CASE SERIES

PULMONARY ENDARTERECTOMY FOR CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

Tahir Iqbal[1], Azam Jan[1], Naseer Ahmed[1], Amir Muhammad[1], Sayed Mumtaz Shah[1], Sajid Khan[1], Imran Tahir[1], Husain Shah[1], Nabil Iftikhar[1], Jamil-ur-Rehman[1]

[1]Rehman Medical Institute, Hayatabad, Peshawar, Pakistan

Chronic thromboembolic pulmonary hypertension (CTEPH) is a serious complication of unresolved pulmonary embolism. CTEPH is a potentially curable disease and the treatment of choice is pulmonary endarterectomy (PEA) with complete clearance of pulmonary arteries being the principle of surgery. The surgery is performed under circulatory arrest during cardiopulmonary bypass circulation.

We report 3 cases of CTEPH in 2018-2019 at department of cardiothoracic surgery, Rehman Medical Institute, Peshawar. They were detected by echocardiography (TTE) and confirmed by CTPA. Pulmonary endarterectomy was performed with good peri-operative outcome and significant improvement of hemodynamics.

Keywords: pulmonary thromboembolism, pulmonary hypertension, pulmonary endarterectomy, right heart failure

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is defined as precapillary pulmonary hypertension (PH) confirmed by right heart catheterization (mPAP $\geq$25 mm Hg and PAWP $\leq$15 mm Hg at rest) and mismatch on ventilation/perfusion scintigraphy ("V/Q single-photon emission computed tomography [SPECT]") with at least one large perfusion defect in one segment or in two sub-segments, or evidence of pulmonary vascular lesions on computed tomography (CT) and/or magnetic resonance imaging (MRI) or pulmonary angiography (PA). These findings should be obtained after 3 months of effective anticoagulation.[1] CTEPH is the most common subset of precapillary pulmonary hypertension. It is classified as group 4 in the present clinical classification of pulmonary hypertension by "European Society of Cardiology (ESC)" / "European Respiratory Society (ERS)" guidelines.[2] CTEPH is a late and relatively rare complication of acute or multiple episodes of pulmonary embolism. The incidence of CTEPH is about 3-5 individuals per million per year.[3] In a recently data, the estimated cumulative incidence of CTEPH was found to be 1.0% after 06 months, 3.1% after 01 year, and 3.8% after 02 year; with an overall incidence of approximately 3% after pulmonary embolism.[4]

CTEPH is a progressive pulmonary vascular disorder with a multifactorial and complex pathophysiology. All causes of venous thrombo-embolism (VTE) and pulmonary embolism (PE) are potential risk factors for CTEPH, including hypercoagulability (of any etiology), venous injury, venous stasis, thrombophilia or pro-thrombotic factors, non-O type ABO blood group, splenectomy and hereditary spherocytosis.[2,3] CTEPH is caused by obstruction and vascular remodeling of pulmonary arteries. After an acute event of PE, unresolved thrombus becomes organization due to fibrosis. Together with fibro-intimal hyperplasia and vascular remodeling, this leads to obstruction of pulmonary blood flow. This causes elevated pulmonary artery pressures, elevated pulmonary vascular resistance (PVR) and progressive right heart failure. Recent studies showed that CTEPH involves persistent organized thrombi in proximal (main, lobar and segmental pulmonary arteries) as well as distal small vessels. In this prospect, the role of small vessel arteriopathy is very important regarding progression of disease, treatment options and prognosis.[5] The untreated CTEPH has a poor outcome and the main prognostic factors are the degree of PVR and right heart failure.[6] The estimated 5-year survival is around 30% for patients with mPAP >40 mmHg and 10% for patient with an mPAP >50 mmHg.[7]

Like Pulmonary embolism, the diagnosis of CTEPH is usually based on high index of suspicion. If there is evidence of PAH on transthoracic echocardiography in a patient (after an episode of PE or history of recurrent PE), it is recommended to evaluate the patient for confirmation of CTEPH as well assessment for surgical treatment.[1,2] A number of radiological modalities are used for diagnosis, its

extent and assessment for surgery. For suspected CTEPH, the (V/Q scintigraphy SPECT) is the initial modality to differentiate PAH of CTEPH from other causes of PAH. V/Q scan has a 96-97% sensitivity and 90-95% specificity.[2] Today CT pulmonary angiography (CTPA) and magnetic pulmonary angiography (MRA) are widely and together with V/Q SPECT scan, these radiological modalities accurately detect and evaluate the disease.[1,7] Finally, pulmonary angiography (PA) is the gold standard imaging modality for the location and extent of the disease, thus suitability for surgery.[8] After a confirm diagnosis of CTEPH, right heart catheterization is the next step for assessment towards pulmonary endarterectomy (PEA). As pre- and post-operative PVR are long term predictors of prognosis therefore, pressure measurements in RA, RV and the PA pressures (systolic, diastolic, mPAP, PAWP), determination of cardiac output volume and oxygen saturation (PA and vena cava) and calculation of PVR is important.[1]

Once CTEPH has been diagnosed, the current recommendation is to assess every CTEPH patient for surgery. The recommended treatment of choice is pulmonary endarterectomy (PEA) if patient is considered operable.[1,2] The decision for operability is largely subjective and based on experience due to lack of a standard international criteria. Even if a patient is labelled as inoperable, a second CTEPH center opinion should be taken for PEA consideration.[6,8] Age, general health condition, comorbidity, underlying severe parenchymal lung disease, degree of right heart failure, high PVR and technical feasibility of the thrombus (location) are main decision-making factors.[3,7]

Pulmonary endarterectomy has four basic principles: (1) the endarterectomy must be bilateral and performed through a median sternotomy; (2) perfect visualization, so cardiopulmonary bypass and periods of deep hypothermic circulatory arrest (usually limited to 15-20) are obligatory; (3) correct dissection plane; and (4) complete and meticulous endarterectomy.[2,7]

Although PEA is technically demanding, it has good outcome and provides a number of clinical benefits like improvements in functional class, reduced PAH and PVR, restoration of right ventricular hemodynamics, quality of life and survival benefit.[9] Postoperative complications include acute reperfusion lung Injury, noncardiac pulmonary edema, and cognitive impairment due to DHCA.[8]

Persistent PH is the presence of hemodynamic signs of PH remaining after PEA. Up-to one third of patients may have persistent PH despite apparently successful PEA surgery and it is a significant cause of postoperative morbidity and mortality.[7]

Persistent PH may be due to failure or incomplete removal of thrombi and/or presence of concomitant small-vessel arteriopathy in patients with operable proximal disease. Preoperative PVR >1200 dyn•s•cm-5, poor right ventricular function and more distal disease is associated with increased risk of postoperative residual PH and these patients have poor post-surgical outcome.[6,8] Treatment of these patients is challenging as they have right heart failure, low cardiac output and may experience difficulty from weaning off CPB. Postoperatively the risk of reperfusion lung injury is also high in this proportion of patients. In this prospect, ECMO is mandatory, veno-arterial ECMO for hemodynamic compromise and v eno-venous ECMO for reperfusion lung injury alone. Recurrent PH after PEA is the development of PH in patients who had previous successful PEA clearance and confirmed normal hemodynamics after surgery. Although recurrent PH is less common than persistent PH, its prevalence is generally underestimated as most of the studies have followed 5 years. A longer hemodynamic follow up is required for recurrent PH monitoring. A second PEA can be considered for patients with surgically accessible recurrent PH, or for persistent PH after PEA who have had an incomplete endarterectomy.[6-8]

Interventional balloon pulmonary angioplasty (BPA) is another option for technically inoperable patients or having an unfavorable risk vs. benefit ratio for PEA. In some experienced centers, BPA is also considered for persistent or recurrent PH after PEA (selected cases). In a study, survival after BPA was 85% over a mean follow up period of 51 months. However persistent PH up-to 23% is also reported.[7]

Life-long anticoagulation with warfarin titrated to target INR of 2.0 to 3.0 is recommended for all patients with CTEPH.[1,10] Medical therapy is used in inoperable cases, persistent/recurrent PH after PEA and bridging therapy prior to PEA.[7] Riociguat (the soluble guanylate cyclase stimulator) is the only pharmacological therapy, approved for treatment of inoperable CTEPH and persistent or recurrent CTEPH following PEA.[1,2] Other medical therapies which are commonly used, but not approved in CTEPH treatment include endothelin receptor antagonists, phosphodiesterase type 5 inhibitors and prostacyclin pathways targeting therapies. Medical therapies as a bridge to PEA or BPA is based on some studies that medical therapies before PEA can reduce PVR, which may potentially improve the post-surgical outcome in severe CTEPH. Dihydropyridine calcium channel blockers (amlodipine and nifedipine) for pulmonary vasodilator properties, and diuretics (furosemide

and hydrochlorothiazide) are also used for volume overload reduction.[7,10]

CASE 1

A 35-years old male, shopkeeper by profession, presented with chronic history of worsening shortness of breath (NYHA class III, IV) for the last 20-months. He had a past history of acute pulmonary embolism after an event of deep venous thrombosis (post hip joint surgery for traumatic hip joint fracture) about 23-months back. He was diagnosed as severe pulmonary artery hypertension by his family physician. He was using oral anticoagulants and medical treatment of PAH. Upon presentation to tertiary care cardiothoracic unit, he was having dyspnea class III/IV and tachypnea. His physical examination revealed blood pressure 105/65 mmHg, pulse rate 110 beats/min, respiratory rate 27 breaths/min, SO2 90% at room air, jugular venous distension, pitting edema grade II in both lower extremities. Blood biochemistry and CBC was normal. Blood group was B-negative and INR was 1.7. Arterial blood gas analysis revealed PH 7.47, PCO2 27 mmHg, PO2 67 mmHg and O2 saturation 89%. Thrombophilia screening was non-significant. Electrocardiogram showed sinus tachycardia, Right axis deviation and right ventricular hypertrophy. Chest x-ray showed enlargement of right ventricle and both main pulmonary arteries. Initial transthoracic echocardiography was performed that showed severe pulmonary hypertension (RVSP 100 mmHg), RV dysfunction with dilated and overload right heart chambers (RV 55mm), severe tricuspid's regurgitation (TR +3) and suspected large thrombus in main pulmonary artery (MPA). CT pulmonary angiography (CTPA) was done for the evaluation and extension of pulmonary artery thrombus (Figure 1). CTPA showed an extensive chronic pulmonary embolism involving MPA, RPA and LPA with some of their lobar and segmental branches. Chronic thrombo-embolic pulmonary hypertension (CTEPAH) was diagnosed.

CASE 2

A 27-years old lady who was a house wife, presented with progressively worsening shortness of breath (NYHA class IV) for the last 18 months. She had history of acute pulmonary embolism 18-months ago after an episode of deep venous thrombosis of right lower limb (following cholecystectomy and re-exploration of abdomen for post collection drainage). She was treated with anticoagulation therapy, but her compliance of taking medication was not good. Sub-therapeutic anticoagulation and unresolved PE was complicated to severe PAH. Upon physical examination she was tachypneic with respiratory rate 28 breaths /min, pulse rate 115 beats /min and blood pressure 95/55 mmHg, distended jugular veins, mild-moderate hepatomegaly. Normal Blood biochemistry and CBC showed hemoglobin of 17gm/dl. INR was 2.1 and blood group O +ve. Arterial blood gas analysis revealed PH 7.48, PCO2 26 mmHg, PO2 66 mmHg and O2 saturation 88%. Thrombophilia screening was non-significant. Electrocardiogram showed sinus tachycardia, Right axis deviation and right ventricular hypertrophy. Chest x-ray showed enlarged right ventricle and both main pulmonary arteries. Trans thoracic echocardiography showed severe PAH (RVSP 90 mmHg), Dilated RV (RV 46mm) and overload right chambers with RV dysfunction and severe TR (+3). CTPA was performed that showed chronic pulmonary embolism involving MPA, LPA and almost complete occlusion of RPA with involvement of segmental branches. Chronic thrombo-embolic pulmonary hypertension (CTEPAH) was diagnosed.

CASE 3

A 22-years old male, presented with progressive chronic history (2-years) of shortness of breath (NYHA class IV) and hemoptysis. He had a past history of un-provoked pulmonary embolism for which sub-therapeutic treatment was given. Due to high index of suspicion, he was admitted in cardiothoracic unit for stabilization and workup of CTEPH. At admission, his physical examination showed dyspnea class IV and tachypnea with respiratory rate 32 breaths/min, blood pressure 98/58 mmHg, pulse rate 115 beats/min, room air saturation 90%, jugular venous distension, mild hepatomegaly. Blood biochemistry and CBC was normal except hemoglobin 10gm/dl (due to hemoptysis). Blood group A+ve. INR was 1.9, thrombophilia screening was found non-significant. Arterial blood gas analysis revealed PH 7.46, PCO2 30 mmHg, PO2 70 mmHg and O2 saturation 90%. Electrocardiogram showed sinus tachycardia, right axis deviation and right ventricular hypertrophy. Chest x-ray showed right ventricle and bilateral PAs enlargement. Transthoracic echocardiography showed severe pulmonary artery hypertension (RVSP 115 mmHg), RV dysfunction with dilated and overload right heart chambers (RV 52mm), severe tricuspid's regurgitation (TR +3). CT pulmonary angiography (CTPA) showed saddle embolism in pulmonary trunk extending into MPA and occluding LPA and its lobar branches with resultant PAH and RV strain. PE in BL segmental branches. Chronic thrombo-embolic pulmonary hypertension (CTEPAH) was diagnosed.

Each case was discussed in a multi-disciplinary team including cardiac surgeons, cardiologist, cardiac anesthetist, pulmonologist and intensivist for surgical and subsequent post-surgical management. Although indicated, right heart catheterization was not performed as clear CTPA evidence and patient hemodynamics. Main pulmonary artery was not accessible for pressure measurements in right heart Cath and there was no severe distal small vessel disease. The outcome and prognosis were discussed with patient and family. After preparation and informed written consent, we proceeded for PEA. PEA was performed through median sternotomy, cardio-pulmonary bypass established via aortic & bi-caval cannulation with systemic heparinization (ACT >500sec). Deep hypothermic circulatory arrest (DHCA) was not adopted, rather we preferred a lower temperature of 22-25C with plan of institution DHCA on demand (if clear surgical field is not achievable or need of distal segmental branches endarterectomy). After aortic cross clamp and antegrade cardioplegia, MPA was opened through vertical incision (Figure 2).

Chronic Thrombus from MPA was extracted followed by endarterectomy and extension towards LPA and its lobar branches. RPA endarterectomy was performed on a separate incision over RPA respectively. Total CPB time was 120min, 70min and 74 min and aortic cross clamp time was 75min, 34min and 36min respectively. Un-eventful weaned-off CPB. Postoperative hemodynamic recovery was good and recovery was smooth. 2 cases were extubated after 20-hours and 1 case within 8-hours. Total ICU stay (mean 04days, range 03-05days) and hospital stay (mean 10days, range 08-13days).

In subsequent post-operative and follow-up period, all patients showed significant symptomatic improvement (NYHA class, 6 min walk distance, and decrease in RVSP and room air oxygen saturation). They were discharged to home with anticoagulation (VKA) and medical treatment of PAH. Postoperative Echocardiography showed significant improvements in right ventricular function, decrease PAH and symptoms (Table 1).
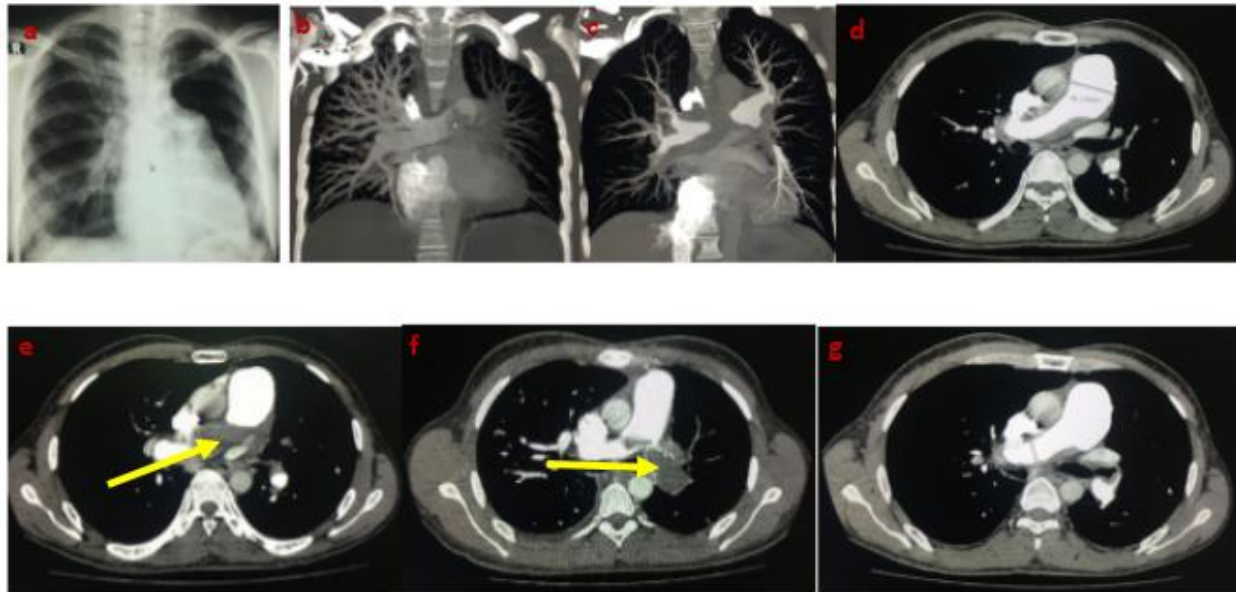

Figure 1: a: Chest X-ray showing prominent pulmonary vasculature, b & c: thrombus in PA sagittal view, d-g: thrombus in PA on transverse section. Yellow arrow on "e" illustrating large thrombus in right pulmonary artery, yellow arrow in "f" showing large thrombus in left pulmonary artery

Table-1: Basic demographic characteristics and pre, intra and post-operative parameters

Pre-operative detail			
	Case 1	Case 2	Case 3
Gender	Male	Female	Male
Age (years)	35	27	21
Weight (kg)	54kg	56kg	65kg
Height (cm)	168cm	156cm	164cm
Body mass index (kg/m^2)	19.1	20.6	24.2
Thrombophilia screening	Negative	Negative	Negative

Blood group	B -ve	O +ve	A +ve			
International Normalized Ratio (INR)	1.7	2.1	1.9			
Intra-operative detail						
Cardiopulmonary Bypass Time (min)	120 min	70 min	74/min			
Aorta Cross Clamp time (min)	75 min	34 min	36/min			
Ventilation (hours)	08 hours	20 hours	20 hours			
Intensive Care Unit stay (days)	03 days	4 days	5 days			
Hospital stay (days)	08 days	13 days	9 days			
Comparison before and after Pulmonary Endarterectomy (PEA)						
	Before PEA			**After 3 months of PEA**		
	Case 1	**Case 2**	**Case 3**	**Case 1**	**Case 2**	**Case 3**
NYHA class	III/IV	IV	IV	II	III	II
Room air saturation	90%	88%	89%	94%	91%	92%
Respiratory rate	27/min	28/min	32/min	21/min	23/min	24/min
Pulse rate	110/min	115	115/min	102/min	100/min	98/min
Blood pressure	105/65mmHg	95/55mmHg	98/58mmHg	108/65mmHg	105/60mmHg	110/65mmHg
6MWD	369 meters	340 meters	355 meters	460 meters	405 meters	418 meters
RV	55mm	46mm	52mm	46mm	40mm	43mm
RVSP	100 mmHg	90 mmHg	115 mmHg	78mmHg	70mmHg	80mmHg
TR	+3	+3	+3	+2	+2	+2

NYH = New York Heart Association, 6MWD = six minute walk distance, RV = right ventricular, RVSP = right ventricular systolic pressure, TR = tricuspid regurgitation
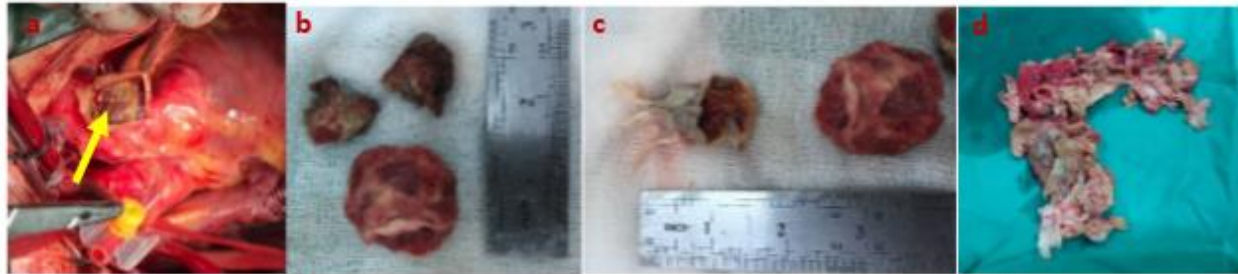
Figure 2: a: showing open main pulmonary artery with thrombus inside, b & c: large chunks of organized thrombus larger than an inch removed from PA, d: complete thrombus evacuated from pulmonary artery

DISCUSSION

Recommended treatment for patients with CTEPH, if considered operable by an experienced multidisciplinary CTEPH team, including at least one experienced surgeon.[1] For operability the disease must be surgically accessible with a proportional PVR and absence of extensive small vessel vasculopathy. However not all patients with CTEPH are suitable for PEA, rather 10-50% of patients are inoperable. In European CTEPH registry, up to 37% diagnosed CTEPH patients were found inoperable, having extensive distal disease (48%), high proportional PVR (10%) and comorbidity (13%) were main reasons for being in-operable.[6,7]

Pulmonary endarterectomy provides a number of clinical benefits like improvements in quality of life, functional class of NYHA and Bruce protocol, reduction in PVR and PAH, restoration of right ventricular hemodynamics and reverse remodeling and survival benefit.[9] From the UCSD (University of California, San Diego) and international CTEPH databases, improvements from PVR (700–800 to 250 dyn•s•cm-5, a fall of ~65%.), mPAP (from 46 to 26 mmHg) and median 6-min walking distance (from 362 to 459 m) has been noted.[6] Today, in-hospital mortality is below 5% in high volume centers

and its improving over time.[7] In a retrospective case series from UCSD (The most experienced center for PEA), a reduction of in-hospital mortality from 5.2% to 2.2% was noted in consecutive 1000 and 500 cases respectively. In the prospective European CTEPH registry (including centers of high volume with extensive experience and some low volume with less experience centers), over-all in-hospital mortality was 4.7%.[8] A number of studies has been conducted regarding survival benefit and long-term outcome of PEA. According to European international CTEPH prospective registry the post PEA estimated survival at 1, 2, and 3 years was 93%, 91% and 89% respectively.[6] The Papworth group has reported a 5-year survival of 92.5%.[8] A prospective study reported cumulative survival of 84% at 5 years and 72% at 10 years.[7]

Outcome of PEA depends upon several factors like, experience of CTEPH team, chronicity and distribution of the disease, pre-operative PVR, patient's NYHA functional class, comorbidities and residual PH after PEA.[1,6] Higher pre-operative PVR is associated with poor outcome, and operative mortality can be 5-10-fold higher in patients with PVR >1200 dyn•s•cm-5. Data from the international CTEPH registry showed

approximately 3 times greater in-hospital mortality between pre-operative PVR >1200 vs. 400–800 dyn•s•cm-5. However, it is important to note that patients with a high PVR gain most from PEA because of greatest relative improvement and potential prognostic benefit. For this reason, high PVR should not be considered as an absolute contraindication for PEA and the current recommendation is to obtain a second opinion from another CTEPH center if a patient has been considered inoperable by one CTEPH center.[3,6,8]

CONCLUSION

Pulmonary endarterectomy is the only definitive therapy with proven beneficial effects on survival and hemodynamic improvement of CTEPH. For this reason, every CTEPH patient must be evaluated and operated at experienced center by an expert surgical team, using recommended diagnostic and therapeutic protocol. Because of the complexity of CTEPH and PEA, a multi-disciplinary team work including radiological, medical, surgical, and anesthetic consultation is mandatory.

AUTHORS' CONTRIBUTION

TI: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. AJ, NA, AM, SMS, SK, IT, HS, NI, J: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

Conflict of interest: Authors declared no conflict of interest.

Address for Correspondence:
Dr. Naseer Ahmed, Department of Medicine, Rehman Medical Institute, Hayatabad, Peshawar, Pakistan
Email: dr.naseer99@gmail.com

REFERENCES

1. Wilkens H, Konstantinides S, Lang IM, Bunck AC, Gerges M, Gerhardt F, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): Updated Recommendations from the Cologne Consensus Conference 2018. Int J Cardiol. 2018;272:69–78.
2. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2016;37(1):67-119.
3. Dartevelle P, Fadel E, Mussot S, Chapelier A, Hervé P, de Perrot M, et al. Chronic thromboembolic pulmonary hypertension. Eur Respir J. 2004;23(4):637-48.
4. Pengo V, Lensing AWA, Prins MH, Marchiori A, Davidson BL, Tiozzo F, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med. 2004;350(22):2257-64.
5. Lang IM, Dorfmüller P, Noordegraaf AV. The pathobiology of chronic thromboembolic pulmonary hypertension. Ann Am Thorac Soc. 2016;13:S215-21.
6. Jenkins D, Madani M, Fadel E, D'Armini AM, Mayer E. Pulmonary endarterectomy in the management of chronic thromboembolic pulmonary hypertension. Eur Respir Rev. 2017;26(143):160111.
7. Madani M, Ogo T, Simonneau G. The changing landscape of chronic thromboembolic pulmonary hypertension management. Eur Respir Rev. 2017;26(146):170105.
8. Jenkins D. Pulmonary endarterectomy: The potentially curative treatment for patients with chronic thromboembolic pulmonary hypertension. Eur Respir Rev. 2015;24(136):263-71.
9. Nižňanský M, Ambrož D, Prskavec T, Jansa P, Lindner J. Surgical treatment of chronic thromboembolic pulmonary hypertension. Vnitr Lek. 2019;65(5):353-8.
10. Banks DA, Auger WR, Madani MM. Pulmonary Thromboendarterectomy for Chronic Thromboembolic Pulmonary Hypertension. Kaplan's Essentials Card Anesth Card Surg. 2018;(5):504-33.