Case report

Pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension: A case report and review of the literature

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Summary

Chronic thromboembolic pulmonary hypertension is a progressive and disabling disease with high morbidity and mortality. Pulmonary endarterectomy has been approved as a first choice treatment for chronic thromboembolic pulmonary hypertension with obstruction of proximal pulmonary arteries. The aim of the article is to describe our first experience in this kind of treatment. Diagnosis of chronic thromboembolic pulmonary hypertension, criteria for the surgery, operative technique and results, perioperative management are discussed.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a severe disease with high morbidity and mortality. CTEPH is defined as a pre-capillary pulmonary hypertension (PH) in patients with multiple chronic organized occlusive thrombi or emboli in the pulmonary arteries \cite{1}. The prognosis depends on severity of PH. The 5-year survival rate in patients with a mean pulmonary artery pressure (PAP) 30 mmHg is 30\%, and in patients with mean PAP of 50 mmHg this rate is only 10\% \cite{2,3}.

The real prevalence of CTEPH is unknown, but according to data of the studies it occurred in approximately 1–3.8\% of the patients 2 years after the acute pulmonary embolism (PE) \cite{4,5}.

Pulmonary endarterectomy (PEA) is the treatment of choice for patients with CTEPH as it is a potentially curative option \cite{1,6–10}.

Case report

A seventy-year-old male was referred to our Pulmonary hypertension coordinative centre with a suspicion of CTEPH. He suffered from severe dyspnoea, fatigue and low exercise tolerance. Coronary artery disease was diagnosed 4 years ago and percutaneous angioplasty with stent implantation in the diagonal branch of the left coronary artery was performed. Dyspnoea started a week after the procedure and acute pulmonary embolism was diagnosed. Anticoagulation with heparin was started and, later on, switched to warfarin. As the symptoms had progressed, he was reinvestigated at our hospital. The deep vein thrombosis of lower extremities was diagnosed. A contrast enhanced computed tomographic (CT)
pulmonary angiography revealed partially organized thrombi in the pulmonary artery. On echocardiography, the systolic pulmonary artery pressure of 80 mmHg was found. CTEPH was diagnosed. Warfarin dose was adjusted to maintain INR in a range of 2–3. Arterial hypertension was controlled with diltiazem. Diuretics (torasemide and spironolactone) were prescribed. Despite this treatment, his condition was worsening, dyspnoea was progressing.

On examination, the patient was in WHO functional class 3: breathlessness on mild physical exertion, tachypnoea (22 breaths/min), cyanotic lips, light swelling of the feet were present. The lung sounds were normal; an accentuated second heart sound in the second left intercostal space and mild systolic tricuspid valve (TV) insufficiency murmur were audible. The blood pressure (BP) was normal (130/80 mmHg). The ECG revealed ST depression in II, V5–V6, no signs of right atrial and ventricular hypertrophy. Chest X-ray showed mild enlargement of the right pulmonary artery, obliteration of the right pleural sinus, partial relaxation of the right hemidiaphragm and mildly enlarged cardiac contour (Figure 1). The echocardiography revealed dilatation of the right ventricle (RV) – diastolic diameter 3.5 cm, right atrium (RA) (Figure 2A) and pulmonary artery, mild dysfunction of the right ventricle: tricuspid annular plane systolic excursion (TAPSE) was 1.8 cm, Tei [11] index – 0.62, moderate TV insufficiency (grade II) and severe PH (grade III, systolic gradient RV–RA 101 mmHg, systolic pulmonary artery pressure ≈ 111 mmHg) were present. The left ventricle (LV) was normal in size (diastolic diameter – 4.9 cm) and the systolic function was sufficient (EF 52%). Valvular pathology and congenital heart diseases were excluded. The respiratory function tests revealed decreased lung diffusion capacity for carbon monoxide (DLCO, 51% of predicted), no signs of restrictive (total lung capacity, 88% of predicted) or obstructive (FEV1/FVC, 69%; lower limit of normal 62%) lung disease were found out.

The CT pulmonary angiography revealed chronic pulmonary thromboembolism with eccentric thrombi in pulmonary arteries, chronic occlusion of the right middle lobe pulmonary artery, and tight stenosis of the distal left lower lobe pulmonary artery with an abrupt diameter reduction of basal segmental pulmonary arteries (Figure 3A, B). Cardiac catheterization confirmed the diagnosis of pulmonary arterial hypertension. The elevated mean pulmonary artery pressure (PAP) – 47 (85/25 mmHg), normal pulmonary capillary wedge pressure (PWP) – 12 mmHg and high pulmonary vascular resistance (PVR) – 7.6
Wood units (WU) or 608 dyn·s·cm\(^{-5}\) were found. The cardiac index was low (2.1 l/min/m\(^2\)) and the acute vasoreactivity test with adenosine was negative. The coronaryography showed mild stenosis of the left descending and diagonal (in-stent) branches, (25 and 30\%, respectively). The invasive pulmonary angiography revealed occluded right middle lobe and left lower lobe pulmonary arteries (Figure 4A, B).

A target pulmonary hypertension therapy with phosphodiesterase type 5 inhibitor sildenafil 20 mg 3 times per day was initiated and the patient was scheduled to pulmonary endarterectomy. Anticoagulation with warfarin and basic therapy (diuretics, digoxin) were continued.

The patient’s condition and functional capacity slightly improved after 4 months of the treatment (a 6-minute walk test: the distance increased from 300 to 343 m, brain natriuretic peptide (BNP) level decreased from 225 to 116 ng/l). The contrast-enhanced CT and conventional angiography revealed no new changes of pulmonary arteries.

On September 23, 2010 the pulmonary endarterectomy was performed in accordance with the technique reported by Mayer [12] using cardiopulmonary bypass (CPB), crystalloid cardio-

Figure 2. Transthoracic echocardiography, four chamber view. (A) Before pulmonary endarterectomy. Enlarged right heart chambers. (B) After pulmonary endarterectomy. Normal heart chamber ratio.
Figure 3. Contrast enhanced CT images prior to pulmonary endarterectomy (A and B) and post-operative contrast enhanced CT images (C and D). (A) Axial contrast-enhanced CT scan shows eccentric chronic thrombus in the left pulmonary artery (arrowheads); (B) Axial contrast-enhanced CT scan shows eccentric chronic thrombus with irregular contour in the right interlobar pulmonary artery totally occluding right middle lobe pulmonary artery (white arrow); right lower lobar pulmonary artery contains a residual intraluminal band (black arrow); markedly stenosed poorly enhancing anteromedial segmental artery of the left lower lobe (open arrow); (C) Homogeneous luminal enhancement and smooth posterior wall of the left pulmonary artery (arrowheads); (D) Recanalised homogeneously enhancing right interlobar, middle lobar (arrow) and inferior lobar arteries; restored and intensely opacified anteromedial segmental artery of the left lower lobe (open arrow).

Figure 4. Invasive pulmonary angiography showing occluded right middle lobe and left lower lobe pulmonary arteries before pulmonary endarterectomy (A and B, black arrows) and after pulmonary endarterectomy (C and D, black arrows).

plegia, profound hypothermia (18–20°C) and limited total circulatory arrest. After median sternotomy, the ascending aorta, both v. cavae were cannulated and CPB was started. In order to reduce intra-cardiac pressure, the left atrium and right ventricle were drained. Then cardioplegia was performed. The superior vena cava was withdrawn from ascending aorta with an expander. The right pulmonary artery was dissected longitudinally. The thickened intima with organized thrombi was removed from the right pulmonary artery lobar and segmental arteries and the artery was sutured. The same procedure was performed to the left pulmonary artery. Cumulative periods of circulatory arrest were 10 + 9 min. The aorta cross-clamping time was 84 min. After the removal of cross-clamp of the aorta, an active re-warming of the patient and artificial lung ventilation with positive expiratory function were started. Patient was managed in the intensive care unit 5 days. Extubation was performed on the second postoperative day. A low dose catecholamine therapy (noradrenaline infusion with maximal dose 0.06 mkg/kg/min) was given for 2 days. A negative fluid balance was maintained. The prophylaxis of re-occlusion using heparin intravenously was started 6 hours after the surgery and switched to warfarin after 8 days (INR 2.5–3).

The pulmonary endarterectomy was effective: the decrease the size of the right heart chambers, systolic pulmonary pressure (from 118 to 40 mmHg) as well as improvement of RV function and disappearance of TV regurgitation were observed. The contrast-enhanced computed tomographic pulmonary angiography showed complete reopening of the left and right pulmonary arteries and their lobar and segmental branches ten days after the surgery (Figure 4C, D).

Our patient was treated with diuretics, digoxin, beta-adrenoblockers, non-steroidal anti-inflammatory drugs. Warfarin dose was adjusted to maintain INR in a range of 2.5–3. The patient was advised to wear compressing stockings. Sildenafil was prescribed for one month. The patient was directed to rehabilitation hospital on the 17th day after the surgery.

The cardiac catheterisation was repeated 7 months later and no signs of pulmonary hypertension were found (the mean PAP – 21 mmHg, PWC – 12 mmHg, PVR – 1.8 WU (150 dyn·s·cm⁻⁵). The invasive pulmonary angiography revealed patent, thrombi-free proximal (large and medium size) pulmonary arteries (Figure 4C, D). The invasive coronary angiography demonstrated haemodynamically insignificant changes.

The patient was pretty well and no recurrence of pulmonary embolism was observed one year after the surgery. The exercise ECG testing (Bruce
protocol) demonstrated satisfactory exercise tolerance (exercise time 4.34 min; maximum load 100 W, heart rate (HR) 113 → 150 beats/min), hyperkinetic hemodynamic reaction (BP 120/75 → 180/90 mmHg) with no signs of coronary insufficiency. Ventricular premature beats were recorded during investigation. 24 hour ECG Holter monitoring revealed mild tachycardia (average HR 86 beats/min) and ventricular arrhythmia: couplets, bigeminy episodes. The dose of metoprolol was increased after the investigation, because of the hyperkinesis and the positive correlation of the number of ventricular premature beats with the increasing HR. The echocardiography showed normal size of RV (diastolic diameter 2.2 cm) and RA (Figure 2B), RV hypertrophy and mild dysfunction (TAPSE – 1.87 cm, Tei index 0.5), mild tricuspid insufficiency and systolic PAP was 35 mmHg. Normal size and hypertrophy of LV (diastolic diameter 5.1 cm, interventricular septum diastolic diameter 1.3 cm), good systolic LV function (EF 55%) and diastolic dysfunction (impaired relaxation) were found. Healthy lifestyle, control of weight, BP and dyslipidemia as well as lifelong anticoagulation was recommended.

Discussion

Chronic tromboembolic pulmonary hypertension is diagnosed if pulmonary hypertension persists after 3–6 months of efficient anticoagulation in patients who had suffered from the acute pulmonary embolism [10,14]. The diagnostic criteria include elevation of the mean pulmonary artery pressure (≥25 mmHg), normal pulmonary wedge pressure (≤15 mmHg), high pulmonary vascular resistance (≥2 WU) on invasive pressure measurement and the presence of lung perfusion defects on ventilation-perfusion scan; or/and organized thrombi in the pulmonary artery on computed tomographic pulmonary angiography or ventilation–perfusion lung scanning and/or invasive pulmonary angiography [1]. The other causes of PH should be excluded. In patients with silent PE adequate anticoagulation with warfarin (INR 2.0–3.0) should be applied 3 months prior to cardiac catheterisation in order to exclude patients with sub-acute PE [14]. Our patient met these criteria of CTEPH.

The idiopathic nature and the recurrence of PE as well as large perfusion defects at diagnosis have been focused on as risk factors for the occurrence of symptomatic CTEPH [4]. Our patient had a recurrent PE despite anticoagulation. The first episode was related to transient risk factor – hospitalization (for coronary angiography). The permanent risk factors (coagulation disorder, the presence of lupus antibodies, active cancer, and familiar venous thromboembolism) were excluded; however, it was found out that our patient suffered from chronic deep vein thrombosis.

It is generally accepted that most patients with CTEPH treated with anticoagulation alone have progressive disease with high morbidity and mortality [1,14]. Peripheral vasculopathy with micro-vascular changes indistinguishable from idiopathic pulmonary arterial hypertension can then occur even in the areas of the pulmonary vascular bed that have not been affected by thromboembolism [15]. These changes of small pulmonary vessels can contribute to the development and progression of PH in CTEPH [16]. It has been hypothesized that in situ thrombosis and pulmonary arteriopathy are common causes of vascular occlusion leading to CTEPH and that PE is unlikely to be a common cause of this disease [17]. This hypothesis may be partially proved by the low percentage of CTEPH (1.5–3.8%) found in patients after acute PE episode [4,5]. Up to 20.1–32% of CTEPH patients had very distal thrombi (Jamieson CTEPH class IV [18,19]) and could not be selected for surgery [20,21]. Moreover, the history of venous thromboembolism was found to be significantly less frequent in inoperable patients than in those who underwent PEA (49 versus 62%; p = 0.01) [22,23].

However, in recent screening study [24] up to 8.8% of patients had signs of PH at echocardiographic examination in the presence of residual perfusion defects 6 months to 1 year after PE, and half of them were asymptomatic. These data suggested that CTEPH following acute PE was much more common than reported previously.

Routine echocardiographic evaluation to detect PH within 6 months after acute PE may lead to early diagnosis of CTEPH [10]. Patients with PH and findings of PE on computed tomographic pulmonary angiography or ventilation–perfusion lung scanning and those with unexplained elevations in pulmonary artery systolic pressure on echocardiography should be referred to specialized PH centres where PEA could be performed [1,10]. Earlier referral to surgery might avoid the occurrence of a secondary vasculopathy in the unaffected areas of the pulmonary vascular tree, and therefore further improve early and long-term results.

The first PEA was performed in 1967 [25]. Significant improvements in symptoms, pulmonary hemodynamic and functional class in patients with CTEPH were found after this operation in large patients cohorts [13,21,25–27]. In those who survived surgery to 3 months, the proportion with WHO functional class I or II disease increased from 12% at the baseline to 88% at 3 months [21].
The PEA became widely performed only during the last decade because of very complicated surgical technique and perioperative care. The specialised centres for PEA were established in the US, Canada and Europe and operative mortality was reduced from 24% to 4–10% [7,11,21,25,26,28]. Currently, the 30-day mortality ranges from less than 5% in the most experienced centres to 10% elsewhere [7].

Results of PEA depend on the accuracy of diagnosis, patient selection, surgical experience and postoperative management [29]. The increased survival of surgical patients that was observed may have been due to a combination of the improvements in surgical selection and perioperative management over time, that are typical for the centres undertaking PEA surgery, together with an increased use of disease-modifying therapy before surgery [21,30]. The establishment of pulmonary hypertension referral centres with dedicated multidisciplinary teams and achievements in non-invasive diagnostics (echocardiography, high-resolution computed tomographic and magnetic resonance pulmonary angiography, ventilation–perfusion pulmonary scintigraphy) resulted in a more precise diagnosis and better patient selection for PEA [21,30]. Our centre has all diagnostic tools and enthusiastic multidisciplinary team trained in two well-known PEA centres. A panel of cardiologists, pulmonologists, radiologists, and cardiothoracic surgeons reviewed each CTEPH case.

The right heart catheterization with pulmonary angiography continues to be the gold standard for establishing the diagnosis of CTEPH and assessing operability [10,29–31]. Angiographic evidences of pouching webs or bands with or without post-stenotic dilatation, intimal irregularities, abrupt narrowing or total occlusion are pathognomonic for CTEPH, show outspread and localisation of thrombi and availability for surgical removing. A positive response to acute vasoreactivity testing could be indicative of increased long-term survival among patients with CTEPH who undergo PEA [32]. Pulmonary vascular resistance should, therefore, continue to be very important to the decision-making process regarding suitability for surgery [24]. PEA is indicated for symptomatic patients with PVR ≥3.75 WU or 300 dyn·s·cm⁻⁵ (except for patients with unilateral disease), surgical accessible thromboembolic lesions and absence of severe comorbidities [7,12,29,33]. Our patient met these criteria.

The patients with a PVR ≥12.5 WU had a 2.4 times higher risk of dying during the perioperative period than patients with a lower PVR [15]. The combination of persistent macrovascular obstruction, small vessel arteriopathy, and vasoconstriction results in PH and right ventricular pressure overload that exceeds the level expected from macrovascular obstruction alone [14]. Small-vessel disease as suggested by a PVR out of proportion to the degree of large-vessel obstruction is a contraindication to PEA [8,26]. As a rule, a patient should not be considered inoperable as long as the case has not been reviewed by an experienced surgeon [1]. Our patient was consulted by professor E. Mayer. Patients with supra-systemic pulmonary artery pressures and excessive elevation of PVR (>18.75 WU) could also be accepted for surgery, although the operative risk is significantly increased [15,34,35].

Preoperative predictors of favourable outcomes include a PVR of less than 15 WU and the absence of major coexisting conditions [20]. Despite technically successful surgery, patients with associated medical conditions had worse outcomes with higher perioperative mortality (24% vs. 9%) and an increased incidence of postoperative PH [20]. Associated medical conditions such as splenectomy, ventriculotrial shunt for the treatment of hydrocephalus, permanent central intravenous lines, inflammatory bowel disease, osteomyelitis, thyroid hormone replacement therapy, malignancy and female gender should be taken into account predicting the risk of surgery [20,36,37]. Severe underlying chronic lung disease is a contraindication to PEA [8,31]. Our patient had a low operative risk (despite the age and coronary artery disease).

Patients in whom the postoperative PVR was decreased by at least 50%, to a value of less than 6.25 WU, have a more favourable prognosis after surgery than those who did not [6]. According to the data from international prospective registry of 26 European centres, PEA perioperative complications occurred in 49.2% of the patients [13]. Reperfusion pulmonary oedema developed in 9.6–16.2%, infection in 10.8–18.8%, bleeding in 4–10.2% of the cases [13,29]. The residual PH was present up to 16.7–31% of the patients [13,38]. Interestingly, despite marked worsening of the symptoms and functional capacity, caused by the residual PH, no decrease of medium-term survival was observed [38]. Luckily, our patient averted the postoperative complications.

The histopathologic changes similar to pulmonary arterial hypertension (PAH) are characteristic for the patients with CTEPH, therefore, the disease-modifying therapies used in treatment of PAH pulmonary arterial hypertension have been used as a bridge to surgery in selected patients with surgically accessible disease [21]. There is only limited data mostly from non-randomized trials regarding the efficacy of these disease-modifying therapies in CTEPH [1,39–45].
Use of sildenafil does not appear to predict hemodynamics or outcomes after PEA [46]. Specific PAH drug therapy may exert hemodynamic and clinical benefits in selected CTEPH patients, if the pre-operative treatment is deemed appropriate to improve haemodynamics, regardless of whether these patients were considered operable or inoperable [1,47]. We treated our patient with sildenafil 6 months before surgery. This treatment improved his condition and, we believe, allowed him to attain until we prepared for the PEA.

Lung transplantation is not an option for the vast majority of CTEPH patients and should be considered for selected patients who are not accepted for PEA, only. It may be an option for very severe patients with very high PVR and advanced distal CTEPH [12,20]. In experienced centres even extreme CTEPH survival rates after PEA are higher in comparison with those after lung or heart/lung transplantation [34].

The patients with symptomatic chronic thromboembolic pulmonary hypertension, surgically accessible disease, and an acceptable perioperative risk should be referred for pulmonary endarterectomy. We believe that the PEA program will successfully continue in our centre.

Conclusion

Pulmonary endarterectomy is an effective and curative surgical treatment for selected patients with chronic thromboembolic pulmonary hypertension. Based on the effort of a multidisciplinary team, the operative risk could be reduced to an acceptable level and this operation can be successfully performed even in a small country.

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References


