INTERSTICIJUMSKE BOLESTI PLUĆA I SEKUNDARNA PLUĆNA HIPERTENZIJA

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REVIEW ARTICLE

INTERSTITIAL LUNG DISEASES AND SECONDARY PULMONARY HYPERTENSION

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SAŽETAK

Intersticijumske bolesti pluća, same po sebi, mogu imati lošu prognozu, a kada su udružene sa plućnom hipertenzijom, dolazi do značajnog sniženja stope preživljavanja. S obzirom da je incidencija plućne hipertenzije kod pacijenata sa intersticijumskim bolestima pluća veoma visoka, a simptomi slični, zbog čega često ostaju neprepoznati, cilj ovog teksta jeste da istaknemo značaj obeju ovih bolesti, te da navedemo kliničare da posumnjaju na prisustvo plućne hipertenzije. Kroz kratak osvrt na patohistološke promene, dijagnostičke metode i kliničku sliku obeju ovih bolesti, prikazane su sličnosti i razlike među njima, što može pomoći u svakodnevnom radu sa ovim pacijentima. Takođe, prikazane su i najnovije preporuke lečenja, kao i dejstvo antifibrotske terapije (nintedanib i pirfenidon) na plućnu hipertenziju.

Ključne reči: antifibrotska terapija, nintedanib, pirfenidon, plućna hipertenzija

ABSTRACT

Interstitial lung disease alone can have a poor prognosis, and when associated with pulmonary hypertension there is a significant reduction in survival rates. Since the incidence of pulmonary hypertension in patients with interstitial lung diseases is very high and the symptoms are similar and often unrecognized, our aim is to point out the significance of both coexisting diseases and to prompt clinicians to suspect pulmonary hypertension. Through a brief review of the pathohistological changes, diagnostic methods, and the clinical presentation of these diseases, the similarities and differences that can help in the management of these patients, are shown. The latest treatment guidelines, with a special focus on the impact of antifibrotic treatment (nintedanib and pirfenidone) on pulmonary hypertension, are presented.

Key words: antifibrotic treatment, nintedanib, pirfenidone, pulmonary hypertension

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UVOD

Intersticijumske bolesti pluća (engl. *interstitial lung disease – ILD*) predstavljaju raznovrsnu grupu oboljenja pluća koje karakterišu slične radiografske i kliničke manifestacije, kao i slične patološke promene plućnog parenhima. Naziv intersticijumske bolesti ukazuje na to da sve ove bolesti inicijalno potiču iz plućnog parenhima, no kod većine postoji i opsežno oštećenje alveolarne arhitektonike, ali i samih disajnih puteva. Intersticijum predstavlja područje unutar i oko zidova alveola, gde se, u suštini, odvija razmena gasova [1,2].

Osnovna podela ovih bolesti je na one sa poznatim uzrokom i na idiopatske. Takođe, postoji podela na one sa genetskom predispozicijom (manje od 20%) i na stečene [3]. Približno kod oko trećine pacijenata znamo da je uzrok bolesti delovanje agenasa iz spoljašnje sredine (hipersenzitivni pneumonitis, pneumokonioze, bolesti uzrokovane lekovima, zračenjem, postinfektivne bolesti – bakterije, virusi, gljivična oboljenja), dok je kod ostale dve trećine pacijenata uzrok nepoznat (sarkoidoza, idiopatska intersticijumska pneumonija, intersticijumske bolesti u sklopu sistemskih bolesti vezivnog tkiva, itd.). Idiopatska intersticijumska pneumonija se dalje klasifikuje na: idiopatsku plućnu fibrozu (IPF) sa uobičajenom intersticijumskom pneumonijom (UIP), nespecifičnu intersticijumsku pneumoniju (NSIP), intersticijumsku bolest pluća sa respiratornim bronhitisom, deskvamativnu intersticijumsku pneumoniju (DIP), kriptogenu organizujuću pneumoniju (engl. *cryptogenic organizing pneumonia – COP*), limfoidnu intersticijumsku pneumoniju (LIP), i akutnu intersticijumsku pneumoniju (AIP) [4]. Epidemiologija nije sasvim precizna zbog otežanog postavljanja dijagnoze. Neke zemlje imaju registar ovih bolesti, ali se postavlja pitanje koliko su validni ti registri, jer su podaci krajnje oprečni. Prema dostupnim podacima, najčešće inetersticijumske bolesti su sarkoidoza i idiopatska plućna fibroza (čine preko 50% ILD-a) [5].

DIJAGNOSTIKA

Tegobe zbog kojih se ovi pacijenti javljaju lekaru su nespecifične, i to najčešće u vidu zamaranja, neproduktivnog kašlja i otežanog disanja; one su naročito izražene tokom fizičke aktivnosti i progresivno se pogoršavaju. Često se ove tegobe i ne prepoznaju kod pacijenata koji imaju udružene bolesti (kao što su kardiološki pacijenti, pacijenti sa sistemskim bolestima vezivnog tkiva, pacijenti sa drugim plućnim bolestima). Kako bi se pravovremeno došlo do prave dijagnoze, uvek se moraju detaljno uzeti anamnestički podaci (obavezno obratiti pažnju na profesionalne bolesti, ostale udružene bolesti), mora se obaviti klinički

INTRODUCTION

Interstitial lung disease (ILD) is an umbrella term for a group of diverse pulmonary diseases characterized by similar radiographic and clinical manifestations, as well as similar pathological changes in the lung parenchyma. The term interstitial disease indicates that all of these conditions initially originate from the lung parenchyma, however, in most of these diseases there is also extensive damage to the alveolar architecture as well as to the airways themselves. The interstitium is the area inside and around the alveolar walls, where, in fact, gas exchange occurs [1,2].

These diseases are primarily categorized as those with a known cause and idiopathic diseases. Also, they can be categorized as those with a genetic predisposition (less than 20%) and acquired diseases [3]. In approximately one third of the patients, we know that the disease is caused by the effect of environmental agents (hypersensitive pneumonitis, pneumoconioses, drug-induced diseases, diseases caused by radiation, postinfectious diseases – bacteria, viruses, mycoses), while in the remaining two thirds of the patients the cause is unknown (sarcoidosis, idiopathic interstitial pneumonia, interstitial diseases within systemic connective tissue disorders, etc.). Idiopathic interstitial pneumonia is further classified as: idiopathic pulmonary fibrosis (IPF) with usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), interstitial lung disease with respiratory bronchitis, desquamative interstitial pneumonia (DIP), cryptogenic organizing pneumonia (COP), lymphoid interstitial pneumonia (LIP), and acute interstitial pneumonia (AIP) [4]. The epidemiology is not quite precise due to difficulty in establishing the diagnosis. Some countries have a registry of these diseases, however, the issue remains as to the validity of these registries, as the data are quite contradictory. According to available data, the most frequent interstitial diseases are sarcoidosis and idiopathic pulmonary fibrosis (they account for over 50% of ILDs) [5].

DIAGNOSTICS

The complaints that these patients report to the doctor are nonspecific, most commonly these are fatigue, non-productive cough, and difficulty breathing. These are particularly pronounced during physical activity, and they become progressively worse. Frequently, these complaints are not even recognized in patients with associated diseases (such as cardiological patients, patients with systemic connective tissue disorders, patients with other pulmonary diseases). In order to reach the correct diagnosis on time, anamnestic data must always be recorded correctly (attention must be given to the existence of occupational diseases, other associat-

pregled, moraju se uraditi testovi disajne funkcije, radiografija grudnog koša (dostaviti na uvid trenutne i sve prethodne snimke, ukoliko ih pacijent poseduje), te kompjuterizovana tomografija grudnog koša visoke rezolucije (engl. *high-resolution computed tomography – HRCT*), i, po potrebi, bronhološko ispitivanje sa analizom aspirata bronha, bronhoalveolarnog lavata (BAL) ili samog tkiva. U nekim kliničkim situacijama, indikovane su i invazivnije dijagnostičke metode, kao što je hirurška biopsija pluća.

Bez obzira na uzrok nastanka intersticijumskih bolesti, uvek postoji provocirajući faktor koji će izazvati odgovor osetljivog domaćina. U početku se javlja upalni proces zida alveola, intersticijuma i terminalnih bronhiola, a potom proliferacija vezivnog tkiva, koja menja mikro-arhitektoniku pluća, što vodi ka stvaranju ireverzibilne fibroze. Kao posledica progresije intersticijumskih bolesti pluća, javljaju se respiratorna insuficijencija, sekundarne plućne infekcije, kao i sekundarna plućna hipertenzija [6,7].

PLUĆNA HIPERTENZIJA

Plućna hipertenzija (PH) je patofiziološki poremećaj koji može obuhvatiti više kliničkih stanja i biti povezan sa različitim kardiovaskularnim i plućnim bolestima. Definiše se kao povećanje plućnog arterijskog pritiska (PAP) ≥ 20 mmHg u miru, što procenjujemo kateterizacijom desnog srca. Termin plućna arterijska hipertenzija (PAH) opisuje grupu pacijenata sa plućnom hipertenzijom koji se hemodinamski karakterišu prisustvom prekapilarne PH, definisane plućnim arterijskim wedge pritiskom (engl. *pulmonary artery wedge pressure – PAWP*) 15 mmHg i plućnim vaskularnim otporom (engl. *pulmonary vascular resistance – PVR*) > 2 Wood jedinice [8].

Poslednjih godina je napravljen značajan napredak u dijagnostici i lečenju plućne hipertenzije, te je u Vodiču Evropskog udruženja kardiologa i Evropskog respiratornog udruženja (engl. *European Society of Cardiology – ESC*; *European Respiratory Society – ERS*), iz 2022. godine, korigovana i definicija, u smislu promene graničnih vrednosti PAP-a i PVR-a. Prema Svetskoj zdravstvenoj organizaciji, uzroci plućne hipertenzije su svrstani u pet grupa (na osnovu etiologije nastanka). U registrima, polovina plućnih arterijskih hipertenzija pripada idiopatskoj, naslednoj i grupi uzrokovanoj lekovima; u grupi stanja udruženih sa plućnom arterijskom hipertenzijom, najčešći uzrok su bolesti vezivnog tkiva (dominira sistemska skleroza) [9]. Teški oblik plućne arterijske hipertenzije se može verifikovati kod kombinovanog emfizema/fibroznog sindroma, gde je prevalencija bolesti visoka.

ed diseases), a clinical examination must be performed, respiratory function tests must be carried out, as well as a chest X-ray (examination of current and previous X-ray images, if they are available, is necessary), and high-resolution computed tomography (HRCT) of the chest, and, if needed, bronchological examination with analysis of the bronchial aspirate, the bronchoalveolar lavage fluid (BALF), or of the tissue itself. In some clinical situations, even more invasive diagnostic methods are indicated, such as surgical lung biopsy.

Regardless of the cause of the development of interstitial diseases, there is always a factor provoking a response in a sensitive host. First, an inflammatory process develops in the alveolar wall, the interstitium, and the terminal bronchioles, followed by connective tissue proliferation, altering the pulmonary microarchitecture, thus leading to irreversible fibrosis. As the result of the progression of interstitial lung disease, respiratory insufficiency, secondary pulmonary infections, as well as secondary pulmonary hypertension develop [6,7].

PULMONARY HYPERTENSION

Pulmonary hypertension (PH) is a pathophysiological disorder which may encompass a number of clinical conditions and may be linked to different cardiovascular and pulmonary diseases. It is defined as the elevation of pulmonary arterial pressure (PAP) ≥ 20 mmHg at rest, which we assess with right heart catheterization. The term pulmonary arterial hypertension (PAH) describes a group of patients with pulmonary hypertension who are hemodynamically characterized by the presence of precapillary PH, defined by pulmonary artery wedge pressure (PAWP) 15 mmHg and pulmonary vascular resistance (PVR) > 2 Wood units [8].

In recent years, significant progress in the diagnostics and treatment of pulmonary hypertension has been made, and the definition of this disease was amended, in the sense that the cut-off levels of PAP and PVR were revised, in the 2022 ESC/ERS1 Guidelines for the diagnosis and treatment of pulmonary hypertension. According to the World Health Organization, the causes of pulmonary hypertension are categorized into five groups (based on the etiology of their development). In the registries, half of the pulmonary arterial hypertensions belong to the idiopathic, hereditary, and drug-induced groups; in the group of conditions associated with PAH, the most common cause are connective tissue diseases (with a dominance of systemic sclerosis) [9]. The severe form of PAH can be verified in combined pulmonary fibrosis and emphysema syndrome, where the prevalence of the disease is high.

1 European Society of Cardiology/European Respiratory Society

UTICAJ FIBROZE PLUĆA NA NASTANAK PLUĆNE HIPERTENZIJE

Osnovni patofiziološki mehanizam nastanka plućne hipertenzije kod pacijenta sa ILD-om je plućna vazokonstrikcija, koja nastaje usled nedovoljne količine kiseonika i anatomske redukcije plućnog vaskularnog korita [10]. Kao odgovor na to stanje dolazi do proliferacije endotelnih ćelija, ćelija glatke muskulature i fibroblasta, uz hipertrofiju medije i adventicije. Svi slojevi plućnih arterija pokazuju koncentrično i ekscentrično remodelovanje; široko rasprostranjena hiperplazija intime je posledica prisustva endotelnih ćelija, dok u mediji i adventiciji postoji zadebljanje koje je posledica hipertrofije i/ili hiperplazije ćelija glatkih mišića i fibroblasta. U mediji se mogu uočiti uzdužno orijentisane glatke mišićne ćelije, što je karakteristično za hipoksičnu plućnu hipertenziju. Kapilarna mreža je, u delovima pluća prožetih fibrozom, proređena, a prostor između kapilara i bazalne membrane je proširen. U venama dolazi do zadebljanja adventicije, hiperlpazije glatkih mišićnih ćelija, okluzije lumena, fibroze intime i zadebljanja elastične lamine [11]. Sve ove promene krvnih sudova mogu biti prisutne kod pacijenata sa ILD-om, bez obzira da li je prisutna i plućna hipertenzija, ali su češće kod pacijenata sa obe bolesti [12]. Kod pacijenata sa plućnom fibrozom, morfološke promene vaskularne mreže dešavaju se nezavisno od uzroka, a remodelovanje je prisutno u svim tipovima krvnih sudova širom pluća. Lumen krvnih sudova se progresivno sužava. Krajnji rezultat ovih promena je trajno povećanje plućne vaskularne rezistencije, odnosno razvoj hronične plućne hipertenzije [13]. Međutim, mnoga sprovedena klinička istraživanja nisu pronašla nikakvu korelaciju između opsežnosti plućne fibroze i PAP-a, merenog kompjuterizovanom tomografijom grudnog koša visoke rezolucije. Stoga, oštećenje plućnog tkiva i stvaranje ožiljnog tkiva ne objašnjava razvoj plućne hipertenzije kod pacijenata sa ILD-om [14].

Prvi simptomi koji se javljaju kod pacijenta sa plućnom hipertenzijom su takođe nespecifični i vrlo slični onima koji se pojavljuju kod pacijenata sa intersticijumskom bolešću pluća, a dominiraju dispneja pri naporu i progresivno zamaranje, koji vremenom napreduju, dok se ne razvije teža forma plućne hipertenzije sa svim znacima slabosti desne komore (bolovi u sredogrudju, sinkopa pri naporu, povećanje telesne težine zbog zadržavanja tečnosti, pojava ascitesa, bolovi u abdomenu zbog kongestije jetre, itd.). Često, simptomi nisu prepoznati, i to naročito u grupama starijih pacijenata, potom kod pacijenata narušenog opšteg stanja, i kod onih sa mnogobrojnim komorbiditetima [15]. Prema nekim statističkim podacima,

THE EFFECT OF PULMONARY FIBROSIS ON THE DEVELOPMENT OF PULMONARY HYPERTENSION

The basic pathophysiological mechanism of the development of pulmonary hypertension in patients with ILD is pulmonary vasoconstriction resulting from a decreased quantity of oxygen and the anatomical reduction of the pulmonary vascular bed [10]. As a response to this condition, a proliferation of endothelial cells, smooth muscle cells, and fibroblasts occurs, together with a hypertrophy of the media and adventitia. All layers of the pulmonary arteries exhibit concentric and eccentric remodeling; a widely distributed hyperplasia of the intima is the result of the presence of endothelial cells, while in the media and the adventitia there is a thickening which is the result of hypertrophy and/or hyperplasia of the smooth muscle cells and fibroblasts. Longitudinally oriented smooth muscle cells can be seen in the media, which is characteristic of hypoxic pulmonary hypertension. The capillary network is, in the parts of the lungs that are infiltrated with fibrosis, reduced, while the space between the capillaries and the basement membrane is increased. In the veins, the adventitia thickens, smooth muscle cell hyperplasia occurs, the lumen occludes, fibrosis of the intima develops, and the elastic lamina thickens [11]. All of these changes to the blood vessels may be present in patients with ILD, regardless of whether pulmonary hypertension is present as well, however, they are more frequent in patients with both diseases [12]. In patients with pulmonary fibrosis, morphological changes in the vascular network develop independently of the cause, while remodeling is present in all types of blood vessels throughout the lungs. The blood vessel lumen becomes progressively narrower. The end result of these changes is permanent increase of pulmonary vascular resistance, i.e., the development of chronic pulmonary hypertension [13]. However, many clinical studies that have been carried out did not find any correlation between the extent of pulmonary fibrosis and PAP, measured with high resolution computed tomography of the thorax. Therefore, damage to the lung tissue and the development of scar tissue does not explain the development of pulmonary hypertension in patients with ILD [14].

The first symptoms that occur in patients with pulmonary hypertension are also nonspecific and are very similar to those occurring in patients with interstitial lung disease, with the dominant ones being dyspnea on exertion and progressive fatigue, which become more pronounced with time, until a more severe form of pulmonary hypertension develops with all the signs of right ventricular weakness/failure (middle chest pain, syncope with exertion, body weight increase due to

preko 20% pacijenata ima simptome plućne hipertenzije duže od 24 meseca pre nego što dijagnoza bude ustanovljena [16].

DIJAGNOSTIKA PLUĆNE HIPERTENZIJE

Plućna hipertenzija je čest komorbiditet kod pacijenata sa intersticijumskim bolestima pluća, ali kao što je već spomenuto, dijagnoza se teže postavlja zbog nespecifičnih simptoma. Zlatni standard je kateterizacija desnog srca, iako je procedura invazivna i skupa. Još uvek se ne radi rutinski kod pacijenata sa ILD-om (osim kod pripreme za transplantaciju pluća), ali ulažu se veliki napori za pronalaženje pouzdane neinvazivne metode, koja bi olakšala postavljanje dijagnoze plućne hipertenzije kod ovih pacijenata [17].

Kod pacijenata sa ILD-om, testovi disajne funkcije se koriste za procenu stepena oštećenja pluća. Forsirani vitalni *kapacitet (engl. forced vital capacity – FVC*) i difuzijski kapacitet pluća za CO (engl. *diffusing capacity of the lungs for carbon monoxide – DLCO*) su dva pokazatelja plućne funkcije od najvećeg interesa. Oba parametra su snižena kod pacijenata sa ILD-om i koreliraju sa progresijom bolesti. DLCO je parametar koji može biti snižen kod pacijenata sa plućnom hipertenzijom, a da ti pacijenti nemaju intersticijumsku bolest pluća [18]. Stoga, svako sniženje vrednosti DLCO-a koje nije srazmerno stepenu plućne fibroze može da bude znak pridružene plućne arterijske hipertenzije. Zisman i saradnici su razvili matematičku formulu koja predviđa vrednost PAP-a, koristeći FVC, DLCO i saturaciju kiseonikom [18]. Preciznost ove formule je potvrđena u dve studije, ali sa malim brojem pacijenata sa IPF-om, te je potrebna potvrda na većoj grupi ispitanika radi validacije formule. S obzirom da sniženje DLCO-a (najčešći parametar disajne funkcije koji odstupa od normalnih vrednosti kod pacijenata sa PAH-om) nije specifičan znak (nalazimo ga kod emfizema, hronične plućne embolije, plućnog edema, anemije), zaključuje se da samo ispitivanje disajne funkcije ima ograničenu prediktivnu vrednost za otkrivanje plućne arterijske hipertenzije kod pacijenata sa fibrozom pluća [19].

Ultrazvuk srca je trenutno najčešće primenjivana neinvazivna dijagnostička metoda za skrining pacijenata sa plućnom hipertenzijom. Međutim, kod pacijenata sa uznapredovalom bolešću pluća, ova metoda ima ograničenu tačnost za rano otkrivanje plućne hipertenzije. U studiji od 374 pacijenta, koji su pripremani za transplantaciju pluća, grupa autora je otkrila da je korišćenje ultrazvuka za otkrivanje plućne hipertenzije kod pacijenata sa opstruktivnim i intersticijumskim bolestima pluća bilo moguće samo u 44% slučajeva, dok je u 52% pacijenata ove grupe izmerena vrednost plućfluid retention, the development of ascites, abdominal pain due to liver congestion, etc.). The symptoms are often unrecognized, especially in the groups of older patients, in patients with a deteriorating general health status, and in those with a number of comorbidities [15]. According to some statistical data, over 20 % of patients have symptoms of pulmonary hypertension for longer than 24 months before the diagnosis is established [16].

DIAGNOSTICS OF PULMONARY HYPERTENSION

Pulmonary hypertension is a frequent comorbidity in patients with interstitial pulmonary disease, however, as mentioned previously, the diagnosis is more difficult to establish due to nonspecific symptoms. The golden standard is right heart catheterization, although the procedure is invasive and expensive. It is still not performed routinely in patients with ILD (except within preparations for lung transplantation). However, significant effort is being made to find a reliable noninvasive method that would make it easier to establish the diagnosis of pulmonary hypertension in these patients [17].

In patients with ILD, respiratory function tests are used for assessing the degree of lung damage. Forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DLCO) are two indicators of pulmonary function of the greatest interest. Both parameters are reduced in patients with ILD and they correlate with the progression of disease. DLCO is a parameter which may be decreased in patients with pulmonary hypertension, without the presence of interstitial lung disease in these patients [18]. Therefore, any decrease of the DLCO value which is not proportionate to the degree of pulmonary fibrosis may be the sign of associated pulmonary arterial hypertension. Zisman et al. developed a mathematical formula which predicts the value of PAP, by using FVC, DLCO, and oxygen saturation [18], and the precision of this formula has been confirmed in two studies, but with a small number of patients with IPF, which is why confirmation is necessary on a larger group of subjects, in order to validate the formula. Since the decrease of DLCO (the most common parameter of respiratory function deviating from normal values in patients with PAH) is not a specific sign (we find it in emphysema, chronic pulmonary embolism, pulmonary edema, anemia), the conclusion is that testing respiratory function alone has limited predictive value for discovering pulmonary arterial hypertension in patients with pulmonary fibrosis [19].

Ultrasound of the heart is, at present, the most commonly applied noninvasive diagnostic technique for screening patients with pulmonary hypertension, however, in patients with advanced lung disease, this meth-

ne hipertenzije bila netačna [20]. Veliki uticaj na ovakve rezultate ima i postojanje lošeg „ehosonografskog prozora" kod pacijenata sa plućnim bolestima.

Kompjuterizovana tomografija visoke rezolucije (HRCT) se koristi u dijagnostičke svrhe kod pacijenata sa ILD-om, ali može da posluži i za otkrivanje plućne hipertenzije, procenom dimenzija plućne arterije. Sprovedeno je nekoliko studija u kojima su dobijeni oprečni rezultati. Devaraj i saradnici su na 30 pacijenata sa ILD-om pokazali da nema značajne korelacije između dijametra plućne arterije i vrednosti PAP-a ili PVR-a, merenih kateterizacijom desnog srca [21], dok su Čin i saradnici, u dosta obimnijoj studiji, koja je obuhvatila 101 pacijenta, pokazali korelaciju između dijametra plućne arterije i PAP-a. Međutim, proširenje plućne arterije se može pronaći kod pacijenata sa IPF-om koji nemaju plućnu hipertenziju, čime se ograničava upotreba ove metode. Predloženo je da se zbog toga, kao indirektni pokazatelj plućne hipertenzije, uzme uvećanje dijametra segmentnih arterija (tri od četiri segmentne arterije treba da budu uvećane kako bi nalaz upućivao na PH) [22].

Od drugih neinvazivnih metoda, ergospirometrija može biti od velike koristi. Nekoliko studija je pokazalo da parametri koji se prate tokom testa i njihov odnos (minutna ventilacija, produkcija CO2, parcijalni pritisak CO2) mogu pokazati ne samo postojanje, već i težinu plućne hipertenzije kod pacijenata sa ILD-om [23]. Magnetna rezonanca srca nije pokazala nikakve prednosti u odnosu na HRCT grudnog koša, što se tiče dijagnoze plućne hipertenzije, a metoda je dosta skuplja i manje dostupna pacijentima. Na kraju, kada se sve analizira, još uvek ne postoji niti jedna neinvazivna metoda koja može sa velikom preciznošću verifikovati postojanje plućne hipertenzije, međutim, njihova primena može navesti kliničara da posumnja u pravcu iste, a potom da se dijagnoza potvrdi kateterizacijom desnog srca.

TERAPIJA

Pacijenti sa ove dve udružene bolesti imaju veoma lošu prognozu, a sekundarna plućna hipertenzija, koja ima visoku prevalenciju kod pacijenata sa *ILD*-om, predstavlja značajan prediktor mortaliteta [24]. Prema podacima iz literature, za sada nema suštinskog napretka u lečenju treće grupe pacijenata sa plućnom hipertenzijom. Na prvom mestu je lečenje osnovne bolesti, kojim se pokušava smanjenje hipoksije, koja je i uzročnik plućne hipertenzije. Od suportivme terapije, savetuje se redovna fizička aktivnost, respiratorna rehabilitacija, prekid pušenja, te redovna sezonska vakcinacija [25]. Uvođenje kontinuirane oksigenoterapije indikovano je samo kod pacijenata

od has limited accuracy for early detection of pulmonary hypertension. In a study involving 374 patients who were being prepared for lung transplantation, a group of authors discovered that the application of ultrasound for discovering pulmonary hypertension in patients with obstructive and interstitial pulmonary diseases was possible in only 44% of the cases, while in 52% of patients of this group the measured value of pulmonary hypertension was incorrect [20]. The existence of a poor 'echosonographic window' in patients with pulmonary disease also has a significant impact on these results.

High resolution computed tomography (HRCT) is used for diagnostic purposes in patients with ILD, but it may also be used for discovering pulmonary hypertension by assessing the dimensions of the pulmonary artery. Several studies have been carried out yielding conflicting results. In a study involving 30 patients with ILD, Devaraj et al. showed that there is no significant correlation between the diameter of the pulmonary artery and the value of PAP or PVR, measured with right heart catheterization [21], while Chin et al. demonstrated a correlation between the pulmonary artery diameter and PAP, in a much larger study, which included 101 patients. However, widening of the pulmonary artery can be found in patients with IPF, who do not have pulmonary hypertension, which limits the application of this method. This is why it has been proposed that the increase in the diameter of segmental arteries (three of the four segmental arteries need to have an increased diameter in order for the finding to indicate PH) should be taken as an indirect indicator of pulmonary hypertension [22].

As to other noninvasive methods, ergospirometry may be very useful. Several studies have shown that the parameters which are followed during the test as well as their proportion (minute ventilation, CO2 production, partial pressure of carbon dioxide) may show, not only the existence of pulmonary hypertension in patients with ILD, but also its severity [23]. Magnetic resonance imaging of the heart did not reveal any advantage, as compared to HRCT of the thorax, in the diagnosis of pulmonary hypertension, and the method is significantly more expensive and less accessible to patients. Finally, when all is analyzed, there still is no single noninvasive method that can verify the existence of pulmonary hypertension with great precision, however, the application of the said methods may lead the clinician to first suspect PH, and then confirm the diagnosis with right heart catheterization.

THERAPY

The patients with these two comorbidities have a very poor prognosis, and secondary pulmonary hypertension, which has a high prevalence in patients with ILD,

kod kojih se verifikuje hronična respiratorna insuficijencija [26]. Nema dokaza da je antikoagulantna terapija od koristi ovim pacijentima [27].

Što se tiče specifične terapije, pacijenti su podeljeni u dve grupe, oni sa lakom i srednje teškom formom i oni sa teškim oblikom plućne hipertenzije. Za prvu grupu pacijenata predviđena je samo suportivna terapija, uz redovno praćenje na 6 – 12 meseci. Druga grupa pacijenata, u koju spadaju bolesnici sa teškim oblikom plućne hipertenzije (ehokardiografski procenjen sistolni pritisak desne komore – SPDK > 60 mmHg ili kateterizacijom desnog srca procenjen mPAP > 35 mmHg), uglavnom se tretira suportivnom terapijom, a manji procenat dobija specifičnu terapiju [27]. Kada kod pacijenta visoko funkcionalne grupe (prema klasifikaciji Svetske zdravstvene organizacije) nema koristi od suportivne terapije, ipak se odlučujemo za primenu specifičnog načina lečenja [28]. Lekovi koji se koriste su iz grupe agonista prostaciklina (iloprost, treprostinil, epoprostenol, seleksipag), inhibitori fosfodiesteraze tipa 5 (sildenafil, tadalafil), te stimulatori solubilne guanilat ciklaze (riociguat). Ovi lekovi imaju dokazanu efikasnost u lečenju pacijenata prve grupe, dok je u trećoj grupi (gde pripadaju pacijenti sa *ILD*-om) njihova primena ograničena, a u nekim situacijama može biti i štetna. Osim inhalatornog treprostinila, nijedan drugi lek nije odobren za lečenje plućne hipertenzije u ovoj grupi pacijenata [29]. Loš efekat lekova može biti posledica njihovog vazodilatatornog dejstva, koje pogoršava ventilaciono-perfuzijski odnos, što dalje pogoršava razmenu gasova, koja je već narušena kod plućnih pacijenata. Lekovi iz grupe antagonista endotelinskih receptora, kao što je ambrisentan, nisu pokazali efikasnost, i povezani su sa čestim neželjenim dejstvima (pogoršanje saturacije kiseonikom, progresija osnovne bolesti, te česte hospitalizacije) [30].

Transplantacija pluća može biti opcija kod pacijenata iz treće grupe, kod kojih se stanje pogoršava uprkos terapiji. Uticaj plućne hipertenzije na ishod transplantacije je neizvestan. Nekoliko studija sugeriše da nema negativnog uticaja plućne hipertenzije na preživljavanje pacijenata sa *ILD*-om koji su podvrgnuti transplantaciji. Međutim, neke studije pokazuju da PH predstavlja faktor rizika za 90-dnevni mortalitet nakon transplantacije jednog pluća, te da PH može predstavljati veći rizik za primarnu disfunkciju grafta [31].

Nintedanib i pirfenidon su jedina dva leka sa antifibrotskim delovanjem koja su zvanično navedena u smernicama za lečenje idiopatske plućne fibroze. Nintedanib ima šire indikacije za upotrebu kod autoimunih intersticijumskih bolesti pluća i kod *ILD*-a u sklopu sistemskih oboljenja vezivnog tkiva, a od 2014. godine,

is a significant predictor of mortality [24]. According to the data from literature, there is as yet no significant progress in the treatment of the third group of patients with pulmonary hypertension. Primarily, treatment of the underlying disease is performed, attempting to reduce hypoxia, which is the cause of pulmonary hypertension. As to supportive therapy, regular physical exercise is recommended, as well as respiratory rehabilitation, smoking cessation, and regular seasonal vaccination [25]. Introducing continuous oxygen therapy is indicated only in patients in whom chronic respiratory insufficiency is verified [26]. There is no proof that anticoagulation therapy is beneficial to these patients [27].

As to specific therapy, the patients were divided into two groups, those with the mild and the moderately severe forms, and those with the severe form of pulmonary hypertension. Only supportive therapy is recommended for the first group of patients, together with regular follow-up, every 6 to 12 months. Patients in the second group, i.e., those with the severe form of pulmonary hypertension (echocardiographically assessed right ventricular systolic pressure – RVSP > 60 mmHg or mPAP > 35 mmHg assessed with right heart catheterization), are generally treated with supportive therapy, while a smaller percentage of them receive specific therapy [27]. When supportive therapy brings no benefit to the patients belonging to the highly functioning group (according to the World Health Organization classification), we opt for applying specific treatment [28]. The drugs applied belong to the group of prostacyclin agonists (iloprost, treprostinil, epoprostenol, selexipag), inhibitors of phosphodiesterase type 5 (sildenafil, tadalafil), and soluble guanylate cyclase stimulators (riociguat). These drugs have proven efficacy in treating patients belonging to the first group, while in the third group (where ILD patients belong), their application is limited, and in some situations, it may even be harmful. Apart from treprostinil inhalations, no other drug has been approved for treating pulmonary hypertension in this group of patients [29]. The negative effect of drugs may be the result of their vasodilatory effect, which worsens the ventilation-perfusion ratio, which further worsens gas exchange that is already damaged in patients suffering from pulmonary disease. The drugs belonging to the group of endothelin receptor antagonists, such as ambrisentan, did not prove efficient and have been connected with frequent adverse effects (drop in oxygen saturation, progression of the underlying disease, frequent hospitalizations) [30].

Lung transplantation may be an option in patients belonging to the third group, in whom their condition deteriorates despite treatment. The effect of pulmonary hypertension on the transplantation outcome is

zvanično je odobren za lečenje IPF-a [32]. Malo se zna kako ova dva leka utiču na plućnu vaskularnu mrežu. Nintedanib je inhibitor tirozin kinaze koji se vezuje za receptore faktora rasta, a koji igra važnu ulogu u obe bolesti. Dve velike randomizovane studije su pokazale da nintedanib usporava sniženje *FVC*-a kod pacijenata sa IPF-om [33]. Postoje oskudni podaci o uticaju nintedaniba na plućnu vaskularnu mrežu i remodelovanje desne komore srca. Ispitivanje sprovedeno na miševima, kod kojih su izazvane promene plućnog parenhima koje odgovaraju promenama u sistemskoj sklerozi, pokazalo je da primena nintedaniba nije poboljšala samo histološke karakteristike plućne fibroze već i promene na krvnim sudovima. U kasnijim izveštajima pokazalo se da lek nije sprečio remodelovanje malih krvnih sudova, ali nije uticao ni na sniženje sistolnog pritiska desne komore srca. Učinjeno je praćenje kod pacijenata sa plućnom hipertenzijom (mala grupa) koji su tretirani nintedanibom, a rezultati su pokazali pogoršanje *PVR*-a i minutnog volumena [34]. Pirfenidon se koristi u lečenju IPF-a, a u toku je i ispitivanje koje procenjuje kombinovano lečenje pirfenidonom i sildenafilom, kod pacijenata sa IPF-om i visokim rizikom za plućnu hipertenziju. U studijama na životinjama je uočena zaštitna uloga pirfenidona kod remodelovanja plućne vaskularne mreže [35].

ZAKLJUČAK

Koegzistiranje *ILD*-a (IPF) i plućne hipertenzije, usložnjava dijagnostički i terapijski pristup. Antifibrotici deluju tako što usporavaju progresiju plućne fibroze, utiču na smanjenje broja pogoršanja i poboljšavaju kvalitet života obolelih. Istraživanja na polju uticaja antifibrotika na plućnu vaskularnu mrežu su u toku. Kada su prisutne obe bolesti, sužene su terapijske opcije za plućnu hipertenziju. U jednoj retrospektivnoj studiji, medijana preživljavanja pacijenata sa IPF-om je bila 23 meseca, dok je medijana preživljavanja kod pacijenata sa IPF-om i plućnom hipertenzijom iznosila samo 11 meseci [36]. Plućna hipertenzija, kada se javi zbog hipoksije, progresivnija je i povezana je sa povećanim morbiditetom i mortalitetom.

Posle svega izrečenog, stav autora ovog teksta je da uvek treba razmišljati o postojanju plućne hipertenzije kod intersticijumskih bolesti pluća, preduzeti sve potrebne dijagnostičke procedure, dokazati a potom i pratiti tok bolesti. Pravovremena suportivna terapija može olakšati svakodnevni život pacijenta, a sprovođenjem kliničkih studija baš u ovoj grupi pacijenata, možemo očekivati i pronalaženje delotvorne ciljane terapije.

Sukob interesa: Nije prijavljen.

uncertain. Several studies suggest that there is no negative effect of pulmonary hypertension on survival in patients with ILD who had undergone transplantation. However, some studies show that PH is a risk factor for ninety-day mortality after transplantation of a lung, and that PH may pose a higher risk for primary graft dysfunction [31].

Nintedanib and pirfenidone are the only two drugs with an antifibrotic effect which are officially listed in the guidelines for treating idiopathic pulmonary fibrosis. Nintedanib has broader indications for use in autoimmune interstitial lung diseases and in ILD within systemic connective tissue diseases, and as of 2014, it has officially been approved for IPF treatment [32]. Little is known on how these two drugs affect the pulmonary vascular network. Nintedanib is an inhibitor of tyrosine kinase which binds to growth factor receptors, and which plays an important role in both diseases. Two large, randomized studies have shown that nintedanib slows down the reduction of FVC in patients with IPF [33]. There are limited data on the effect of nintedanib on the pulmonary vascular network and on right ventricular remodeling. Research conducted on mice, in which changes to the lung parenchyma consistent with those occurring in systemic necrosis were induced, showed that the application of nintedanib did not only improve the histological characteristics of pulmonary fibrosis but also the anomalies in the blood vessels. In later reports, it was demonstrated that the drug did not prevent the remodeling of small blood vessels, however, it did not reduce the right ventricular systolic pressure either. Follow-up was performed in patients with pulmonary hypertension (small group) which were treated with nintedanib, and the results showed a deterioration of PVR and of the cardiac output [34]. Pirfenidone is applied in the treatment of IPF, and research assessing the combined therapy with pirfenidone and sildenafil in patients with IPF and a high risk of pulmonary hypertension is ongoing. In animal studies, the protective role of pirfenidone in the remodeling of the pulmonary vascular network was registered [35].

CONCLUSION

The coexistence of ILD (IPF) and PH renders the diagnostic and therapeutic approach more complex. Antifibrotics act by slowing down the progression of fibrosis, by decreasing the number of exacerbations of the disease, and by improving the quality of life of the patients. Research regarding the effect of antifibrotics on the vascular network of the lungs is ongoing. When both diseases are present, therapeutic options are limited with regards to pulmonary hypertension. In a retrospective study, median survival for patients with IPF

was 23 months, while median survival in patients with IPF and pulmonary hypertension was only 11 months [36]. Pulmonary hypertension, when it develops due to hypoxia, is progressive and is associated with increased morbidity and mortality.

Bearing in mind all that has been said, the opinion of the authors of this article is that the possibility of pulmonary hypertension should always be considered in patients with interstitial lung disease, and all necessary diagnostic procedures should be carried out in order to determine the existence of the disease and then further monitor the course of the disease. Timely supportive therapy may make the everyday life of patients easier, while by carrying out clinical studies in this very group of patients we may expect to discover effective targeted therapy.

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