Srce i krvni sudovi 2023; 42(2): 32-36

Review article

Chronic thromboembolic pulmonary disease

Slobodan Obradovic[1,2], Boris Dzudovic[2,3]

[1]Clinic of Cardiology, Military Medical Academy, Belgrade, [2]School of Medicine, University of Defense, Belgrade, Serbia, [3]Clinic of Emergency Internal Medicine, Military Medical Academy, Belgrade

Abstract Chronic thromboembolic pulmonary disease (CTEPD) with or without pulmonary hypertension (CTEPH) is rare, very often progressive complication of pulmonary embolism (PE). There was significant improvement in diagnostics and treatment of this disease in the recent years.
The aim of this review is to present current knowledge and guidelines for the management of CTEPH. We reviewed epidemiology, pathophysiology, diagnostics, risk stratification and various types of treatment options: medicament, balloon pulmonary angioplasty (BPA) and pulmonary endarterectomy (PEA). It is clear that multimodality treatment is the best approach for most of the patients with CTEPH and this became a part of 2022 European Society of Cardiology guidelines for the first time. The last 2019 ESC PE guidelines for the first time also recommend active follow-up of high-risk and symptomatic patients after acute PE for the early diagnosis of CTEPH. Both of these guidelines significantly improve the awareness for this rare disease and treatment of these patients.

Kew words chronic thromboembolic pulmonary hypertension, balloon pulmonary angioplasty, pulmonary endarterectomy

Epidemiology and pathophysiology

Chronic thromboembolic pulmonary disease with or without pulmonary hypertension is a rare complication of acute PE (CTED or CTEPH). It is classified as type IV PH, as PH caused by the obstruction in the pulmonary circulation. In the prospectively well-designed studies, the incidence of CTEPH is 1.6% after 6 months and 2,3% after 2 years of follow-up in the FOCUS study, and 1% after 6 months and 3.8% after 2 years in the Thromboembolic Pulmonary Hypertension Study Group.[1,2] It is unknown why the percentage of patients with CTEPH rise from 6 months to two years. Is it because of the recurrent venous thromboembolism during that period, or is it the evolution of the first process? It is interesting that approximately one third of the patients do not have an earlier history of acute pulmonary embolism and it is logical to assume that even low-risk PE can result in severe CTEPH.
The main pathophysiology of CTEPH is absence of thrombus dissolution and fibrotic changes of the thrombus which cause obstruction of the pulmonary artery tree and possible remodeling of the small arteries and paracrine reaction as a response to diminished pulmonary perfusion[3]. Hypercoagulable states and insufficient fibrinolysis are recognized as risk factors for CTEPH development. Hereditary deficiency of protein C and antithrombin, 4G PAI-1 homozygote state are the most important hereditary risk factors and antiphospholipid syndrome (primary or secondary) is the most important acquired thrombophilia which is related to CTEPH. Even large thrombus masses can dissolve in a few months after acute PE, and the presence of thrombophilia is probably more important than the burden of the thrombi. Chronic myeloproliferative and lymphoproliferative diseases are also associated with CTEPH development which might underline the role of leukocytes in the thrombus dissolution which is impaired in these diseases.

Diagnosis and risk stratification

We have already mentioned that one third of CTEPH patients have no history of acute PE. Since that there are two different pathways in the diagnostics of CTEPH. The first one, after acute PE, purport the follow-up of patients after acute PE, where patients who have dyspnea or effort intolerance after PE should have echocardiography examination and brain natriuretic peptide blood measurement, and if there we found tricuspid regurgitation velocity greater than 2.8 m/s together with some other signs of right ventricle dysfunction, especially with the elevated BNP blood levels, this patient should be refer to the center specialized for the management of pulmonary hypertension[4]. Computed tomography (CT) of the lungs and pulmonary angiography (CTPA) are important for the differential diagnosis of PH. Proximal organized thrombi means that patient has CTEPH that can be treated with pulmonary endarterectomy (PEA). Enlarged, tortuous proximal PA with poor peripheral arborization is classical finding in PH of different etiology. Perfusion lung scintigraphy shows typical multiple perfusion defects in patients with CTEPH. Six minutes walking test and exercise testing serve for the risk stratification. After non-invasive examination,

Address for correspondence: Prof. Slobodan Obradovic, MD, PhD, Clinic of Cardiology, Military Medical Academy, Belgrade; School of Medicine, University of Defense, Belgrade, Serbia. E-mail: sloba.d.obradovic@gmail.com

Table 1. Risk stratification in patients with PH. However, each parameter does not have the same value for the risk stratification. Clinical features are probably more accurate.

Parameters	Low <5%	Intermediate 5-20%	High >20%
Clinical signs of HF	No	No	Yes
Symptom progression	No	Slow	Rapid
Syncope	No	Occasional	Repeated
WHO-FC	I, II	III	IV
6-minute walking test	>440 m	165-440 m	<165 m
CPET	PeakO_2>15ml/min/kg	Peak$O_2$11-15ml/min/kg	PeakO_2<11ml/kg/min
BNP	<50pg/ml	50-800pg/ml	>800pg/ml
NT-proBNP	<300pg/ml	300-1100pg/ml	>1100 pg/ml
Echocardiography			
RA area	>18cm^2	18-26cm^2	>26cm^2
TAPSE/sPAP	>0.32mm/mmHg	0.19-0.32mm/mmHg	<19mm/mmHg
Pericardial effusion	No	Minimal	Moderate or high
MRI			
RVEF	>54%	37-54%	<37%
SVI	>40ml/m^2	26-40ml/m^2	<26mg/m^2
Hemodynamics			
RAP	<8mmHg	8-14mmHg	>14mmHg
CI	>2.5L/min	2.0-2.5L/min	<2.0L/min
SvO_2	>65%	60-65%	<60%

HF – heart failure, WHO-FC – world health organization functional capacity, CPET – cardiopulmonary exercise test, BNP – brain natriuretic peptide, NT-proBNP – N-terminal BNP, RA – right ventricle, TAPSE – tricuspid annulus plane systolic excursion, sPAP – systolic pulmonary artery pressure, MRI – magnetic resonance imaging, RVEF – right ventricle ejection fraction, SVI – systolic volume index, RAP – right atrium pressure, CI – cardiac index, SvO_2 – saturation of the venous blood.

right heart catheterization is necessary to prove the diagnosis of PH. Mean pulmonary arterial pressure greater than 20 mmHg, with pulmonary wedge pressure lower than 15 mmHg and pulmonary vascular resistance greater or equal to 3 Wood units are the criteria for precapillary PH[3]. Selective segmental pulmonary angiography is also necessary when balloon angioplasty is planned for the treatment of CTEPH.

The risk stratification is important for the treatment escalation of CTEPH patients and it is based on the risk of mortality in three risk stratums, where low risk patients have 1-year mortality risk less than 5%, intermediate risk patients have 1-year mortality risk of 5-20% and the highest risk group have 1-year mortality risk greater than 20%.(3) The most usable parameters for risk assessment are presented in table 1.

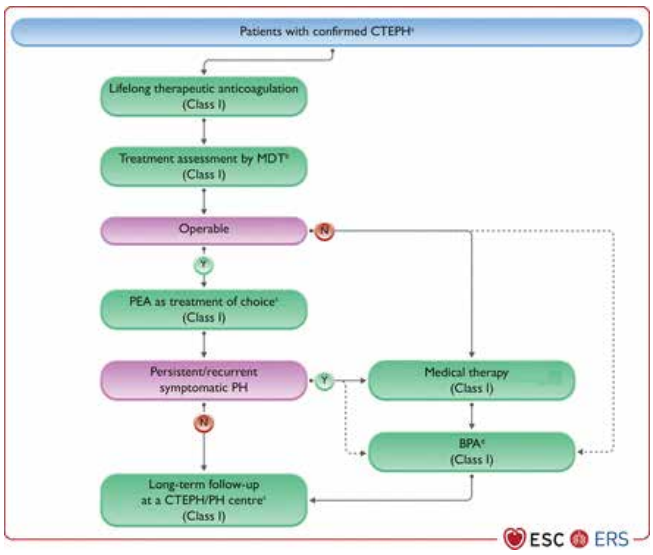

Figure 1. Management strategy in chronic thromboembolic pulmonary hypertension. Modified from ESC guideline 2023.[3]

Treatment

Treatment decision should be made by multidisciplinary team (MDT). If CTEPH patient is operable, PEA is class 1 recommendation according to the current guideline. If the patient is not operable, refuses operation or is susceptible to multi-modality approach, BPA and medical treatment should be considered. (3) (Figure 1). Today, medical therapy includes: riociguat (stimulator of soluble guanylate cyclase), treprostinil (prostacyclin vasodilator), macitentan and bosentan (endothelin receptor antagonists), sildenafil and tadalafil (5PDE inhibitors).

Balloon pulmonary angioplasty

Introduction (justification of catheter interventions in CTEPH and success of treatment)

Balloon-pulmonary-angioplasty (BPA) is one of the modalities of treatment of patients with CTEPH and is used in patients in whom pulmonary endarterectomy cannot be performed, or who refuse surgery. It can also be a part of a multi-modality approach where the patient has previously undergone surgery and/or drug treatment. The level of the pulmonary vascular tree that is most susceptible to this type of intervention is the segmental and subsegmental branches of the pulmonary arteries. In the last ten years, there has been an expansion in the

number of BPA procedures worldwide, and the latest recommendations for pulmonary hypertension from 2022 place BPA in class 1 recommendations for the treatment of CTEPH in patients in whom pulmonary endarterectomy is not possible.[3]

The efficacy of BPA has been demonstrated in CTEPH patients in terms of a 49%-66% reduction in peripheral vascular resistance (PVR), as well as an increase in six-minute walk distance (6MWD), right heart function, and quality of life.(ref) Efficacy is also directly proportional to the experience of the center dealing with BPA procedures, meaning that the number of performed procedures and hemodynamic improvements, together with the reduction of complications, follow a learning curve.[5] The results of recent research have shown that in CTEPH patients with PVR > 4 wood units, medical treatment before performing BPA reduces the frequency of complications.[6]

History of BPA in the world and in Serbia

The first case of BPA in CTEPH was published in 1988. The intervention was successfully performed by Dutch doctors (in Leiden) on a thirty-year-old patient.[7] In 2001, Feinstein et al published the first series of patients with CTEPH treated with BPA.[8] In 2003 and 2005, the first BPA interventions in two patients were performed in Serbia at the Military Medical Academy.[9] Years after, starting in 2012 Japanese, followed by the Poles and Norwegians in 2013, published their first series of cases. Today, these procedures are performed routinely in centers around the world. By May 2023, more than 100 BPA interventions have been performed at the Military Medical Academy.

Performing the procedure

The performance of BPA itself is a multi-phase procedure with a limited number of pulmonary arteries to be intervened in each procedure. This requires extensive preparation before each procedure that includes clear visualization and definition of lesion types, and then selection of lesions to be treated in one procedure. Diagnostic methods such as: MDCT-PA, V/Q scan and catheter-PA with precise hemodynamic parameters are used for this purpose. The patient should be presented to a multidisciplinary team that decides on the way to treat the patient and all the steps in order to prepare the patient as effectively as possible for the procedure itself. Careful selection of arteries and types of lesions to be treated, especially in the first few procedures, is very important in order to reduce the risk of complications and achieve the desired result. It is recommended that lighter lesions that have been shown to have a high degree of success (such as ring and web lesions) be performed during the first procedure. In the later stages, after the previous procedures have reduced the mean pressure in the pulmonary arteries (mPAP), more demanding lesions such as subtotal and total occlusions, possibly even tortuous lesions (only for very experienced centers, generally avoided) should be attempted. The strategy can be different, such as “segment by segment” treatment, or on the contrary, solving several different segments with lighter lesions per procedure, which is certainly decided by the interventional cardiologist team that performs the intervention. Previous reduction of mPAP, which is achieved by medical pretreatment and resolution of less complicated lesions, significantly reduces the probability of reperfusion edema of the lung segment, which occurs most often after the opening of total occlusion of a large segmental branch. The example of BPA procedure is depicted in Figure 1.

Standard introducer sheaths, catheters and workhorse wires, such as in standard PCI procedures are used for BPA as well. Namely, the most common approach is through the right or left femoral vein, with the use of a long introducer sheath of 6Fr or 7Fr, 0.035-inch wire (type and length may vary depending on the complexity of the procedure), then guide catheters, usually the JR, MP, AL (6Fr or 7Fr), but also other, standard workhorse 0.014-inch wire for passing the target lesion, or harder wires in case of total occlusions and balloons of variable diameter (2mm-8mm). During the intervention, constant monitoring of the patient is necessary, including: ECG, arterial pressure, O2 saturation. In most cases, BPA is completed by balloon inflation to achieve adequate reperfusion of a partially or completely occluded blood vessel of one or more lung segments. In some situations, however, stent implantation is allowed, in cases where the desired effect could not be achieved after balloon dilatation. In the case of stent implantation, it is not necessary to introduce antiplatelet therapy, but the patient continues with anticoagulant therapy, as in the case of only balloon dilatation.

The goal is to reduce mPAP as much as possible, ideally below 30 mmHg, and especially below 38 mmHg, be-

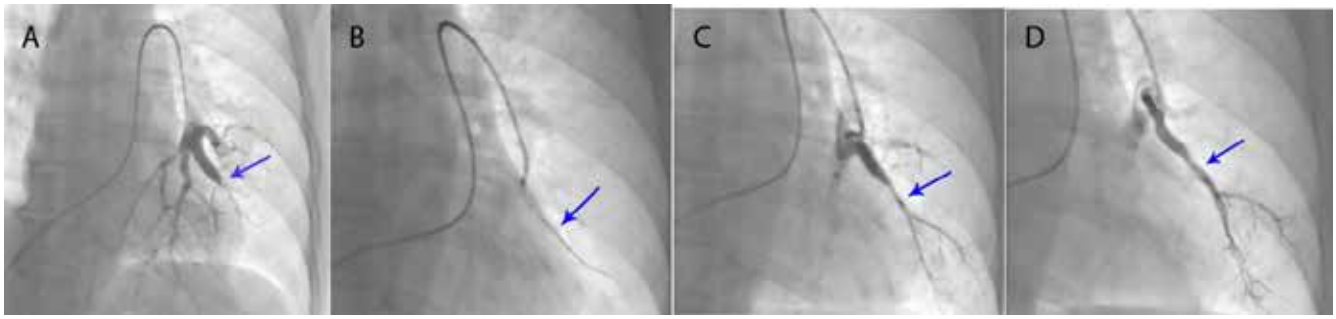

Figure 2. Total occlusion of the segmental left lower lobe artery (A); wire cross and balloon dilatation (B), opened segmental artery after BPA (C); final look after using bigger balloons (D). *The procedures were done in the Cath lab of the Military Medical Academy.*

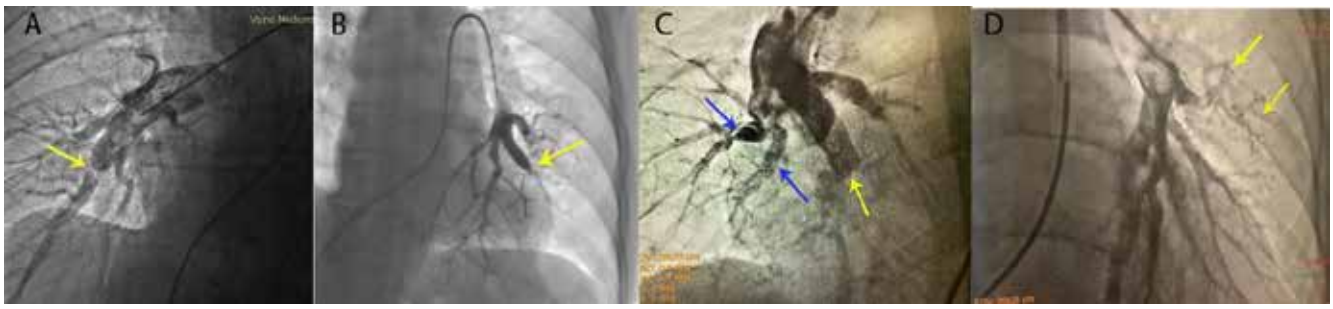

Figure 3. Types of lesions in CTEPH. Ring lesion (panel A);subtotal oclusion (panel B);Total oclusion (yellow arrow) and web and slit lesions (blue arrows) (panel C); tortuous lesion (panel D)

cause it has been shown that patients with mPAP ≥ 38mmhg have a significant reduction in life expectancy. Namely, multivariable analysis has shown that CTEPH patients with mPAP ≥ 38mmHg have long term mortality hazard ratio of 3.8, whereas it is 1.5 and 0.6 for thpse with mPAP below 38 mmHg and 30 mmHg, respectively.[10] The average number of procedures per patient that achieves optimal improvement of hemodynamic parameters is 4-6. They can be performed in time intervals from a few days to even a few months and depend on the general condition of the patient, the success of the previous procedures and the time needed to evaluate the effect of the drug/procedure.

Complications (types of complications and treatment)

Balloon pulmonary angioplasty, although very effective, carries some risk, and the frequency varies depending on the experience of the operator and the complexity of the lesions. This association of types and complexity of lesions determined on the basis of selective pulmonary angiography and success/complications performed in the same act was described in a paper published by Kawakami et al. in 2016.[11] Namely, Kawakami et al. defined 5 basic types of lesions at the level segmental and subsegmental branches. These lesions are mostly located before subsegmental branches such as the ring lesions, web and slit lesions, subtotal and total occlusions. The only lesion that is located on the subsegmental level is tortuous lesion (Figure 3 A-D). The tortuous type of lesion is definitely the most dangerous when it comes to complications during the BPA procedure (>40%), such as dissection or perforation and subsequent bleeding. These lesions are not only technically difficult for balloon dilatation, but it is a type of lesion that affects the distal parts of the subsegmental arteries, which can be very small in diameter (up to 0.5 mm) and are therefore more prone to injury. In contrast, the success rate of intervention in ring and web lesions is the highest reaching 90%-100%. Success in subtotal and total occlusions was 52.2% - 63.6%.

The most common complications are wire perforations, dissections or perforations due to balloon inflation. The consequence of these complications can be bleeding, which is most often manifested through hemoptysis. Another type of very common complication is edema of a segment or the entire lobe of the lung, which occurs as a result of reperfusion damage caused after the opening of a larger segmental branch that was previously totally occluded, and in conditions of elevated sPAP, usually > 40 mmhg. (Figure 3) Although these complications can end fatally, with adequate and timely treatment, they usually pass without major consequences. Perforations/ruptures with consequent bleeding can also heal spontaneously, by interrupting the procedure and giving oxygen through a mask. And yet, in most cases, intervention is necessary in the form of prolonged inflation of the balloon (about 5 min) with

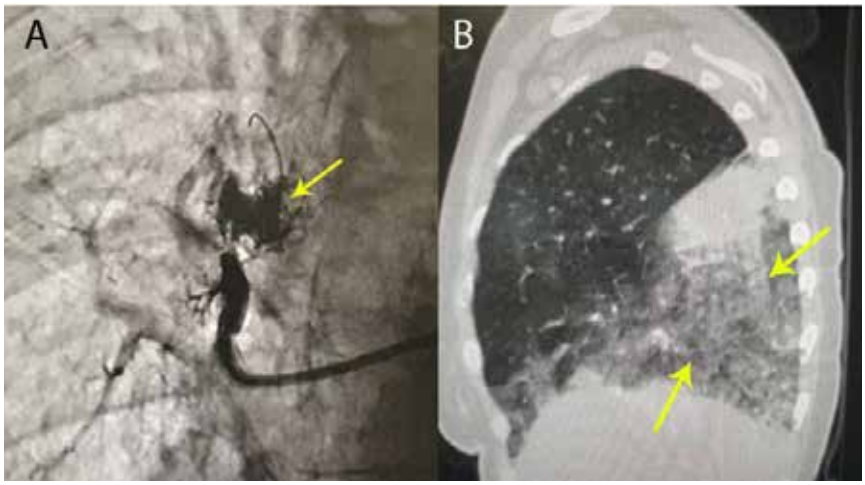

Figure 4. Examples of complications during the BPA procedures: Perforation od subsegmental branch and consequental bleeding with hemoptysis (A); reperfusion oedema of the left posterobasal segment of the lang (B).

complete occlusion of the bleeding blood vessel, administration of protamine sulfate to neutralize the effect of heparin and/or embolization of the blood vessel using a bioabsorbing gel or metal coil, or by implanting a covered stent.[12-14] In the case of localized reperfusion edema, the most important treatment measure is oxygen supplementation (most often in the form of substitution through a mask, administration of pressurized oxygen through a full-face mask or short-term intubation) along with other supportive measures. All patients with such complications must be treated and monitored in an intensive care unit

References

1. Valerio L, Mavromanoli AC, Barco S, et al. Chronic thromboembolic pulmonary hypertension and impairment after pulmonary embolism: the FOCUS study. Eur Heart J 2022;43:3387–3398.
2. Pengo V, Lensing AWA, Prins MH, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med 2004;350:2257-2264.
3. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2022;43:3618-3731.
4. Konstantinides S, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart Journal 2020;41:543-603.
5. Brenot P, Jaïs X, Taniguchi Y, et al. French experience of balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. Eur Respir J 2019;53:1802095 [https://doi.org/10.1183/13993003.02095-2018].
6. Jaïs X, Brenot P, Bouvaist H, et al. Balloon pulmonary angioplasty versus riociguat for the treatment of inoperable chronic thromboembolic pulmonary hypertension (RACE): a multicentre, phase 3, open-label, randomised controlled trial and ancillary follow-up study. Lancet Respir Med 2022. doi:10.1016/S2213-2600(22)00214-4.
7. Voorburg JA, Cats VM, Buis B, Bruschke AV. Balloon angioplasty in the treatment of pulmonary hypertension caused by pulmonary embolism. Chest 1988; 94:1249–1253.
8. Feinstein JA, Goldhaber SZ, Lock JE, Ferndandes SM, Landzberg MJ. Balloon pulmonary angioplasty for treatment of chronic thromboembolic pulmonary hypertension. Circulation 2001; 103:10–13.
9. Obradovic S, Rusovic S, Gligic B. Plućna tromboembolija kroz prikaze slučajeva. Belgrade, MST Gajić, November 2011.
10. Cannon JE, Su L, Kiely DG, Page K, et al. Dynamic risk stratification of patient long-term outcome after pulmonary endarterectomy. Results from the United Kingdom national cohort. Circulation 2016;133:1761–1771.
11. Kawakami T, Ogawa A, Miyaji K, et al. Novel angiographic classification of each vascular lesion in chronic thromboembolic pulmonary hypertension based on selective angiogram and results of balloon pulmonary angioplasty. Circulation: Cardiovascular Interventions 2016;9:e003318.
12. Ejiri K, Ogawa A, Matsubara H. Bail-out technique for pulmonary artery rupture with a covered stent in balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. JACC Cardiovasc Interv 2015; 8:752–753.
13. Inami T, Kataoka M, Shimura N, et al. Incidence, avoidance, and management of pulmonary artery injuries in percutaneous transluminal pulmonary angioplasty. Int J Cardiol 2015; 201: 35–37.
14. Hosokawa K, Abe K, Oi K, et al. Balloon pulmonary angioplasty-related complications and therapeutic strategy in patients with chronic thromboembolic pulmonary hypertension. Int J Cardiol 2015; 197: 224–226.

Sažetak

Hronična tromboembolijska plućna bolest

Slobodan Obradović,[1,2] Boris Džudović[2,3]

[1]Klinika za Kardiologiju, Vojnomedicinska Akademija, Beograd, [2]Medicinski Fakultet, Univerzitet Odbrane, Beograd, [3]Klinika za Urgentnu Medicinu, Vojnomedicinska Akademija, Beograd

Hronična tomboembolijska plućna bolest (HTEPB) sa ili bez plućne hipertenzije (HTEPH) je retka, često progresivna komplikacija plućnog embolizma (PE). Beleži se značajan napredak u dijagnostici I tretmanu ovih bolesnika u poslednjim godinama.

Cilj ovog revijalnog rada je da prikažu savremeno znanje i preporuke za tretman HTEPH. Prikazana je epidemiologija, patofiziologija, dijagnostika, klasifikacija rizika, I različite metode za lečenje: lekovima, balon plućnim angioplastikama (BPA), I plućna end-arterektomija (PEA). Jasno je da je multimodalni pristup lečenja najbolji za većinu bolesnika sa HTEPH I ovakav stav je iznesen I u poslednjim preporukama za PH koje je objavilo Evropsko Udruženje Kardiologa 2022 godine. U poslednjim preporukama za tretman PE, takođe je preporučeno da se obrati pažnja na mogući razvitak HTEPH kod bolesnika koji imaju povišen rizik za razvoj ove komplikacije i/ili imaju tegobe koje bi mogle da ukažu na razvoj ove komplikacije u mesecima nakon akutne PE. Obe preporuke podižu svesnost o postanju ove retke komplikacije I poboljšavaju tretman ovih bolesnika.

Ključne reči: *hronična tromboembolijska plućna hipertenzija, balon angioplastika plućnih arterija, plućna endarterektomija*