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A 35-year old man with dyspnea on exertion, history of acute pulmonary embolism and ischaemic stroke

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Abstract

We present a case of a 35-year old man with a history of an acute pulmonary embolism and ischaemic stroke, who after several weeks of adequate antithrombotic treatment experienced functional deterioration with severe dyspnea and haemoptysis. Detailed evaluation reveled chronic thromboembolic pulmonary hypertension, deep vein thrombosis of his right thigh and patent foramen ovale. No laboratory signs of a hypercoagulable conditions were found. After through assessment the patient was referred for pulmonary endarterectomy and patent foramen ovale closure. Both procedures were performed successfully with the significant improvement in patient's clinical status. Patient remained clinically stable with no signs of right ventricle dysfunction in the follow-up. This article provides details regarding etiopathogenesis, clinical features and diagnostic evaluation of chronic thromboembolic pulmonary hypertension related to an acute pulmonary embolism. It covers the latest guidelines for screening and therapy as well as information regarding innovations in health care, and social care. JRCD 2012; 1: 24–29

Key words: Pulmonary embolism; Chronic thromboembolic pulmonary hypertension; Pulmonary endarterectomy

Case presentation

A 35-year old man was admitted to our hospital because of fatigue and dyspnea on exertion. He felt shortness of breath after walking approximately 100m on flat or after climbing half flight of stairs.

He had a history of idiopathic acute pulmonary embolism (PE) with intermediate risk of in-hospital death and deep venous thrombosis (DVT) of his right leg 4 months before current admission. At that time he also suffered from ischaemic stroke with aphasia and central paresis of right facial nerve. He was treated with subcutaneus enoxaparin (1 mg/kg, twice daily) for 5 days in the acute phase of pulmonary embolism and oral anticoagulant subsequently with target INR level between 2.0 and 3.0. After a few weeks of improvement he started to complain of a new onset of shortness of breath and fatigue. One month before current admission he had an episode of haemoptysis.

Physical examination revealed a well-developed man in significant distress with breathlessness when talking. He was considered to be in New York Heart Association (NYHA) functional class III. His vital signs were as follows: body temperature of 36.6 °C, respiratory rate (RR) of 22 breath per minute, heart rate (HR) regular of 95 beats per minute (bpm), blood pressure (BP) of 120/80 mm Hg, oxygen saturation on room air of 88%. Heart auscultation revealed increased second heart sound accentuation and a systolic murmur best audible over the apex. Liver was slightly enlarged, palpable 1 cm below right costal margin in midclavicular line. Hepatojugular reflux was positive. Pitting oedema of the right ankle was present. Blood tests revealed elevated NT-proBNP level of 1456 pg/ml and troponin T elevation up to 0.5 ng/ml. Total bilirubin of 1.7 mg/dl was mildly elevated. Other biochemical parameters were within normal ranges. Coagulation studies revealed INR of 2.4 and prolonged activated partial thromboplastin time (APTT) of 42.4s. Capillary blood gas analysis disclosed alkalosis (pH – 7.48), hypoxemia (pO_2 – 63 mm Hg) and hypocapnia (pCO_2 – 33 mm Hg). Complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), urinalysis were all within normal limits. Lupus anticoagulant and antyfospholipid antibodies were negative.

Resting ECG (Figure 1) displayed: sinus rhythm of 97 bpm, right axis deviation, incomplete right bundle branch block (RBBB), negative T waves in precordial leads of V1 to V4.

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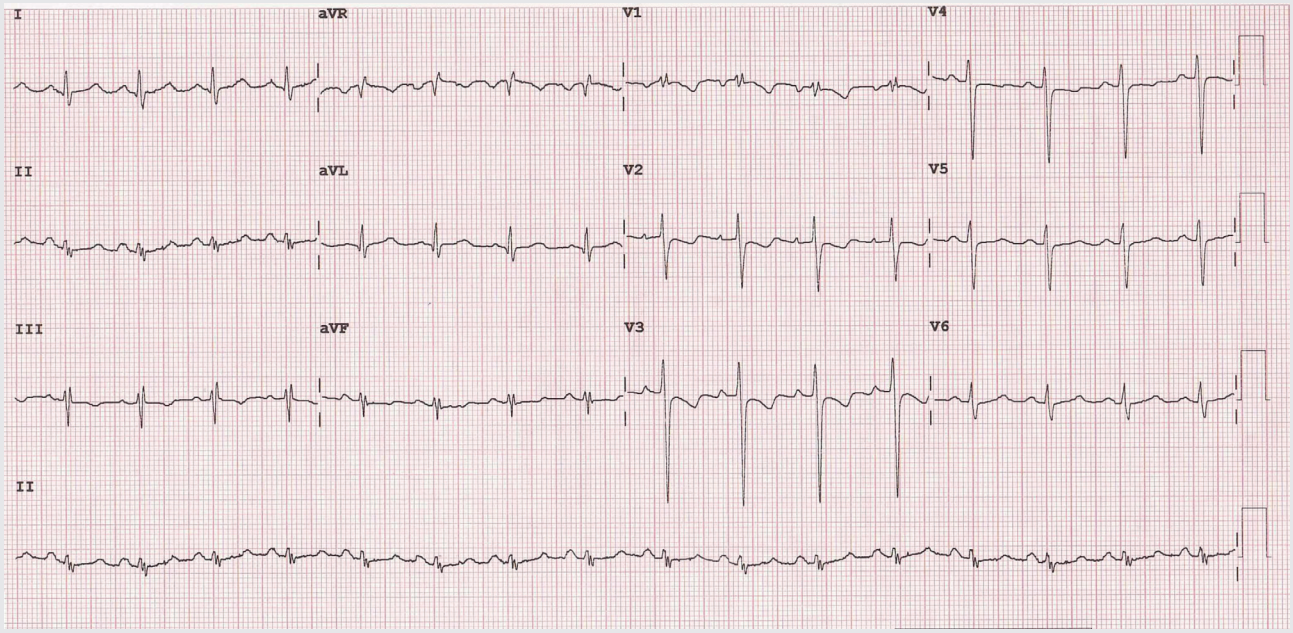

Figure 1. Resting ECG: sinus rhythm 97 bpm, right axis deviation, incomplete RBBB, negative T waves in precordial leads V1-V4

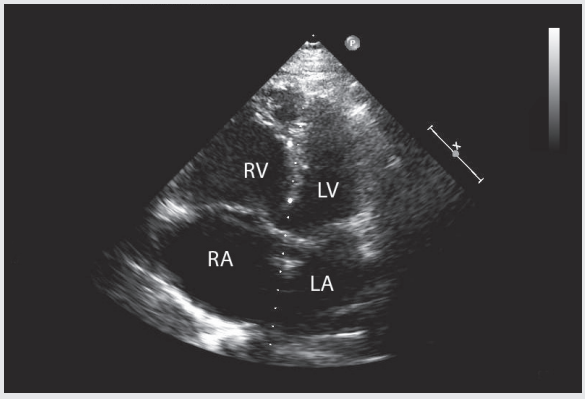

Figure 2. Transthoracic cardiac echo study: enlargement of the right ventricle (RV) and the right atrium (RA), compression on the left ventricle (LV) and left atrium (LA) by RV and RA

Transthoracic cardiac echo study (Figure 2) revealed enlarged right ventricle diameter (RVd – 27 mm) and right atrium area (RAA – 35 cm^2) with significant tricuspid insufficiency and signs of severe pulmonary hypertension (tricuspid valve systolic gradient- TVPG of 70 mm Hg, acceleration time – AcT of 63 ms, pulmonary artery valve insufficiency gradient – PAVI of 21/14 mm Hg, tricuspid annulus plane systolic excursion – TAPSE of 16 mm). Left ventricle and atrium showed compression by enlarged right ventricle and right atrium. A small pericardial effusion was present. Left ventricle ejection fraction was intact (LVEF – 80%).

Impaired exercise capcity was confirmed by 6-minute walking test (6MWT), with a distance walked of only 411 m and detection of significant oxygen desaturation from 93% to 88%. Tachycardia was present during the test (HR before test – 100 bpm and after – 127 bpm).

Transoesophageal echocardiography displayed persistent foramen ovale (PFO) with a small right to left shunt not haemodynamically significant. Venous ultrasound compression test showed organized thrombus narrowing right popliteal vein by 40%.

128-slice spiral computed tomography of the chest (Figure 3) revealed chronic thromboembolic material located in the distal part of the right pulmonary artery (PA) spreading into inferior lobe artery, medial lobe artery and segmental arteries 4, 5, 9, 10. Chronic thromboembolic material was observed in the inferior lobe artery and in segmental arteries 8, 9 and 10 on the left side also. Mosaic perfusion in pulmonary parenchyma was present in both lungs.

Pulmonary angiography revealed significant narrowing of proximal pulmonary arteries on both side (Figure 4). In the right heart catheterization (RHC) high precapillary pulmonary hypertension was observed with mean pulmonary artery pressure (mPAP) elevation up to 54 mm Hg, pulmonary vascular resistance (PVR) of 817 dyne/s/cm^{-5}, right atrial pressure (RAP) of 12 mm Hg and pulmonary capillary wedge pressure (PCWP) of 13 mm Hg together with decreased cardiac index CI of 2.25 l/min/m^2 and decreased mixed venous saturation of 58%.

Diagnosis: Chronic thromboembolic pulmonary hypertension (CTEPH).

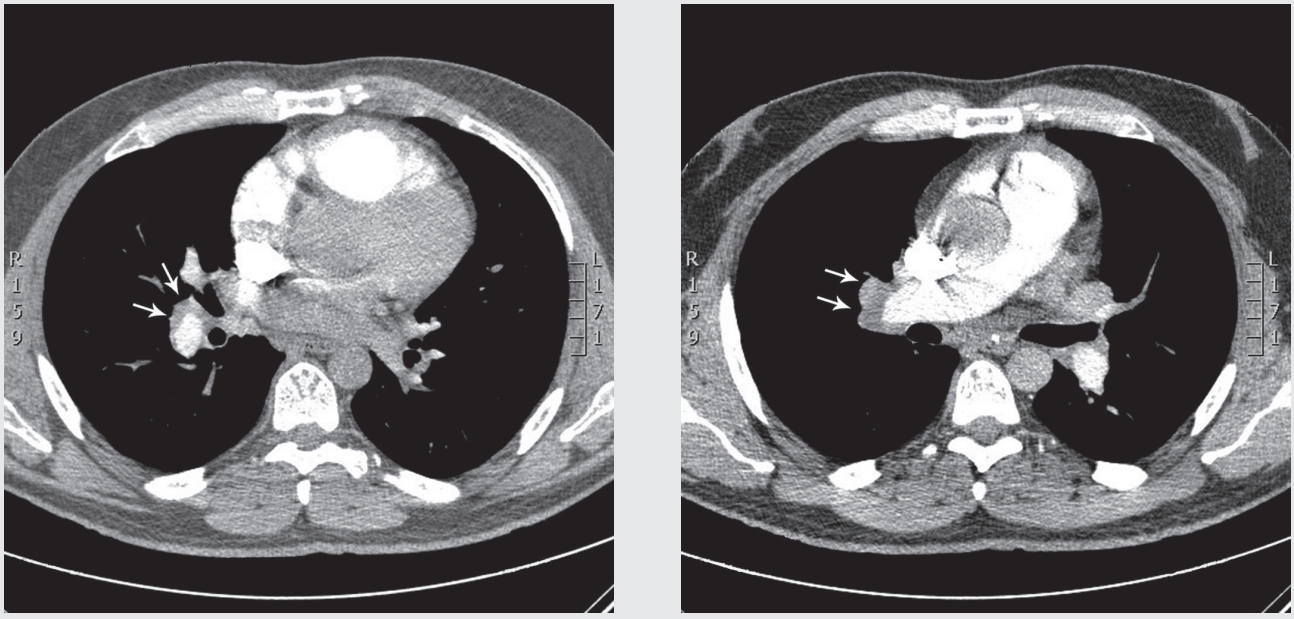

Figure 3. 128-slice spiral computed tomography of the chest: chronic thromboembolic parietal material (arrows) starting in distal part of the right pulmonary artery and spreading into inferior lobe artery. Lack of perfusion in the inferior lobe segmental pulmonary arteries on the left side

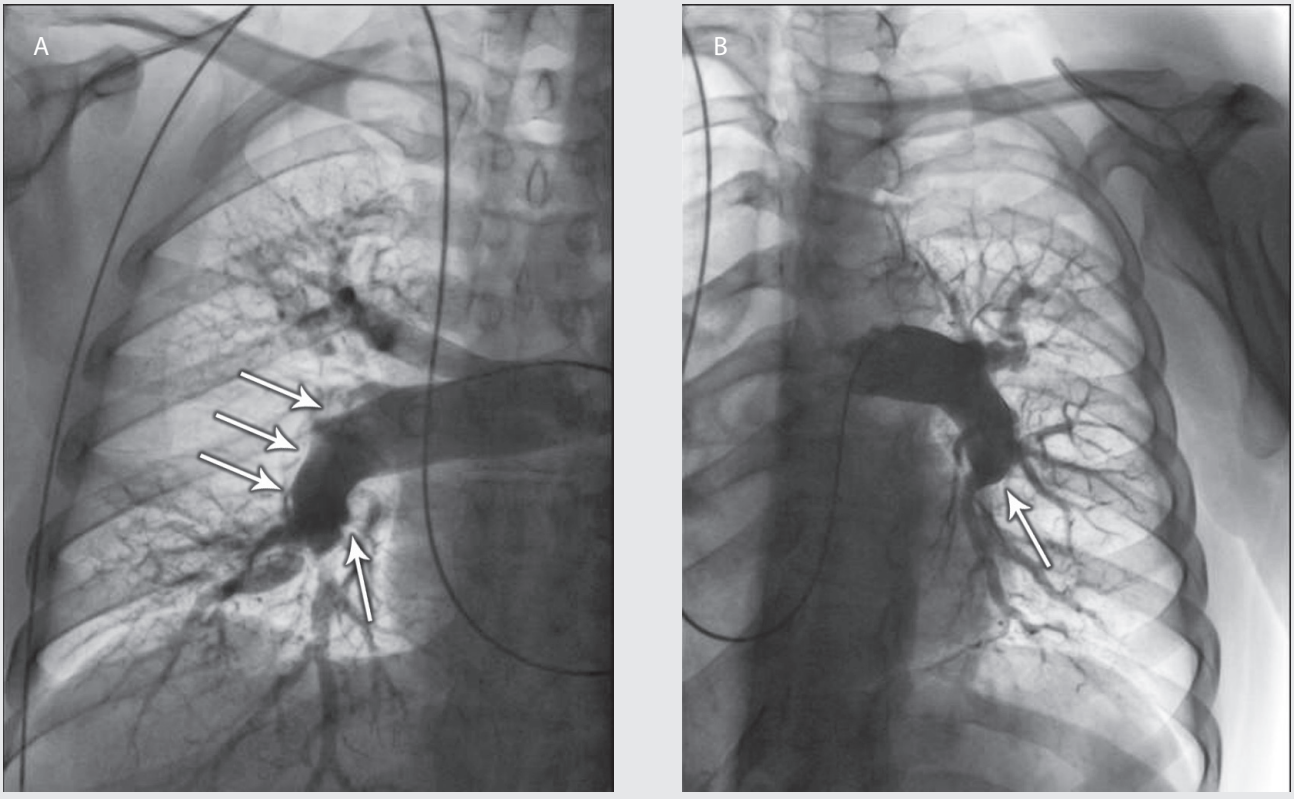

Figure 4. Pulmonary arteriography of the right and the left PA: occlusion of the segmental arteries in both side and narrowing of the distal part of the right PA (arrows). Figure 4A Right PA, Figure 4B Left PA

Literaure review

CTEPH is considered as a rare consequence of an acute pulmonary embolism. It is primarly caused by ineffective recanalization of pulmonary arteries occluded by thromboembolic material [1–7].

Estimated level of diseases incidence is between 0.5–5.0% 2 years after an episode of acute PE [8–10]. Undissolved clots organize and adhere to pulmonary artery walls leading to increase of PVR. Although commonly belived to be a consequence of a thromboembolic disease, Lang et al. showed that up to 63% of CTEPH patients has no history of symptomatic acute PE [11]. This may partly be explained by often unremarkable clinical course of PE but also differences in pathogenesis of CTEPH may play a role. Progression of the disease may be related to occlusion of pulmonary arteries but also to a presence of distal pulmonary vasculopathy in small precapillary vessels in occluded and non occluded arteries. Vascular lesions developed in CTEPH are similar to lesion in idiopathic pulmonary arterial hypertension (IPAH) and consist of endothelial dysfunction, intimal thickening, proliferation and fibrosis of the vessels, smooth muscle hypertrophy and plexiform lesions. Some authors suggest, that local pulmonary thrombosis (in situ) may contribute to CTEPH progression [12–13].

Natural history of the disease leads to development of pulmonary hypertension (PH) (class 4 of PH classification), progressive right heart failure, low output syndrome and death [1–6]. Prognosis in CTEPH without any specific treatment is very poor. Most patients with mPAP ≥ 30 mm Hg die within 2–3 years after diagnosis [14–15].

Pathogenesis of the disease is still under debate. Association of an acute thromboembolic disease, especially idiopathic, with large clots, recurrent character and young age is well known. Other risk factors of developing CTEPH include i.a.: splenectomy, antiphosfolipid syndrome, chronic inflammatory conditions such Crohn's disease or ulcerative colitis, history of malignancy, osteomyelitis, atrioventricular shunts, infected pacemaker, blood group other than 0 or levothyroxine substitution [16–17].

Active screening for CTEPH after acute PE is currently not recommended in asymptomatic patients but the patients with elevated PAP in transthoracic cardiac echocardiography (TTE) or signs of RV overload should be followed-up by echo 3–6 months after acute thromboembolic disease, in order to exclude CTEPH [1].

Symptoms of CTEPH are nonspecific. CTEPH patients typically complain of exertional dyspnea and decline of exercise tolerance. Other symptoms include palpitation, dizziness, presyncope or syncope on exertion, chest pain. Resting dyspnea often appears in the late stage of the disease when the RV is unable to meet metabolic and haemodynamic needs. Physical examination may reveal signs of RV insufficiency, but it may as well be absent in the earlier phases of the disease. When CTEPH progresses, jugular vein distension, right ventricular S_3 gallop, signs of sever tricuspid regurgitation, hepatomegaly, ascites and peripheral oedema may be present [1–6].

Electocardiographic evaluation may present right axis deviation, signs of RV hypertophy, right atrial enlargement, RBBB, T waves inversion in anterior and inferior limb leads. TTE with Doppler imaging is often the first-step noninvasive tool, that reveals elevation of pulmonary artery systolic pressure, right heart chamber enlargement, tricuspid regurgitation or paradoxical interventricular septal motion. Echocardiography is useful to exclude other potential causes of elevated pulmonary pressure and to follow-up the patient.

Initial evaluation include: assessment of functional class according to NYHA classification and evaluation of exercise capacity in 6MWT [1–7]. NT-proBNP plasma level and troponin level may reflect severity of the disease and have prognostic value and can be helpful in making therapeutic decision [18–20].

Pulmonary ventilation-perfusion scan (V/Q scan) is a well-recognized first line test useful for ruling out CTEPH patients from the group of PH patients indicated by echocardigraphy. V/Q scan reveales typical triangle-shaped lacks of perfusion in lung regions with normal ventilation and is useful in distinguishing proximal and distal disease.

In most CTEPH patients however, comprehensive evaluation of pulmonary vasculature requires application of multiple modalities. These include pulmonary scintigraphy, spiral computed tomography and pulmonary angiography. In some cases nuclear magnetic resonance may also be valuable [6]. Computed tomography angiography may reveal mosaic perfusion of the lung parenchyma, pulmonary artery dilation, RA and RV enlargement or chronic organized thrombi in various main, lobar, segmental or subsegmental vessels. Several signs of CTEPH may be present in pulmonary arteriography studies including enlargement of pulmonary arteries, vessel poststenotic dilations, bends, webs or irregular thickening of arterial wall [2–4].

Cardiac catheterization, typically performed with the Swan-Ganz catheter, is carried out to confirm the diagnosis of PH. It is valuable for establishing the severity of PH and the right heart dysfunction as well as for risk stratification of PH patients. Precapillary PH with mPAP ≥ 25 mm Hg and normal PCWP (< 15 mm Hg) are typical findings in patients with CTEPH [1–7]. Some haemodynamic parameters have been identified for their prognostic value and the others are used in patients' selection for the pulmonary endarterectomy (PEA).

Treatment of choice for CTEPH patients with proximal pulmonary lesions (thromboembolic material located in main, lobar or segmental pulmonary arteries) is PEA. It is a cardiac surgical procedure, during which thromboembolic material is removed from pulmonary arteries [21–23]. PEA indications include: NYHA class III or IV, presence of thromboembolic material located in proximal vessels, pulmonary vascular resistance of ≥300 dyn/s/cm^{-5}, mPAP of ≥40 mm Hg and a lack of severe comorbidities [24].

PEA is performed following the San Diego group guidelines [22–23]. A qualified anesthetic care is mandatory during procedure. Lowering of the patient's body temperature to 17–18°C is required before cardiopulmonary bypass is instituted. Cooling-down process generally takes about 45 minutes. In case of life-threatening rhythm abnormalities, such as ventricular fibrillation (VF), cannulas are inserted into superior and inferior vena cava and to the ascending aorta. Additional intermittent episodes of total cardiac arrest are necessary to eliminate bleeding from bronchial arteries. This improves the visibility of the pulmonary artery internal wall, helping recognize the correct endarterectomy plane. Thrombus, together with medial part of the vessel wall is than removed (thrombectomy and endarterectomy is performed). Complete PEA requires usually circulatory arrest time of 15 to 20 minutes for each of the pulmonary arteries. After the endarterectomy is completed, cardiopulmonary bypass is reinstituted and the warming-up process is started.

The re-warming period takes usually from 90 to 120 minutes. Successful endarterectomy leads to the mPAP and PVR decrease and normalizing of the cardiac output (CO). PEA improves outcome of CTEPH patients, with low acceptable perioperative mortality rate and carries excellent long-term result.

Precise patient's qualification for the PEA procedure remains a cornerstone. According to Jameson and Kopelansky classification [22] there are four types of pulmonary occlusive disease depending on the thrombus removed. In type I (20% of all cases) main vessels are affected and thrombus is found in major pulmonary arteries. Those are the best candidates for the operation. In type II (70% of all the cases) no major vessels are affected but thickening of main lobar or segmental vessels are present and the plane of dissection can be usually identified. They are also good candidates for the operation. Type III (10% of all cases), in which only distal disease is present with thickening of segmental and subsegmental vessels. This group remains *gray zone* for experienced centers and experienced operators. In type IV, only signs of distal disease are present [22] and they shouldn't be operated.

Hospital discharge can occur by the sixth or seventh postoperative day, if no complications occur [21–25]. Perioperative mortality rate in experienced centers it is close to 2.0% [21–23]. Possible complications after this intervention include: lung injury and reperfusion oedema, pericardial effusion with cardiac tamponade, persistent PH, postoperative sternal wound infection or atrial arrhythmias [26].

Haemodynamic improvement is typically observed directly after surgery. Clinical studies showed that, significant improvement of arterial blood gases parameters, exercise tolerance and functional status appeared within 3 months after operation. Reverse of RV remodeling and normalization of V/Q scan appears more slowly, approximately 6 to 12 months after the procedure [21–23,27].

For the best practice, all cases of CTEPH should be evaluated in experienced centers. Twenty to 40% of patient in average are inoperable because of: distal lesions (the most common reason), lack of consent or comorbidities (especially severe COPD, malignancy, severe haematologic disorders) [28,29]. Several reports suggested, that the degree of preoperative PVR correlates with postoperative mortality rate. Jamieson at al. observed, that preoperative PVR of more than 1000 dyne/s/cm^{-5} was associated with higher mortality rate of 10.1% compared with 1.3% in subgroup of lower PVR [21]. In some centers (e.g. San Diego, CA, USA) inferior vena cava is inserted before PEA. Up to 20% of patients who underwent PEA have persistent PH after intervention. In such cases lung transplantation, pulmonary artery balloon angioplasty and specific drug treatment may be considered. This applies also to non-operable patients [1–7].

Lifelong anticoagulation for all patients is recommended, with INR level of 2.5 to 3.5 [21–23]. Supportive therapy includes diuretics, digitalis, oxygen. Targeted therapy similar to that approved for pulmonary arterial hypertension (PAH) is often prescribed. Potentially, medical treatment inhibits or slows down pulmonary artery remodeling and pulmonary vasculopathy progression, but does not remove mechanical occlusion. In CTEPH group, best candidates for targeted therapy are patients with contraindications to the surgery or as a bridge therapy to transplantation or to endarterectomy, as well as patients with PH persistent after operation.

There are only a few clinical trials including prostacyclin analogues (epoprostenol, inhaled iloprost, beraprost), dual endothelin receptor antagonist (bosentan) or the phosphodiesterase-5 inhibitors (sildenafil) performed in CTEPH patients [30–33]. A multicenter randomized control trial demonstrated functional class, NT-proBNP and haemodynamic improvement after 16 weeks of bosentan 2×125 mg treatment of 77 patients with non-operable CTEPH or with CTEPH persistent after operation. However, no significant improvement in 6 MWT was observed [30]. In a multicenter randomized placebo controlled trial with iloprost, a subgroup of 33 CTEPH patients was included. Significant improvement of functional class, 6 MWT, haemodynamics after 12 weeks of treatment were observed [31]. Suntharalingam *et al.* in one center study reported on 9 CTEPH patients randomized to sildenafil or placebo, who, after 12 weeks of treatment, improved their haemodynamics and 6 MWT on active treatment [32]. There is still too few data to formally recommend such therapy in CTEPH patients.

Patient management and follow up

Patient was consulted by a cardiologist, radiologist and cardiothoracic surgeon and the PEA was recommended. Because of a history of acute PE and ischaemic cerebral stroke coincident closure of the PFO during PEA was planed.

Patient was treated with an oral anticoagulant (acenocumarol) 4 mg once daily with target INR level between 2.0–3.0 until the operation. Before PEA Greenfield vena cava filter was implanted.

PEA was performed according to the San Diego protocol. An extracorporeal circulation was used during procedure. Operation lasted 4 hours with 30 minutes of full cardiac arrest. Chronic thromboembolic material with intima of pulmonary arteries were removed on both side. Type I of CTEPH according to Jameson and Kopelansky was diagnosed. During re-warming time PFO was closed. The patient was extubated on the second day after operation and discharged from the cardiothoracic surgery department on the 10th postoperative day.

The patient was admitted to cardiology department 1 month after the PEA. He presented in fuctional class II according NYHA classification. No signs of RV dysfunction was present. Sternum cicatrised without any complication. Physical examination revealed BP of 130/80 mm Hg, HR of 64 bpm, normal heart sounds with no murmurs audible, normal liver size. Circumference of right calf was larger than left as before surgical intervention. NT-proBNP level decreased to 113 pg/ml, troponin T level was 0,0013 ng/ml. Capillary blood gas analysis and other laboratory tests were normal. In ECG only incomplete RBBB persisted. In TTE study RV diameter was normal, RV hypertrophy was still present, TVPG decreased to 30 mm Hg, pericardial effusion disappeared. The patient was discharge from the hospital in good condition, on oral anticoagulants. Another clinical follow-up visit was scheduled 6 months after hospital discharge.

Summary

- CTEPH is a rare but severe complication of acute PE. When left untreated, leads to increase of PVR, progressive right heart failure and death.
- In all cases admitted to the hospital with suspicion of PH, CTEPH should be consider as a differential diagnosis. Diagnostic algorithm is presented in Figure 5.
- Patients with CTEPH should be evaluated in specific centers experienced in qualification and surgical treatment of the disease.

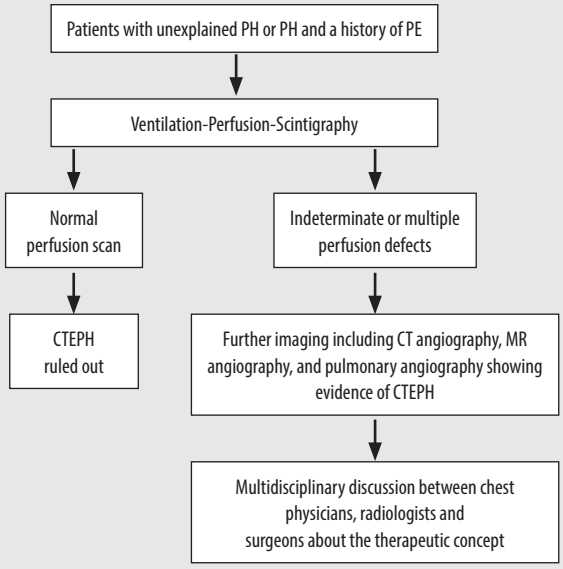

Figure 5. Chronic thromboembolic pulmonary hypertension diagnostic algorithm [6] (CTEPH – chronic thromboembolic pulmonary hypertension, PH – pulmonary hipertension, PE – pulmonary embolism, MR –magnetic resonance, CT – computed tomography)

- The treatment of choice of CTEPH patients with proximal pulmonary lesions (thromboembolic material located in main, lobar or segmental pulmonary arteries) is PEA. Successful PEA improves long term survival of CTEPH patient compared to medical treatment. PEA leads to functional improvement and sustains the decrease of signs of right ventricular overload and dysfunction.
- Specific therapy used in PAH appears as potentially attractive treatment in CTEPH in patients with distal disease, contraindications to PEA, PH persistent after operation, however the evidence is still limited to form recommendations.

Conflict of interest: non declared.

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