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CARDIOPULMONARY INTERACTIONS WITH CONSECUTIVE PULMONARY ABNORMALITIES IN PATIENTS WITH CHRONIC HEART FAILURE

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SUMMARY – Chronic heart failure places heavy burden on patients, their families and on health care resources, accounting for high numbers of hospital admissions. Despite huge improvements in the treatment of many heart disorders, the clinical syndrome of chronic heart failure as a final pathway of heart pathology is an exception, in that its prevalence is rising, and only small prolongations in survival are occurring. It is associated with high morbidity and poor prognosis, and a survival rate worse than that for some malignant tumors. The reasons for the increasing overall prevalence of chronic heart failure in developed countries lie in prolonged survival owing to modern pharmacological or invasive treatment, better secondary prevention, and aging of the population. Chronic pulmonary disease is common in patients with chronic heart failure. Through sharing some risk factors and overlapping pathophysiological processes, they present diagnostic and therapeutic challenge. The aim of this article is to review various mechanisms responsible for the symptoms of chronic heart failure with consecutive pulmonary interaction and abnormalities in lung function.

Key words: *Heart failure; Heart diseases; Lung diseases*

Introduction

Chronic heart failure (CHF) is a clinical syndrome defined by the presence of symptoms, most often as breathlessness and fatigue, and objective clinical signs such as evidence of fluid retention, tachypnea, tachycardia, pleural effusion, pulmonary rales, or ankle swelling. Of course, to establish the diagnosis, these clinical data have to be combined with objective evidence for structural or functional abnormality of the heart. CHF is always a result of the underlying cardiac disease irrespective of whether it involves the myocardium, endocardium with valvar apparatus, or pericardium. The incidence of CHF is reported to be between 2.0% and 5.0 cases *per* 1000 people *per* year in western countries, with the increase in the incidence to up to 40 cases *per* 1000 people *per* year in the population older than 75 years. The prevalence of this condition is estimated to be around 3% with a rise in the prevalence to between 3.0% and 13.0% in the population older than 65[1]. The reasons for the increasing overall prevalence of CHF in developed countries lie in prolonged survival owing to modern pharmacological or invasive treatment, better secondary prevention, and aging of the population. Thus, overall expenditures are rising with approximately 2% of national health budgets being spent on the treatment of these patients[2]. The prognosis in CHF is generally poor. A population based study, Framingham Heart Study, showed the median survival of 3.2 years in men and 5.4 years in women after establishing the diagnosis[3]. Also, mortality as a consequence of CHF increases with age, showing a 27% increase in mortality in men with every de-

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cade of life and 61% increase in women of older age groups[4]. The aim of this article is to review the cardiopulmonary interaction of CHF with consecutive pulmonary abnormalities. The pathophysiology and treatment of acute heart failure was not considered.

Mechanism and Clinical Impact of Dyspnea in Chronic Heart Failure

Dyspnea or breathlessness is the most common symptom of CHF, largely due to the lower quality of life in these patients. Clinical follow-up, treatment and prognostication in CHF have been traditionally based on the New York Heart Association Functional Classification (NYHA), which is based on clinical criteria, primarily dyspnea and exercise intolerance. Shortness of breath or dyspnea is a product of a well-defined, complicated interaction between periphery and cortex of the brain. Namely, various receptors contribute to the process. Hypoxia stimulates peripheral and central chemoreceptors: mechanical stimuli activate mechanoreceptors in upper airways of the chest wall, whereas lung comprises pulmonary stretch receptors, which are activated by lung inflation; irritant receptors are activated with chemical stimuli, which promote bronchoconstriction and C-fibers that are placed in the interstitium and react to pulmonary congestion[5]. Breathlessness in CHF is mainly based on the increased breathing effort secondary to changes of lung or chest wall mechanics and respiratory musculature weakness, although a significant role is played by pulmonary congestion and changes in lung function. Many patients in stable condition with no volume overload, unlike subjects with chronic pulmonary diseases, are not hypoxemic. Changes in lung and chest wall mechanics take place due to fluid retention. Left ventricular failure leads to higher end-diastolic ventricular pressure and pulmonary venous hypertension. There is a gradual increase in pulmonary blood flow from the apex to the base of the lung, which can be expected. Elevated pressure makes blood flow uniformly spread and redistributed across the lung. This pulmonary blood flow redistribution is accomplished through capillary recruitment. If the rise of the pulmonary venous pressures continues, fluid would cross the alveolocapillary barrier. This process has been traditionally defined since Starling first described the basic forces regulating fluid migration, with hydrostatic forces favoring the

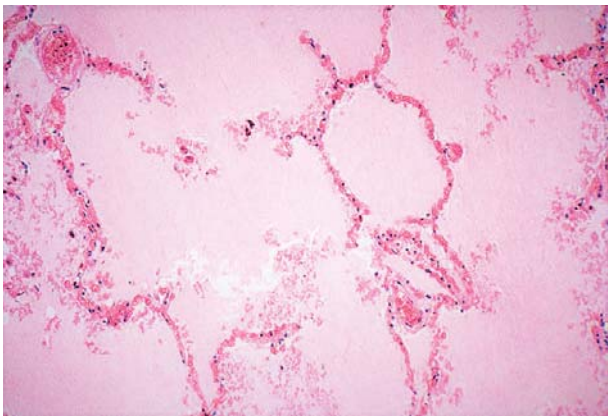

Fig. 1. Histopathologic evaluation of lung edema.

Hematoxylin and eosin histologic analysis shows alveolar walls that are thickened due to distention of capillaries and interstitial edema. Alveolar lumen is filled with transudate and blood (a homogeneous red-pink material) consistent with the diagnosis of lung edema (low-power photomicrograph, original magnification, x100).

crossing of the fluid to alveolar spaces and interstitial oncotic pressures supporting retention of the fluid in the interstitial spaces. Over time, the fluid is being retained in interlobular septa, peribronchovascular interstitium and pleural space with lymphatic system clearing the water overload. Alveolocapillary membrane changes with thickening and fibrosis taking place, which reduces the permeability for fluid. Also, pulmonary veins become thicker and pulmonary arterioles show intimal fibrosis and media thickening. These changes are responsible for relative resistance of the interstitium to high capillary pressures and have been designated as an explanation of how patients with CHF tolerate high pulmonary capillary wedge pressures without experiencing pulmonary edema. Fluid overload in the interstitium, peribronchovascular, hilar and pleural spaces is responsible for lower pulmonary compliance and higher chest stiffness. Because of the long-lasting process of pulmonary venous hypertension in CHF, sometimes damage to alveolocapillary area occurs[6]. Namely, tearing of alveolar epithelium, capillary endothelium and collagen structures of basal membranes takes place and is responsible for extravasation of red blood cells into the alveolar spaces (Fig. 1). This process has been termed pulmonary capillary stress failure. Also, this explains the higher content of hemosiderin in alveolar spaces in patients with long-

standing chronic heart failure, sometimes leading even to pulmonary ossification. Such changes have been especially well described in patients with long-standing mitral stenosis[7].

The Role of Respiratory Musculature in Dyspnea and Exercise Intolerance in Patients with Chronic Heart Failure

Respiratory effort can be simply defined by the sense of 'breathing work' needed to fulfill ventilatory demand in a hypothetical situation. This awareness of effort is a function of the ratio between generated work achieved by respiratory muscles in that hypothetical situation and their maximum capability. Thus, the sense of effort is increased whenever muscles have to generate greater pressure in order to compensate for extra load (such as higher elastic or resistive forces of the lung or chest), or when there is lower pressure generating the capacity of muscles (intrinsic weakness of the respiratory musculature, increase in the chest volume, fatigue of the musculature). A large number of experimental and clinical works have been dedicated to enlighten the role of respiratory musculature in CHF. Most of the work of breathing is done by the diaphragm consisting of 'slow oxidative-fatigue resistant' fibers, which are, on the other hand, very perfusion sensitive. It has been shown that patients with CHF have a significantly reduced strength of respiratory musculature as compared with healthy individuals of the same age[8]. Moreover, in these patients, muscle strength of other regions in the body has not been reduced in that scale, leading to a conclusion that respiratory muscles depend more on the cardiac output but there are reports suggesting that this disorder is a general one, with respiratory muscles to be affected earlier[9]. McParland *et al*. proved that respiratory muscle strength was reduced in patients with CHF, and what is more, that this reduction of respiratory muscle strength correlated with dyspnea on performing everyday activities[10].

In another study, McParland *et al*. confirmed these findings and found no connection of muscle weakness with nutritional or electrolyte status in patients with CHF[11]. Mancini *et al*. demonstrated hypoxia to take place in respiratory muscles during exercise in patients with CHF; in a subsequent study, Mancini *et al*. showed not only linear connection between respiratory muscle strength and dyspnea, but also changes of diaphragm workload and lack of muscle fatigue during exercise in patients with cardiac failure[12,13]. In another study by Evans *et al*., weakness of respiratory muscles in CHF was found again, but without correlation with dyspnea or exercise intolerance[14]. Respiratory muscle endurance defined as the ability of the muscle to resist fatigue is a sign of respiratory musculature dysfunction, which is depressed in CHF patients and tends to correlate with their exercise intolerance[15,16]. Relative inconclusiveness of various studies regarding the connection between respiratory muscle dysfunction and dyspnea or exercise intolerance may be a consequence of different methodology, small number of patients, or variability of patient characteristics. Nevertheless, rehabilitation and training of inspiratory muscles in patients with CHF showed clear benefit[17-19].

Lung Function in Chronic Heart Failure

Changes in lung functions in patients with CHF have been well studied. As regards the fact that dyspnea is the most frequent of all symptoms in these patients, great interest was directed towards understanding of the underlying process. Respective studies used pulmonary function testing and showed that patients with CHF predominantly had a restrictive pattern of breathing. There are several reasons that can explain such findings. Firstly, these patients exhibit volume overload with liquid retention in pulmonary interstitial, alveolar and pleural spaces. Secondly, the size of the heart is enlarged. Agostoni *et al*. conducted a study in which cardiothoracic index on conventional chest x-ray correlated inversely with the parameters of lung function[20]. Thirdly, stiffness of the lung due to water retention contributes as well. Bearing the fact of unique thoracic space in mind, which comprises heart, lungs and other structures in a given volume, these changes are directly reducing the useful lung volume. Indeed, the relation between cardiomegaly and deterioration of lung function was directly studied showing positive correlation[20]. Lung function testing in CHF predominantly shows reduced total lung capacity (TLC) and forced vital capacity (FVC)[21-23]. Consequently, the ratio between forced expiratory volume in first second (FEV1) and FVC is increased. Also, residual volume tends to be increased with reduction of

vital capacity. Namely, accumulation of retained liquid in peribronchovascular spaces leads to erection of distended vessels and compression of bronchioles with air trapping[24]. After intensive diuretic treatment or heart transplantation, all of these changes tend to be corrected[25-27]. Acute heart failure shows completely different lung function disturbance patterns with predominantly obstructive changes in lung function testing[28,29]. This explains wheezing in clinical presentation of such patients. The reason for this lies in airway obstruction due to wall congestion of smaller airways. All of these changes have also been shown to improve following diuretic therapy, although it is interesting that bronchodilator therapy did not improve airway obstruction[28]. Finally, bronchial hyperreactivity in CHF may play a significant role. This can be explained by congestion and thickening of the bronchial mucosa layer with activation of irritant receptors and C-fibers. Vagotomy in experimental animals put in the setting of cardiac failure has shown betterment of lung function[30]. Indeed, patients with CHF were shown to have significantly higher bronchial hyperreactivity with acetylcholine inhalation testing[31]. Lung function during physical activity in patients with CHF shows striking change with regard to the pathologic pattern of ventilation in which patients produce higher respiratory rate with low tidal volume, in contrast to healthy subjects where physical demand is met with the increase in both tidal volume and respiratory frequency, yielding a higher ventilation rate in patients with congestive CHF for a given workload. There are several explanations, most important being changes in lung mechanics with the increase in the overall chest volume and stiffness, lower lung compliance, all of which make respiratory muscles ineffective, weak and prone to fatigue. Moreover, lung diffusion is reduced and dead space ventilation is increased[23]. This hyperventilating pattern correlates with the rate of dyspnea and physical exercise intolerance[32,33]. Also, the severity and prognosis of CHF can be estimated with low ventilatory efficiency defined as high ventilation drive relative to the given carbondioxide production[34-36].

Lung Diffusion in Chronic Heart Failure

Gas diffusion takes place at the alveolocapillary membrane which, in a simplified model, consists of alveolar epithelium, capillary endothelium, and their basal membranes. Electron microscopy has shown that this membrane is not uniformly structured but is composed of a thinner and thicker part with regard to the interstitial matrix content. On the thinner side, capillary endothelium and alveolar epithelium are closely positioned with tight junctions and basal membranes fused, whereas on the thicker side these structures are mediated by the protein-rich interstitium[37]. Thin part of the membrane is designed to optimally fulfill the task of gas diffusion, and the thick part, in the setting of higher hydrostatic pressures (as in CHF), takes over the fluid and removes it from the critical area where gas diffusion takes place. Generally, diffusing capacity of the lung for carbon monoxide (DLCO) is a function of membrane conductance on the one hand, and of the blood volume in the capillaries with the rate of hemoglobin on the other hand. Patients with CHF were shown to have reduced DLCO with linear deterioration of lung diffusion in patients with more severe CHF[38-40]. The reason for reduced DLCO presumably lies in chronic changes of the alveolocapillary membrane with fluid accumulation, fibrosis, and subsequent reduction of membrane conductance. Also, this reduction is obviously not compensated enough with larger volume of capillary blood flow as would be expected giving the fact of pulmonary venous hypertension in these patients. Also, these changes are not completely reversible because patients after heart transplantation keep approximately the same DLCO as before the operation[41,42]. After heart transplantation, DLCO tends to decline at first, which probably resembles the decline in capillary blood flow due to reduction in pulmonary venous pressure[43-45]. All these changes show that DLCO reduction in patients with CHF does not depend solely on fluid retention but rather is a long-lasting process with formation of chronic changes to alveolocapillary membrane, or may be a consequence of accompanying pulmonary disease. This conclusion is supported by the fact that ultrafiltration in patients with CHF improves lung volumes and mechanical properties of the lung but is unable to improve DLCO, which means that this parameter is not completely fluid-dependent[46]. Impaired lung diffusion was shown to be related to depressed exercise capacity in patients with heart failure[47-49]. Also, membrane conductance, of all respiratory function parameters, correlated best with exercise ventilation efficiency and prognosis in patients with heart failure[50,51]. Exercise training in pa-

tients with heart failure can improve DLCO and exercise performance[52].

Ventilation-Perfusion Mismatch in Chronic Heart Failure

As mentioned above, redistribution of pulmonary capillary perfusion takes place in patients with cardiac failure due to pulmonary venous hypertension and volume overload. Changes of lung volumes and mechanics also occur. This makes patients with CHF more prone to ventilation-perfusion mismatching. In normal conditions, there is no alveolar dead space but, rather, dead space is a consequence of anatomic dead space. It has been shown that exercise ventilation pattern in CHF is a pathologic one with hyperventilation and low efficiency. The reason, among others mentioned earlier, lies in the inability of the lung to augment tidal volume during exercise, which makes breathing in these conditions shallow and rapid. Also, the ratio between the dead space volume and tidal volume stays constant in exercise, suggesting that there are areas of high ventilation-perfusion mismatch with under perfused alveolar spaces, probably due to low cardiac output[53]. These facts when summarized bring us to a conclusion that there is a connection between low efficient breathing, exercise intolerance and ventilation-perfusion mismatch with high respiratory drive to compensate for the under perfused areas of the lung[54].

Sleep Disordered Breathing in Chronic Heart Failure

Chronic heart failure is tightly connected with sleep-disordered breathing (SDB). SDB can be divided into obstructive sleep apnea/hypopnea (OSA), which is defined as five or more apnea/hypopnea episodes *per* hour (apnea/hypopnea index, AHI) that occur due to obstruction of upper airways, combined with extreme respiratory effort and central sleep apnea (CSA), which is defined the same as OSA but without traceable respiratory effort during apnea/hypopnea episodes[55-60]. Both OSA and CSA can coexist in some patients. CSA can be accompanied with Cheyne-Stokes respiration, periodic breathing where apneas alternate with rapidly emerging and waning ventilation. Among patients with CHF, 50% of them suffer from SDB, with 80% of them having CSA and the rest having OSA[61]. OSA/CSA result in repetitive oxyhemoglobin desaturations with consequential arousals, activation of sympathetic system, and increase in arterial blood pressure. OSA is thought to be a major causal factor for cardiovascular diseases and CHF, firstly through its clear effect on the incidence of arterial hypertension as a major cardiovascular risk factor, then through mechanical and hemodynamic effects of negative intrathoracic pressures; OSA has also been associated with activation of the sympathetic nervous system, endothelial dysfunction and systemic inflammation[62-67]. CSA with or without Cheyne-Stokes respiration pattern is a consequence of CHF. This form of SDB occurs due to instability of the respiratory system in patients with CHF[68-69]. Respiration during sleep is controlled by the interaction between brainstem centers, respiratory apparatus (inspiratory musculature, pulmonary parenchyma) and chemoreceptors. Tight correlation between the ventilatory cycle duration and left ventricular ejection fraction has led to a conclusion that low cardiac output and timely transport of the chemostimuli to the chemoreceptors are responsible for the prolonged ventilatory cycle in CHF patients[70]. Thus, chemoreceptors produce an exaggerated answer to low partial pressures of carbon dioxide, finally leading to apnea or hypopnea. Low partial pressure of carbon dioxide is, on the other hand, a consequence of hyperventilation or high respiratory drive in CHF. It is believed that partial pressure of carbon dioxide is the most important indicator of respiratory drive control, as confirmed by a study with reversal of CSA with carbon dioxide inhalation[71]. CSA can worsen the existing CHF through its effect on further activation of the sympathetic system, hypoxemia, blood pressure variations, and cardiac arrhythmia, and also worsens the prognosis with increase of mortality in patients with higher AHI[72]. Sleep breathing disorders in CHF can be improved with treatment. OSA has been successfully treated with continuous positive airway pressure[68]. Studies with optimization of chronic pharmacotherapy have shown success in treating CSA in patients with CHF; supplementing oxygen *via* nasal cannula has also been shown effective[74,75]. The administration of bronchodilation agents showed beneficial effect on SDB and acetazolamide-mild diuretic given before sleep produces mild metabolic acidosis, therefore decreases partial pressure of carbon dioxide and resets the apnea/hypopnea threshold resulting in fewer

episodes of apnea, better oxyhemoglobin saturation, and improving the quality of sleep[76,77]. Noninvasive continuous positive airway pressure treatment reduces sympathetic system activation, arrhythmia incidence, arterial hypertension, and improves left ventricular ejection fraction and volume[78,79]. There is no clear effect on mortality reduction[80].

Radiographic Manifestation of Chronic Heart Failure

Chronic heart failure with pulmonary venous hypertension and volume overload brings along characteristic radio-morphological changes in thoracic imaging. Conventional chest radiogram has been traditionally considered to be the most appropriate tool for diagnosis and follow-up of CHF. Normally, pulmonary blood flow has its characteristic distribution pattern with better perfused area of the lung being its basal part and less perfused area of the lung being the apex, accordingly with gravitational force. Pulmonary blood flow is a low-pressure and low-resistance system with large capacity for accommodation in case of pulmonary venous hypertension and volume overload. Rise in left ventricular end-diastolic pressure, which can be approximated with the rise in pulmonary capillary wedge pressure, in patients with CHF leads to changes in pulmonary blood flow. Capillaries in the apical parts of the lung, previously collapsed, are being recruited and those in the base of the lung are being distended. This change in physiological perfusion of the lung is called redistribution of the pulmonary blood flow. Logically, pulmonary artery-to-bronchus diameter ratio changes as well. Namely, with volume overload arteries gain greater diameter and surpass diameter of the accompanying bronchus, especially in lower parts of the lung[81]. Cardiomegaly is another typical radiographic sign of congestive CHF, although not especially sensitive or specific. It has sensitivity of 50% and specificity of around 75%. Cardiomegaly is best appreciated through cardiothoracic ratio. This ratio is calculated by dividing transverse cardiac diameter with transverse chest diameter measured on chest x-ray, and cardiomegaly is present when the ratio surpasses 50%. Another feature of the heart silhouette on chest x-ray, vascular pedicle, which comprises great intrathoracic vessels, widens on chest x-ray. This pedicle is routinely measured as a field that is limited on the right with superior vena cava and on the left with the point of the subclavian artery take-off. Normally, this diameter is 6.0 centimeters or less and is considered pathological when 8.5 centimeters or greater. The azygos vein seen on the chest x-ray when dilated is a sign of increased right atrial pressure. Normal diameter of the vein is about 7.0 millimeters and when the diameter is 10.0 or more millimeters, it should be considered abnormal and suggests volume overload. As pulmonary venous pressure keeps rising, interstitial edema is formed[82,83]. It is a consequence of fluid leakage into the interlobular and peribronchial interstitium. When the fluid leaks into peripheral interlobular interstitium, it can be appreciated as Kerley B lines on chest x-ray. These are peripherally mounted small horizontal lines that run perpendicularly to the pleura. Edema of the peribronchial interstitium presents as bronchial wall thickening. If pulmonary venous pressure would increase further, alveolar edema and flooding of alveolar spaces would take place. Computerized tomography of the chest is not a method of choice for screening or follow-up of patients with CHF for being expensive, relatively inaccessible, and associated with high radiation dose, although patients with CHF demonstrate typical findings such as interstitial edema with thickened septal lines and ground glass opacities in dependent part of the lung[82-84] (Fig. 2).

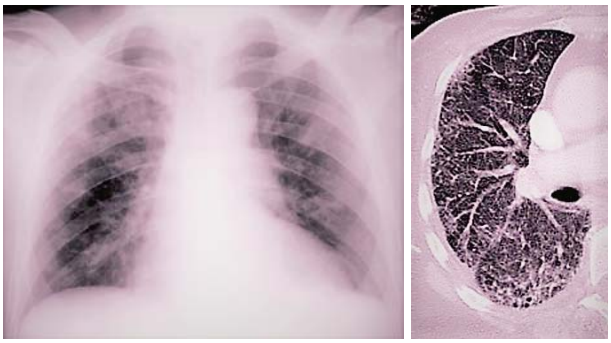

Fig. 2. Radiological evaluation of chronic heart failure.

Chest radiograph of a 65-year-old man with chronic cough and dilatative cardiomyopathy shows interstitial abnormalities. Kerley B lines are notably present in both lung lobes. Cardiomegaly and distension of the right upper lobe and the right lower lobe veins suggest the diagnosis of chronic heart failure (right panel). High-resolution computed tomography scan of the chest reveals pulmonary edema (left panel).

Conclusion

Evaluation of cardiac and pulmonary function and interactions between CHF and consequential chronic lung disease is complex and incompletely understood, often problematic and occasionally misleading. Both conditions are systemic disorders with overlapping pathophysiological processes, and they present diagnostic and therapeutic challenge. Pulmonary function is frequently abnormal, with a decrease in vital capacity shown to precede clinical recognition of CHF. DLCO is often mildly reduced and does not normalize following heart transplantation. Reduced lung compliance, increased dead space ventilation, and muscle weakness contribute to the preceding abnormalities in producing exercise limitation. Sleep apnea, particularly of the central variety, is associated with chronic CHF and confers worse prognosis. Various limitations of clinical evaluation may lead to difficulties in the diagnosis, and consequently in the treatment of CHF, particularly when the presentation is atypical or when lung disease already exists. The resulting symptomatic and prognostic benefits outweigh those attainable by treating either condition alone. Additional studies providing new data on the pathogenesis and management of patients with CHF are needed, with the purpose of trying to improve the quality of life, appropriate treatment, as well as survival of these patients. While many of these therapies will improve the care of patients with CHF, significant reductions in the prevalence will require vigorous, multifaceted, preventive approaches. Only through high appreciation of the complex interactions between the heart and the lung, diagnostic and treatment-related errors can be minimized. A high degree of cooperation is ultimately required among cardiologists, pulmonologists and radiologists in order to better identify and manage these clinical entities. All clinicians attending these patients should perform an integrated approach to objectively identify both diseases at an early stage, and to optimize control of respiratory and cardiovascular conditions.

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Sažetak

SRČANO-PLUĆNE INTERAKCIJE S POSLJEDIČNIM PLUĆNIM ABNORMALNOSTIMA U BOLESNIKA S KRONIČNIM SRČANIM ZATAJENJEM

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Kronično srčano zatajenje značajno opterećuje bolesnika i njegovu obitelj kao i zdravstveni sustav u cjelini budući da je odgovorno za velik broj hospitalizacija. Unatoč golemim naporima u liječenju većine srčanih poremećaja iznimka ostaje klinički sindrom kroničnog srčanog zatajenja učestalost kojega raste s neznatnim uspjehom produženja ukupnog preživljenja bolesnika. Kronično srčano zatajenje je povezano s visokom stopom pobola te nepovoljnom prognozom, čak lošijom uspoređujući sa stopom preživljenja za neke vrste zloćudnih tumora. Razlog porasta učestalosti kroničnog srčanog zatajenja u razvijenim zemljama je produljenje ljudskog vijeka zahvaljujući mjerama suvremenog farmakološkog i intenzivnog liječenja, boljoj sekundarnoj profilaksi i starenju populacije. Kronična plućna bolest je česta pojava u bolesnika s kroničnim srčanim zatajenjem. Oba stanja predstavljaju dijagnostički i terapijski izazov budući da dijele pojedine zajedničke čimbenike rizika i patofiziološke mehanizme nastanka. Cilj ovoga rada je ispitati različite mehanizme odgovorne za simptome kroničnog srčanog zatajenja s posljedičnim plućnim interakcijama i abnormalnostima plućne funkcije.

Ključne riječi: *Srčano zatajivanje; Srčane bolesti; Plućne bolesti*