



The Pulmonary Thromboendarterectomy Increases Gradually All Over the World; Review

Mehmet Yanartaş¹, Rezzan Deniz Acar², Bedrettin Yıldızeli³

¹ Kartal Koşuyolu High Specialization Training and Research Hospital, Clinic of Cardiovascular Surgery, Istanbul, Turkey

² Kartal Koşuyolu High Specialization Training and Research Hospital, Clinic of Cardiology, Istanbul, Turkey

³ Marmara University Faculty of Medicine, Department of Foundation Economic Enterprise, Istanbul, Turkey

ABSTRACT

Pulmonary endarterectomy (PTE) is a complex surgical procedure that provides functional and haemodynamic improvement in patients with chronic thromboembolic pulmonary hypertension. The use of PTE procedures is increasing all over the world and by getting a high level of surgical expertise; therefore, mortality rates are gradually decreasing day by day. Initially, operative mortality rates were high with a range of approximately 4%-24%. These rates have substantially decreased all over the world. PTE is a surgical technique that aims to remove unresolved thromboembolic material that obstructs the pulmonary arteries. Significant and persistent decreases in pulmonary artery pressures and pulmonary vascular resistance are observed in patients with chronic thromboembolic pulmonary hypertension after the surgery. Nowadays, this operation is offered to those patients who were considered to be inoperable in the past.

Key Words: Pulmonary thromboendarterectomy; chronic thromboembolic pulmonary hypertension

Pulmoner Tromboendarterektomi Tüm Dünyada Giderek Yaygınlaşmaktadır; Derleme

ÖZET

Pulmoner tromboendarterektomi (PTE) kronik tromboembolik pulmoner hipertansiyonda hemodinamik ve fonksiyonel iyileşmeyi sağlayan karmaşık bir cerrahi işlemdir. PTE işlemi uygulaması tüm dünyada giderek yaygınlaşmakta ve cerrahi deneyim arttıkça ölüm oranları her geçen gün giderek azalmaktadır. Başlangıçta %4 -24 gibi yüksek değerlerde olan cerrahi ölüm oranları tüm dünyada önemli oranda düşmüştür. PTE pulmoner arterleri tıkayan ve erimemiş olan trombotik tıkaçı çıkarmayı amaçlayan cerrahi bir tekniktir. Kronik tromboemboliye bağlı pulmoner hipertansiyon olgularında PTE işlemi sonrası pulmoner arter basıncı ve pulmoner vasküler dirençte önemli ve sürekli değişiklikler gözlenmektedir. Son günlerde, daha önceden cerrahi işlem için uygun olmadığı düşünülen bazı olgulara bile artık PTE önerilmektedir.

Anahtar Kelimeler: Pulmoner tromboendarterektomi; kronik tromboembolik pulmoner hipertansiyon

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is defined as an elevated mean pulmonary artery pressure > 25 mmHg, which is caused by thromboemboli in the pulmonary arterial system at least 6 weeks after acute pulmonary embolism (PE). Deep venous thromboembolism (DVT) is the most encountered cause of PE. The short-term mortality for PE has been reported to range from 7% to 11%^(1,2). If CTEPH is left untreated, it could result in serious cause of morbidity and mortality. Pulmonary thromboendarterectomy (PTE) is a potentially curative treatment at an experienced centre.

PATHOGENESIS

Although PE can be treated using anticoagulation, residual thrombus may remain after 1 year in as many as 50% of the patients^(3,4). Moreover, recurrence of embolism and in situ thrombus propagation into branch pulmonary vessels may lead to large- and small-vessel vasculopathy^(5,6). Therefore, in 1-4 weeks, the embolic material becomes incorporated into the pulmonary arterial wall at the main pulmonary artery, lobar, segmental, or subsegmental levels⁽⁷⁾. The initial embolic material is remodelled into the connective and elastic tissues by time. Moreover, this material contains endothelial and smooth muscle precursor cells⁽⁸⁾. Pulmonary microvascular changes contribute to disease progression⁽⁹⁾. Angiosarcoma, tumour emboli into the pulmonary artery, hydatid emboli (Figure 1), pulmonary arteritis and fibrous mediastinitis may resemble CTEPH.

Correspondence

Rezzan Deniz Acar

E-mail: denizacar_1999@yahoo.com

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Figure 1. The “hydatid emboli” specimen after the surgery, which may be differentiated from CTEPH.

DIAGNOSIS

On chest radiography, hilar fullness caused by enlarged central pulmonary arteries, clear or oligemic lung fields and RV enlargement may be found.

Transthoracic echocardiography estimates the pulmonary artery pressure, enlargement of the right side of the heart, leftward displacement of the interventricular septum and encroachment of the enlarged RV on the LV cavity, with abnormal systolic and diastolic function of LV.

A normal ventilation/perfusion scan typically demonstrates mismatched segmental defects caused by obstructive thromboembolism. Any lobar, segmental, or subsegmental defect should lead to further evaluation.

Pulmonary angiography is the “gold standard” test for defining pulmonary vascular anatomy to determine its location and surgical accessibility. With angiography, completely thrombosed vessels can be seen that resemble congenital absence of a vessel. Organized material along a vascular wall produces a scalloped or serrated luminal edge.

Other studies include multidetector CT angiography with three-dimensional reconstruction, single-photon emission CT fusion imaging and magnetic resonance imaging scanning that may be performed in selected patients before PTE.

THROMBOEMBOLIC DISEASE CLASSIFICATION

Four major types of pulmonary occlusive disease, which are based on anatomic location of thrombus and vessel wall pathology and may be useful in predicting outcomes after PTE, are as follows⁽¹⁰⁾:

1. Type 1 Disease: Approximately 25% of cases of thromboembolic pulmonary hypertension. The main or lobar pulmonary arteries contain fresh thrombus (Figure 2).

2. Type 2 Disease: Intimal thickening and fibrosis with or without organized thrombus proximal to segmental arteries. In these cases, only thickened intima can be seen on initial dissection into the pulmonary arteries, occasionally with webs in the main or lobar arteries. This type is found in approximately 40% of cases (Figure 3).

3. Type 3 Disease: Fibrosis, intimal webbing and thickening with or without organized thrombus within distal segmental and subsegmental arteries only. This type of disease presents the most challenging surgical situation. No occlusion of vessels can be initially seen. The endarterectomy plane must be individually raised in each segmental and subsegmental branch. Type 3 disease may represent “burned out” disease,



Figure 2. The type 1 disease; the main or lobar pulmonary arteries contain fresh thrombus.



Figure 3. The type 2 disease; intimal thickening and fibrosis with or without organized thrombus proximal to segmental arteries.

in which most of the proximal embolic material has been reabsorbed. This type is found in approximately 30% of cases (Figure 4).

4. Type 4 Disease: Microscopic distal arteriolar vasculopathy without visible thromboembolic disease. Type 4 disease does not represent classic CTEPH and is inoperable. In this entity, there is intrinsic small-vessel disease, although secondary thrombus may occur as a result of stasis. Small-vessel disease may be unrelated to thromboembolic events that occur in relation to previous (now resolved) thromboembolic vascular occlusion as a result of a high-flow or high-pressure state in previously unaffected vessels. This type is found in fewer than 5% of cases.

Patients with proximal disease (types 1 and 2) have a much better risk-to-benefit ratio from surgery than those with the more distal disease. Those with a pulmonary vascular resistance (PVR) of 1200 dynes.s.cm⁻⁵ have a higher risk of mortality with attempted PTE. In particular, in patients with PVR disproportionately higher than the segmental obstruction visible by imaging, there is less benefit from PTE and a much higher risk of mortality. Guidelines from the American College of Chest Physicians recommend that the following four basic criteria should be met: “New York Heart Association (NYHA)” functional class III or IV symptoms, preoperative PVR of greater than 300 dynes.s.cm⁻⁵, surgically accessible thrombus in the main lobar or segmental pulmonary arteries and no severe comorbidities. Severe underlying chronic lung disease, either obstructive or restrictive, is a contraindication to PTE, regardless of the severity of chronic thromboembolic pulmonary hypertension⁽¹¹⁾.

Decisions regarding operability in some patients depend on the combined clinical experience of the multidisciplinary team. Operative risk is almost totally dependent on CTEPH, and concomitant procedures (CABG, valve replacement, etc.) are performed as necessary without additional risk. The only

comorbidity that may influence the decision to operate is severe parenchymal lung disease, but there are few absolute contraindications to PTE surgery and all patients should be referred after complete investigation for consideration of surgery.

PTE

PTE surgery with deep hypothermic circulatory arrest (DHCA), which allows complete cessation of blood flow and therefore optimum operating conditions, is the most widely used technique. A complete surgical endarterectomy is required to be successful. It has been reported that PTE surgery with DHCA leads to a reduction in pulmonary artery pressure and a lower in-hospital mortality⁽¹²⁾. It is suggested that circulatory arrest is the optimum modality for patients undergoing PTE surgery⁽¹³⁾.

The most important clue is that no patient should be deemed inoperable if the origin of the disease is thromboembolic. The severity of PVR before operation is the largest risk factor. A very high PVR signifies secondary arteriopathy, which is inoperable. Further refinement in pulmonary waveform analysis, pulmonary flow systolic notch analysis, pulmonary angiography, CT imaging and magnetic resonance imaging may be helpful in recognizing patients with severe pulmonary hypertension and minimal clot burden who will not benefit from surgical therapy⁽¹⁴⁻¹⁷⁾. The goal of PTE is to remove sufficient material from the pulmonary arteries to substantially lower PVR and improve the cardiac output.

PTE was first reported by Hurwitt et al. in 1958. The procedure has four basic principles. The approach is through a median sternotomy because the endarterectomy must be bilateral. The plane of dissection has to be identified in each of the segmental and subsegmental branches, and perfect visualization is essential to safely and completely clear all distal vessels of disease. Distal endarterectomy cannot be performed without the use of circulatory arrest. Circulatory arrest is usually limited to 20 min at a time, and with experience, each unilateral endarterectomy can be completed during that period. Patients with type III disease may require longer circulatory arrest. After 20 min, if further endarterectomy is necessary, circulation is restarted for 10 min; then, a second circulatory arrest is performed.

The endarterectomy is started by circumferentially separating the adventitia from the media. The dissection of this layer should be carefully continued to the distally through the segmental and subsegmental branches. Distal branches are fully endarterectomized with no flow obstruction and good “run-off”. The vessel should be intact, and a perforation of the wall should not occur. Because the layer in the proximal vessels without the disease is fragile, possibility of perforation is high. After the endarterectomy is completed on both sides, circulation with warming is restarted. If another procedure is

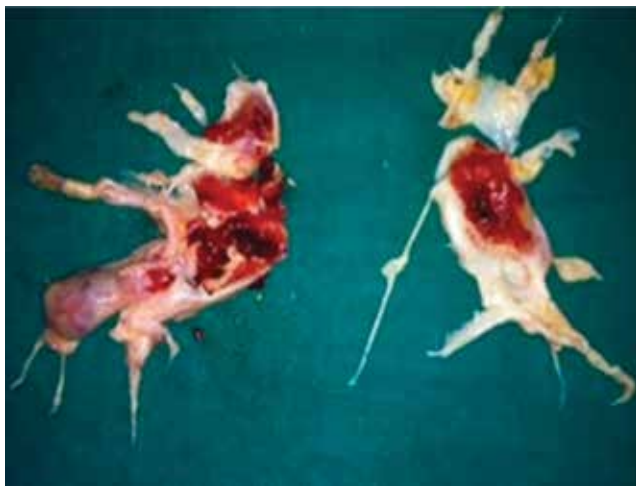


Figure 4. The type 3 disease; fibrosis, intimal webbing and thickening with or without organized thrombus within distal segmental and subsegmental arteries only.

needed, such as coronary bypass grafting, valvular repair or replacement or closure of an atrial septal defect, it should be performed during the rewarming phase of the operation.

Persistent pulmonary hypertension (mPAP > 25 mmHg) is one of the most important complications that may be seen in approximately 10% of the patients. Inadequate endarterectomy, inaccessible distal thrombotic pathology and significant secondary vasculopathy that are likely to lead to RV failure may be responsible for persistent pulmonary hypertension after the procedure⁽¹⁸⁾. Moreover, for controlling of persistent pulmonary hypertension, prostanoid inhalation can be helpful⁽¹⁹⁾. Late referral to the PTE centre is one of the causes of small-vessel arteriopathy, thereby leading to persistent pulmonary hypertension.

Another potential concern with the endarterectomised parts of the lung is reperfusion oedema. Postoperative mechanical ventilation and adequate fluid restriction are important in this situation. The estimated incidence of reperfusion oedema is 10%-15%. It has been reported by Mares et al. that nonaggressive mechanical ventilation and avoidance of positive inotropic agents, which have been used for termination of cardiopulmonary bypass, are associated with a lower incidence of reperfusion pulmonary oedema and right-heart failure⁽²⁰⁾. Moreover, high-dose perioperative methylprednisolone has been used for patients undergoing PTE. Perioperative corticosteroids may reduce complement activation and the release of inflammatory cytokines associated with cardiopulmonary bypass (CPB). CPB is known to be associated with an undesirable systemic inflammatory response that likely contributes to the development of postoperative complications, including respiratory failure, bleeding disorders and renal, hepatic and neurologic dysfunction. Corticosteroids have been used in patients undergoing cardiac surgery with CPB to reduce the systemic inflammatory response syndrome induced by CPB. Kim et al. did not find any difference in postoperative results between patients with and without lung injury⁽²¹⁾. However, the clinical benefit of this intervention is uncertain.

Because of the spiking of pulmonary artery blood pressure, arteriotomy rupture may be seen after PTE. Other adverse outcomes are nosocomial pneumonia and haemoptysis. The rare complications are intrapulmonary bleeding and rethrombosis of the endarterectomized area. There are limited data on the influence of different postoperative treatment strategies on mortality and complications.

Between 2011 and August 2013, 150 cases of PTE for thromboembolic pulmonary hypertension have been performed at Kosuyolu Heart Center, Istanbul, Turkey, by a dedicated team of thoracic and cardiovascular surgeons. We have recently published our preliminary results⁽²²⁾. Our operative mortality is now 12% (unpublished data) and was mostly because of patients

with persistent pulmonary hypertension after endarterectomy.

It is also true for our patients that a patient with very high pulmonary resistance and a low anatomic obstruction is at a high risk, whereas the patient with the same pulmonary resistance but with proximal anatomic obstruction presents with a low risk. In the last 50 patients of the series, we excluded operating on those with the very distal form of thromboembolism associated with severe haemodynamic alterations, and the mortality rate dropped to 8%. After surgery, considerable diminution of pulmonary resistance was usually seen, with a significant improvement in the functional state of the patient.

Mortality rates reported for patients who have undergone PTE all over the world range from approximately 4% to 24% (Table 1). The operative mortality rate from PTE appears to be closely related to haemodynamic severity, with a mortality rate of 4% observed in patients with a preoperative PVR of < 900 dyn/s/cm⁻⁵, 10% in those with a PVR of 900-1.200 dynes.s.cm⁻⁵ and 20% in those with higher preoperative PVR values⁽²³⁾. The site of anatomic obstruction is important in the evaluation of the mortality rate. Patients with a high PVR and a low (distal) anatomic obstruction are at a higher risk than those with a comparable PVR but with proximal anatomic obstruction. Location of the disease, as categorized by the traditional operative classification system, also has effects on haemodynamic parameters after pulmonary endarterectomy⁽²⁴⁾.

LUNG TRANSPLANTATION

In CTEPH, lung transplantation is considered to be a treatment of last resort in patients who are unsuitable for PTE because of inoperable disease, limited access or no or unsustained benefit after previous PTE surgery. Transplantation guidelines based on studies demonstrate that up to 25% of patients with PAH fail to improve on disease-targeted therapy and the prognosis of those who remain in functional class III or IV remains poor^(25,26).

For patients with PAH, choosing transplant is an important facet of preoperative evaluation. Both heart-lung and isolated lung transplantations have been performed for pulmonary vascular disease, but heart-lung transplantation should now be reserved for patients who are not candidates for lung transplantation alone. The threshold of unrecoverable right ventricular dysfunction remains unknown, and severe dysfunction has been shown to be reversible after isolated lung transplantation. Actuarial survival following transplantation for PAH has been well documented by the Registry of the ISHLT. The overall 5-year survival rate is 45%-50%⁽²⁷⁾. Transplantation for PAH is one of the major causes of highest perioperative mortality among the major diagnostic categories of patients undergoing transplantation, and this is explained by the complexity of the surgery in severe PH.

Table 1. Studies of pulmonary thromboendarterectomy (PTE) for chronic thromboembolic pulmonary hypertension (CTEPH)

Author	Year	n	Follow-up	Patient status	Perop mortality	Country
Ando ⁽³¹⁾	1999	24	Postop	NYHA III-IV	21%	Japan
D'Armini ⁽³²⁾	2005	131	36 m	NYHA I-II	9%	Italy
Hagl ⁽³³⁾	2003	30	16 m	NYHA III-IV	10%	Germany
Kramm ⁽¹⁹⁾	1999	54	60 m	NYHA III-IV	22%	Germany
Mellemkjaer ⁽³⁴⁾	2006	50	8 y	NYHA III-IV	24%	Denmark
Menzel ⁽³⁵⁾	2000	39	13 ± 8 d	NYHA I-II-III	Not known	Germany
Thistlethwaite ⁽¹⁰⁾	2001	1100	1 y	NYHA III-IV	6%	USA
Masuda ⁽³⁶⁾	2001	50	10 y	High-Risk	18%	Japan
Rubens ⁽³⁷⁾	2006	104	30 d	High-Risk	9%	Canada
Tscholl ⁽³⁸⁾	2001	69	30 d	NYHA III-IV	10%	Germany
Lindner ⁽³⁹⁾	2006	21	30 d	High-Risk	4%	Czech Republic
Thomson ⁽⁴⁰⁾	2008	151	1 y	NYHA III-IV	15%	Australia
Corsico AG ⁽⁴¹⁾	2008	157	4 y	NYHA III-IV	16%	Italy
Narayana ⁽⁴²⁾	2010	41	6 m	NYHA II-III-IV	12%	India
Blázquez JA ⁽⁴³⁾	2009	30	10 y	High-Risk	17%	Spain
Saouti N ⁽⁴⁴⁾	2009	120	120 y	NYHA III-IV	12%	Netherlands
Gu S ⁽⁴⁵⁾	2010	15	Postop	NYHA III-IV	13%	China
Freed DH ⁽⁴⁶⁾	2011	314	3 m	All	10%	UK
Kunihara T ⁽⁴⁷⁾	2011	279	3 y	All	6%	Germany
de Perrot M ⁽⁴⁸⁾	2011	84	30 d	All	5%	Canada
Ishida K ⁽⁴⁹⁾	2012	77	20 y	All	7%	Japan
Oh SJ ⁽⁵⁰⁾	2013	16	12 y	NYHA III-IV	6%	Korea
Yildizeli B et al.*	2013	49	Postop	NYHA III-IV	14%	Turkey

N: Number of patients enrolled in the study, NYHA: New York Heart Association, Postop: Postoperative, Perop: Perioperative, * The results of our centre⁽²²⁾.

MEDICAL THERAPY

When surgery is contraindicated because of significant comorbidity, medical therapy can be considered⁽²⁸⁾. According to the placebo-controlled trials for CTEPH, which evaluated bosentan in patients with persistent PAH following PTE, patients treated with bosentan demonstrated a reduction in pulmonary vascular resistance (PVR) but no change in 6MW (6-min walking) test was observed compared with the placebo group⁽²⁹⁾.

Riociguat is a member of a new class of therapeutic agents that increase the level of cyclic guanosine monophosphate, resulting in vasorelaxation and antiproliferative and antifibrotic effects. Different from bosentan, riociguat significantly improved the 6MW distance, pulmonary vascular resistance and other clinical outcomes in patients with chronic thromboembolic pulmonary hypertension⁽³⁰⁾.

Diuretics and oxygen are used as indicated. Lifelong anticoagulation therapy is prescribed.

Patients who live far from a designated centre should be admitted to their local hospital in case of emergency; therefore, it is important that a local physician knows the patient.

CONCLUSION

All patients with suspected CTEPH should be evaluated to confirm the diagnosis and assess operability. Because of increased awareness with the understanding of pathogenesis and diagnosis, management of CTEPH is improving, and by good timing for referral, demand for PTE is increasing worldwide.

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