vascular network due to emphysema may lead to right ventricular hypertrophy and right heart failure; together with venous stasis and thrombosis, it increases the risk for the development of pulmonary embolism, further compromising the pulmonary circulation [32].

Preventive Measures and Early Detection of Atherosclerosis and COPD

At the present level of medical science, AS is considered to be an inevitable process, i.e. the fatigue of material. Although it inevitably affects the entire human population, clinical treatment includes only its complications. In other words, AS remains undetected until clinical complications arise, and they claim a life every two seconds worldwide [1].
According to statistics, AS and its most common consequences (myocardial infarction and stroke) are the leading cause of death in Serbia [34]. However, it is encouraging that nearly 80% of premature deaths could be prevented by eliminating key risk factors, such as smoking, unhealthy diet and physical inactivity [1]. Therefore, preventative check-ups and healthy habits must be part of everyday life as a natural and essential necessity of everybody [34]. To this end, in the first place, health care professionals should use positive attitude of the population of Serbia to health as the greatest human value, and in their everyday work teach them how to protect and improve their own health and the health of their families. Good family relations are in the second place, as a prerequisite for healthy development of all its members. Bearing that in mind, a family doctor can examine and slow down the development of many diseases associated with aging, including AS and consequent emphysema. At the same time, the doctor does not necessarily have to treat all family members. However, those individuals who decide to be treated by the same doctor are treated as parts of their families. As such, family doctors often know more about their health problems, especially about chronic diseases, at their preclinical stage. Apart from this, the family doctor understands relationships between family members, even unsaid family issues and recognizes family trauma [35].

The worldwide prevalence of COPD is 0.8%, and it is becoming a growing burden on the health care system. The prevalence of this disease is also high in Serbia [36]. According to the Global Initiative for Chronic Obstructive Lung Disease guidelines, more than half of patients with this disease remain undiagnosed [37]. Therefore, patients should be educated that cough, chronic hypersecretion and shortness of breath are not innocent symptoms and that their recognition is very important when it comes to this disease [38]. That is why family doctors play a crucial role in the health care system, because they can integrate physical, psychological, social, cultural and existential characteristics of patients in order to diagnose the disease as early as possible [36].

**Conclusion**

The pathogenesis of atherosclerosis and subsequent pulmonary emphysema has not been fully elucidated. It is certain though that altered function of alveolar and vascular macrophages is a significant contributing factor in its development. A hope remains that future research on the role of these cells in the pathogenesis of pulmonary emphysema found in atherosclerosis will shed light on yet unknown potential therapeutic modalities.

**References**


