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Chronic thromboembolic pulmonary hypertension

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ABSTRACT: Pulmonary arterial hypertension is a severe disease that has been ignored for a long time. However, over the past 20 yrs chest physicians, cardiologists and thoracic surgeons have shown increasing interest in this disease because of the development of new therapies, that have improved both the outcome and quality of life of patients, including pulmonary transplantation and prostacyclin therapy.

Chronic thromboembolic pulmonary arterial hypertension (CTEPH) can be cured surgically through a complex surgical procedure: the pulmonary thromboendarterectomy. Pulmonary thromboendarterectomy is performed under hypothermia and total circulatory arrest.

Due to clinically evident acute-pulmonary embolism episodes being absent in >50% of patients, the diagnosis of CTEPH can be difficult. Lung scintiscan showing segmental mismatched perfusion defects is the best diagnostic tool to detect CTEPH.

Pulmonary angiography confirms the diagnosis and determines the feasability of endarterectomy according to the location of the disease, proximal *versus* distal. The technique of angiography must be perfect with the whole arterial tree captured on the same picture for each lung. The lesions must start at the level of the pulmonary artery trunk, or at the level of the lobar arteries, in order to find a plan for the endarterectomy.

When the haemodynamic gravity corresponds to the degree of obliteration, pulmonary thromboendarterectomy can be performed with minimal perioperative mortality, providing definitive, excellent functional results in almost all cases.

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Pulmonary arterial hypertension is a severe disease that has been historically neglected. Over the past 20 yrs, chest physicians, cardiologists and thoracic surgeons have shown increasing interest in this disease because of the development of new therapies that have improved the outcome and quality of life of patients. Available options now include prostacyclin therapy, pulmonary endarterectomy and pulmonary transplantation.

Chronic thromboembolic pulmonary hypertension (CTEPH) is caused by obstruction of the large pulmonary arteries by acute and recurrent pulmonary emboli, and organisation of these blood clots. This disease, initially considered to be rare, is being diagnosed more and more frequently. A possible reason for this is the availability of successful medical and surgical treatment. The development of centres specialising in the diagnosis and treatment of pulmonary hypertension, and more consistent follow-up procedures for patients presenting with acute pulmonary emboli may also contribute to the ongoing increase in the number of patients diagnosed and treated for CTEPH.

Pathogenesis or natural history of pulmonary emboli

Haemodynamic failure and death occurs in 20–40% of patients within 1 h of acute pulmonary emboli [1]. Among survivors, the natural evolution, in most cases, is resorption of blood clots by local fibrinolysis with complete restoration of

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the pulmonary arterial bed. In 0.1–0.4% of cases, for reasons which are unknown, resorption does not occur and the emboli evolve to an organised clot inside the pulmonary artery. Abnormalities in haemostasis or fibrinolysis, and recurrent emboli are possible contributors. The pulmonary arterial bed becomes occluded resulting in right heart remodelling. A honeymoon period between the acute pulmonary embolus and the occurrence of symptoms of pulmonary hypertension is common [2–4]. The occurrence of dyspnoea after a symptom-free interval of several years is not due to recurrent emboli, but to the development of local thrombosis. This phenomenon is secondary to the low blood flow upstream from the obstructed pulmonary artery or, more likely, to the development of an arteritis in the nonobstructed territories, similar to those seen in primary pulmonary hypertension. These pathophysiological events explain the inevitable worsening of pulmonary hypertension with time and the occasionally delayed or incomplete regression of pulmonary hypertension after pulmonary endarterectomy.

Pathology

The organisation of a blood clot into fibrous tissue is associated with the disappearance of the intima and an infiltration of the media of the arterial vessel [5]. These lesions are often partially repermeablised at the level of the large trunks, but remain occluded at the ostia of collateral branches, giving the appearance of a "dead tree" on pulmonary angiography. Pseudo-intimal fibrous thickening usually starts at the level of the intrapericardial segment of the pulmonary artery and becomes progressively thicker downstream in lobar and segmental arteries that eventually become occluded (fig. 1).

In 20% of cases, low blood flow upstream, a result of obstruction of segmental and subsegmental branches, causes thrombosis due to sludging, as seen in the advanced stage of primary pulmonary hypertension [6] or in Eisenmenger's syndrome. This thrombus can easily be seen on angiography and on computed tomography (CT) scans, and is the consequence of the disease and not its cause. Hence, thrombectomy (without endarterectomy), as suggested by some authors [7, 8], does not result in a reduction of pulmonary vascular resistance.

Histological examination of the material removed during endarterectomy reveals a true cast of the vascular tree, covered with elastic fibrin and not a simple thrombus.

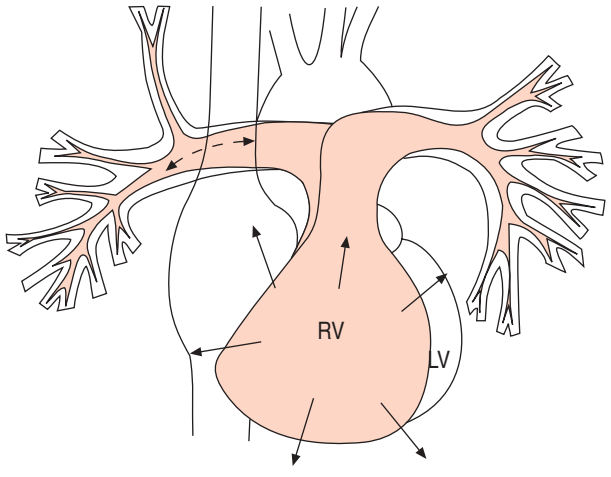

Fig. 1.–This drawing shows right ventricular (RV) distension as well as compression of the left ventricle (LV) due to pulmonary emboli. The lumen of pulmonary arteries, which is initially normal, gets tighter and eventually disappears in the segmental branches.

Pathophysiological mechanisms

Relationship between obstruction and pulmonary vascular resistance

The extent of vascular obstruction is a major determinant of the severity of pulmonary hypertension in patients with CTEPH. In most cases, >40% of the pulmonary vascular bed is obstructed. Worsening of pulmonary hypertension may involve recurrent thromboembolism or *in situ* thrombosis, and remodelling of small distal pulmonary arteries in the nonoccluded areas, similar to that encountered in primary pulmonary hypertension. Several lines of evidence support this hypothesis: 1) a low correlation between the extent of central obstruction and the degree of pulmonary hypertension [9]; 2) documented progression of pulmonary hypertension in the absence of recurrence of thromboembolism [9]; 3) evidence of redistribution of the pulmonary blood flow after thromboendarterectomy from the nonoccluded to the newly endarterectomised areas as a result of the greater vascular resistance in the nonobstructed vascular bed [10]; 4) histopathological evidence of pulmonary vasculopathy with medial hypertrophy, intimal thickening and plexiform lesions [11]; and 5) persistent pulmonary hypertension despite satisfactory central thromboendarterectomy in ~10% of patients. This latter group of patients may represent an overlap syndrome with primary pulmonary arterial hypertension and CTEPH. Interestingly, the current authors recently observed two cases of pulmonary hypertension in two families. The first one was related to CTEPH, and was cured by surgical thromboendarterectomy, whereas the other was due to primary pulmonary arterial hypertension and was successfully treated with prostacyclin infusion (data not shown).

A substantial component of the persistent postoperative pulmonary hypertension may also arise from a distal pulmonary vasculopathy that develops in the occluded pulmonary vascular bed. These alterations have been reproduced in the postobstructive pulmonary vascular bed of animal models by ligation of one pulmonary artery [12]. This postobstructive pulmonary vasculopathy includes development of precapillary bronchial-to-pulmonary vascular anastomoses, pulmonary arterial remodelling and abnormal pulmonary artery vascular reactivity with dysfunction of the pulmonary endothelium [13]. In these animal models the contralateral lung remains normal. Similarly, recent histopathological studies have suggested that, in the advanced form of CTEPH, the distal vasculopathy affected the obstructed pulmonary vessels more than the nonobstructed vessels [14].

In a piglet model of chronic left pulmonary artery obstruction, the present authors have recently shown progressive improvement of pulmonary vascular resistance after reimplantation of the left pulmonary artery, reflecting the slow regression of the structural and functional alterations that had developed in the pulmonary vascular bed during lung ischaemia (data not shown). Similar progressive long-term improvement in pulmonary vascular resistance has been observed in humans with CTEPH after thromboendarterectomy [15]. Thus, long-term improvement in pulmonary vascular resistance after pulmonary thromboendarterectomy may reflect the regression of arteriopathical changes in resistance vessels in both the formerly obstructed and nonobstructed parts of the lung. Lastly, a recent study of patients with the most severe form of CTEPH suggested that chronic prostacyclin administration prior to thromboendarterectomy

decreases pulmonary vascular resistance and improves postoperative course [16]. The authors speculate that prostacyclin therapy may not only provide benefit by dilating pulmonary vessels but also by inhibiting vascular growth and small vessel remodelling.

Cause of thrombi formations

Pulmonary thromboembolism or *in situ* thrombosis in CTEPH may be initiated or aggravated by abnormalities in either the clotting cascade, endothelial cells or platelets, all of which interact in the coagulation process. Platelet abnormalities and biochemical features of a procoagulant environment within the pulmonary vasculature support a potential role for thrombosis in initiation of the disease in some patients. In most cases, however, it remains unclear whether thrombosis and platelet dysfunction are a cause or consequence of the disease. Therefore, it is interesting to compare the abnormalities of coagulation seen in patients with primary pulmonary arterial hypertension and CTEPH, to differentiate whether they are causes or consequences of the pulmonary hypertensive process.

Coagulation takes place on the surface of platelets and endothelial cells. The intrinsic and extrinsic coagulation pathways converge with the binding of activated factors X and V to the cell surface endothelium or platelet to form the prothrombinase complex. This enzyme converts circulating prothrombin into thrombin. Thrombin is responsible for the conversion of fibrinogen into fibrin and releasing fibrinopeptide A. Under normal conditions the procoagulant functions of the endothelial cells appear to be expressed to a minimal degree, while their anticoagulant and profibrinolytic properties predominate. Resting endothelium produces a variety of clotting factors, such as von Willebrand factor, tissue factor and factor V, but in inactive form and in small quantities. These cells also possess potential binding sites for additional clotting factors, including factor IX/IXa, factor X, thrombin and possibly fibrinogen, but the system is down-regulated in such a way that intravascular clotting is normally avoided. The prominent anticoagulant mechanisms include inactivation of factors IIa, IXa and Xa by the heparin-antithrombin III system, inactivation of factors Va and VIIa by the thrombomodulin-thrombin-protein C-protein S system, and inhibition of platelet aggregation by prostacyclin and nitric oxide. The baseline profibrinolytic component includes the elaboration and surface-binding of tissue-plasminogen activator and of plasminogen activator inhibitor type 1. Activation of endothelial cells results in surface expression of tissue factor, down-regulation of the thrombomodulin-thrombin-protein C-protein S system, down-regulation of the profibrinolytic system and a reduction in the release of nitric oxide and prostacyclin. These events favour the participation of endothelium in procoagulant and antifibrinolytic reactions.

There is biological evidence that intravascular coagulation is a continuous process in patients with all forms of pulmonary arterial hypertension. Indeed, the blood level of fibrinopeptide A, which reflects thrombin activity, is markedly elevated in all patients with pulmonary arterial hypertension [17]. Whether these changes are a result of genetic deficiencies of antithrombotic pathways, or dysfunction of endothelial cells and/or platelets secondary to the pulmonary vascular injury, can be questioned.

Antithrombin, protein C, protein S, factor V and factor II mutations, and phospholipid-dependent antibody. The current authors did not find any differences in the frequencies of inherited thrombotic risk factor abnormalities, such as antithrombin, protein C, protein S, factor V and factor II mutations, between the 99 patients studied with pulmonary arterial hypertension and control subjects [18]. Interestingly, the prevalence of all hereditary risk factors studied in the 147 patients with CTEPH was higher, although not significantly different, than that of patients with pulmonary arterial hypertension or controls [18]. This result is in agreement with the previous studies from MOSER *et al.* [3] and LANG *et al.* [19]. This low prevalence of hereditary thrombotic risk factors in CTEPH is unexpected since most of these patients experienced thrombosis. In contrast, there was a very high prevalence of phospholipid-dependent antibodies; close to 10% of patients with pulmonary arterial hypertension and 20% of patients with CTEPH [18]. Positive antibody testing included phospholipid-dependent antibodies measured by immunological method and lupus anticoagulant measured by clotting method [18]. In pulmonary arterial hypertension, the positive patients (10%) were positive for only one test, whereas the positive patients with CTEPH (20%) had higher titre antibodies and were positive for the two tests. This finding brings into question the involvement of these antibodies in the pathogenesis of pulmonary arterial hypertension. Indeed, the presence of phospholipid-dependent antibodies in this setting could reflect an autoimmune process and/or an endothelial dysfunction. In contrast, the prevalence of phospholipid-dependent antibodies in CTEPH is much higher than usually reported in thrombotic patients, and the presence of lupus anticoagulant with high titre antibodies may, therefore, increase the tendency to thrombosis.

Procoagulant activity and fibrinolytic function of the pulmonary endothelium. Several studies have demonstrated that procoagulant activity and fibrinolytic function of the pulmonary endothelium are altered in patients with pulmonary arterial hypertension.

Most studies have found an increase in blood concentration of plasminogen activator inhibitor type 1 with inadequate fibrinolytic activity of the plasma in pulmonary arterial hypertension [20]. Results of measurements of tissue plasminogen activator are more controversial; some authors reported an increase, whereas others reported a decrease or no change [20]. Interestingly, similar fibrinolytic defects were reported in patients with CTEPH [20]. Taken together, these findings suggest that a blunted fibrinolytic response of the pulmonary endothelium developed secondary to the pulmonary vascular disease.

In a small number of patients, pulmonary arterial hypertension occurs in conditions that predispose to thrombosis; these conditions include splenectomy and haemoglobinopathies, *e.g.* sickle cell disease, thalassemia, spherocytosis, presence of phospholipid-dependant antibodies, essential thrombocytosis or polycythaemia vera. The incidence of these prothrombotic disorders is, however, more frequent in patients with CTEPH than primary pulmonary hypertension [20].

In conclusion, with the exception of the high prevalence of phospholipid-dependent antibodies, the abnormalities seen in coagulation or fibrinolysis are similar in patients with CTEPH and pulmonary arterial hypertension, suggesting that these changes are as a result of nonspecific dysfunction of endothelial cells and/or platelets secondary to the pulmonary hypertension.

Diagnosis of chronic thromboembolic pulmonary hypertension

CTEPH is usually diagnosed during assessment for dyspnoea, right heart failure, syncopal episodes during effort,

stress angina, haemoptysis or chest pain [21]. Diagnosis is rarely made during regular, long-term follow-up of patients presenting with acute pulmonary emboli. Occasionally, the disease is uncovered by the presence of abnormally high pulmonary arterial pressure at the time of an acute embolus, suggesting the diagnosis of previous unrecognised emboli.

Clinical history reveals a suspicion of previous pulmonary emboli [22] or deep venous thrombosis of the lower limbs in more than half of the patients with CTEPH. However, in a fair number of cases the past medical history is not relevant. Occasionally, patients mention a history of "pneumonia" or "pleuresy" that is secondarily attributed to pulmonary emboli. Clinical examination may reveal a systolic murmur in the pulmonary field that is suggestive of stenosis of the pulmonary artery branches. A heart murmur secondary to tricuspid regurgitation is also often present. Chest radiography can show an enlarged heart and filling of the aortopulmonary window, suggestive of pulmonary hypertension.

Diagnostic tools

Two investigations orient to the diagnosis [23]:

Echocardiography

Trans-thoracic echocardiography allows diagnosis of pulmonary hypertension and demonstrates the degree of right ventricular distension as well as the compression of the left ventricle. In addition, the pressures in the right atrium and the degree of tricuspid regurgitation are shown, and other cardiac anomalies are excluded. A right to left shunt through a reopening of the foramen ovale is sought during the echocardiogram by intravenous injection of microbubbles in saline (fig. 1).

Pulmonary perfusion scan

A pulmonary perfusion scan is shown in figure 2. Lung perfusion scans reveal segmental, large and usually bilateral defects, whereas the ventilation scan is mostly homogenous. It is essential to differentiate between primary pulmonary hypertension and CTEPH. In primary pulmonary hypertension, the lung perfusion scan is usually near normal or shows patchy nonsegmental defects. However, there is a major and rare exception, veno-occlusive disease, which can be confused with CTEPH [24]. A lung perfusion scan does not, however, reveal the severity of the disease, the prognosis or predict the response to various types of therapy [25].

Evaluation and surgical selection

Right heart catheterisation

Right heart catheterisation is performed during pulmonary angiography. It is essential as it provides unbiased data for the quantification of severity of the disease and postoperative prognosis.

Pulmonary angiography

Pulmonary angiography confirms the diagnosis of chronic pulmonary thromboembolic disease [26–28] and determines the chance of success of endarterectomy according to the location of disease, proximal *versus* distal. Ideal angiographical techniques are required, showing the entire arterial tree of each lung captured in the same frame. Angiography must include serial pictures, from the injection of dye into the pulmonary artery to the venous return in the pulmonary veins, including parenchymography to show the nonperfused areas.

The right pulmonary arterial tree is studied in anterior and lateral views. The mediastinal arteries are well seen on anterior views. Lateral views are required in order to visualise the intermediary arterial trunk and its branches (dorsal to the right upper lobe, middle lobe, superior segment, as well as the four segmental branches of the basilar segments).

The left pulmonary arterial tree is studied in an anterior and left anterior oblique or lateral view in order to differentiate the lingular territory from the basilar segments.

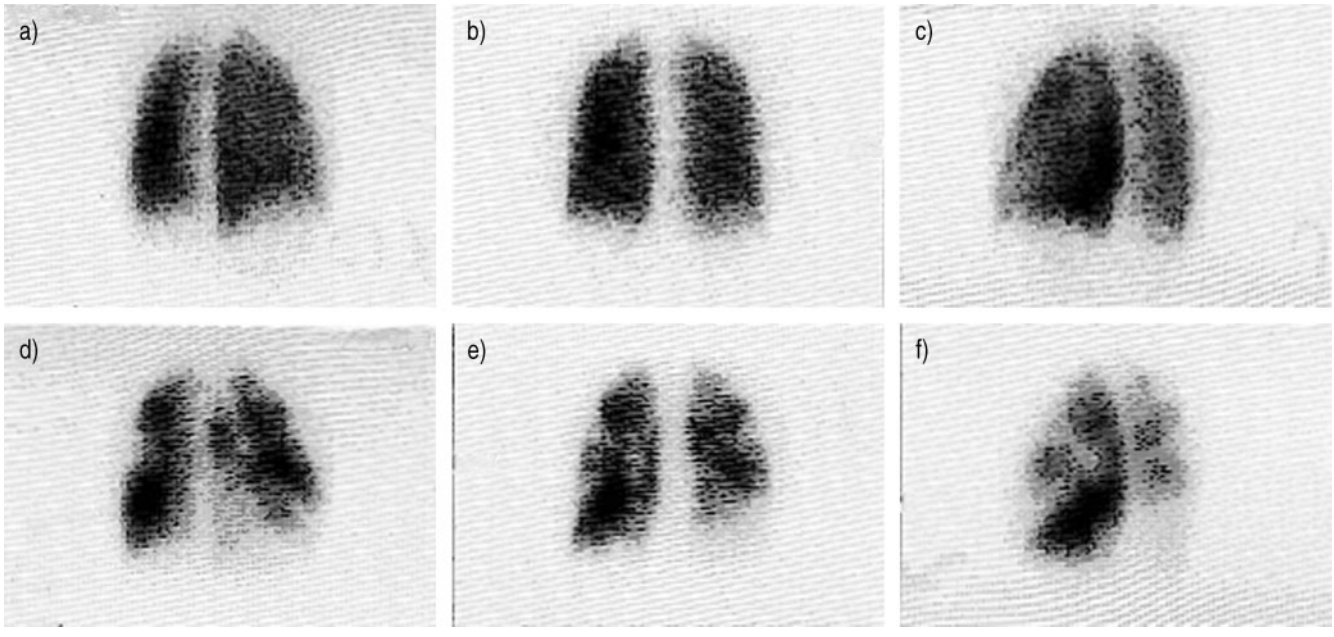

Fig. 2. – Perfusion and ventilation nuclear scan showing homogeneous ventilation (a–c) and segmental defects in the perfusion scan (d–f).

Interpretation of angiography in cases of CTEPH is more difficult than in acute pulmonary emboli, which appears as a discrete intraluminal defect. There are five angiographic features that are characteristic of chronic thromboembolic disease (fig. 3) these are as follows: 1) a sacciform stop from obstruction of the pulmonary artery which when located at the origin of the right or left pulmonary artery, can be mistaken for pulmonary agenesis; 2) transverse bands resembling *chordae* tethering the arterial lumen; 3) irregularities of the arterial wall; and 4) abrupt change in the calibre of the artery; and 5) absence of segmental or lobar arterial branches with parenchymal defects in these territories.

Helical computed tomography

High-resolution helical CT can show obstruction or a reduction in the diameter of the arterial lumen when compared to the external diameter of the pulmonary artery. Very proximal lesions on the right or left pulmonary arterial trunks are well characterised, whereas the distal lesions downstream from the first branches are rarely visible. Hence, a normal CT scan does not exclude the diagnosis of chronic pulmonary thromboembolic disease and does not preclude the possibility of pulmonary endarterectomy.

CT scanning is essential to exclude rare conditions that may present with similar symptoms, such as chronic pulmonary thromboembolic disease. This differential diagnosis includes fibrous mediastinitis, mediastinal carcinoma and sarcoma of the pulmonary artery. CT scans also delineate artheromatous calcifications of the pulmonary artery in long-standing disease, which increase the technical difficulty of the endarterectomy [29]. In the current authors′ view, third generation CT scanners are much better at delineating obstruction of segmental branches and showing the development of the bronchial circulation, which is indicative of the obstructive aetiology seen in pulmonary hypertension (fig. 4).

Differential diagnoses

Thromboembolic pulmonary hypertension is the most common aetiology of obstructive pulmonary hypertension. Other causes of pulmonary arterial obstruction, be it extrinsic, endoluminal or parietal, must, however, be excluded.

Angiosarcoma of the pulmonary artery

This primary malignancy of the pulmonary artery usually has its origin in the pulmonary artery trunk. It surrounds the pulmonary valve and progressively extends towards branches of the pulmonary artery, most often bilaterally. The diagnosis is suggested by slowly progressive symptoms without acute episodes or previous thromboembolic disease, the presence of a large quantity of endoluminal material proximally (particularly in the main pulmonary artery), extraluminal extension of the tumour and by the detection of pulmonary regurgitation on echocardiography secondary to diseased leaflets. One of the series of eight patients recently operated on by the present authors presented with a positron emission tomography (PET) scan positive for activity along the pulmonary artery. While the diagnosis may be suspected based on these findings, it must be confirmed at the time of surgery, on pathological analysis of a frozen section. Surgical treatment of rare cases of unilateral angiosarcoma requires a pneumonectomy extending into the bifurcation of the pulmonary artery. Treatment of bilateral diseases requires

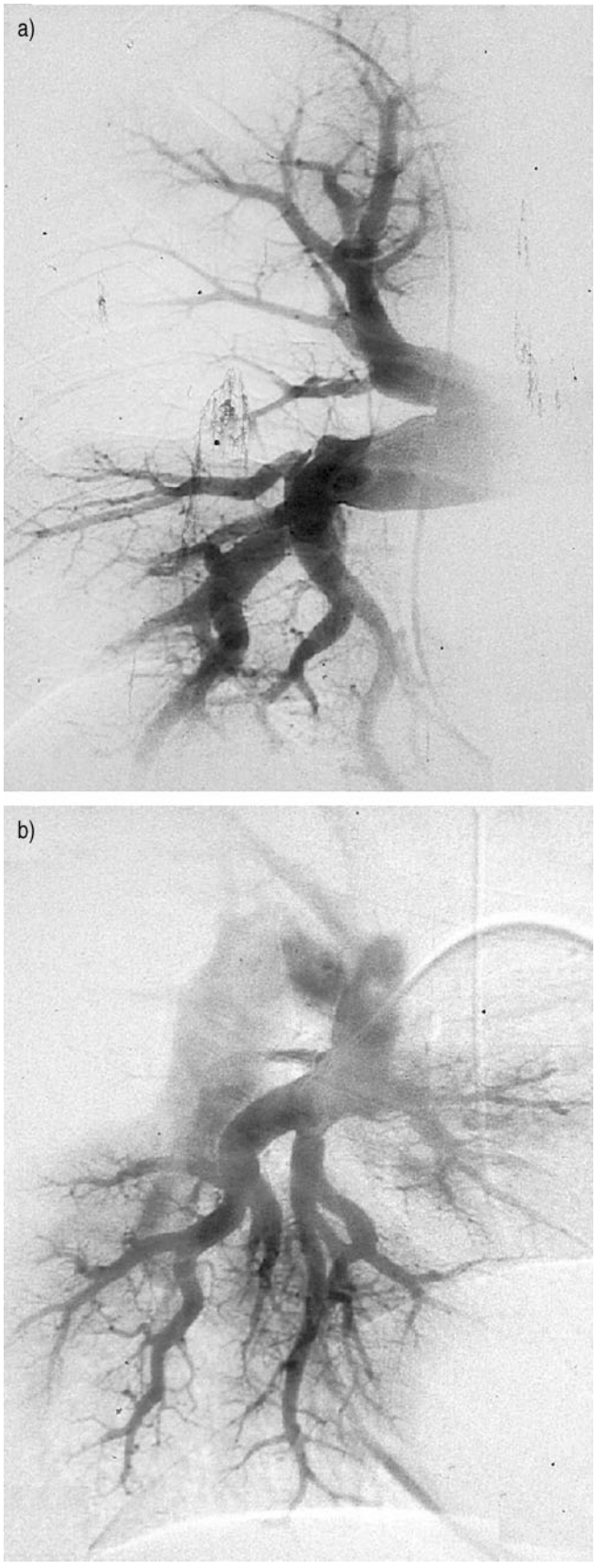

Fig. 3. – Right pulmonary artery angiography in a patient with chronic pulmonary hypertension. Note the typical postembolic angiographic stenosis on the a) anterior view and b) on the lateral view.

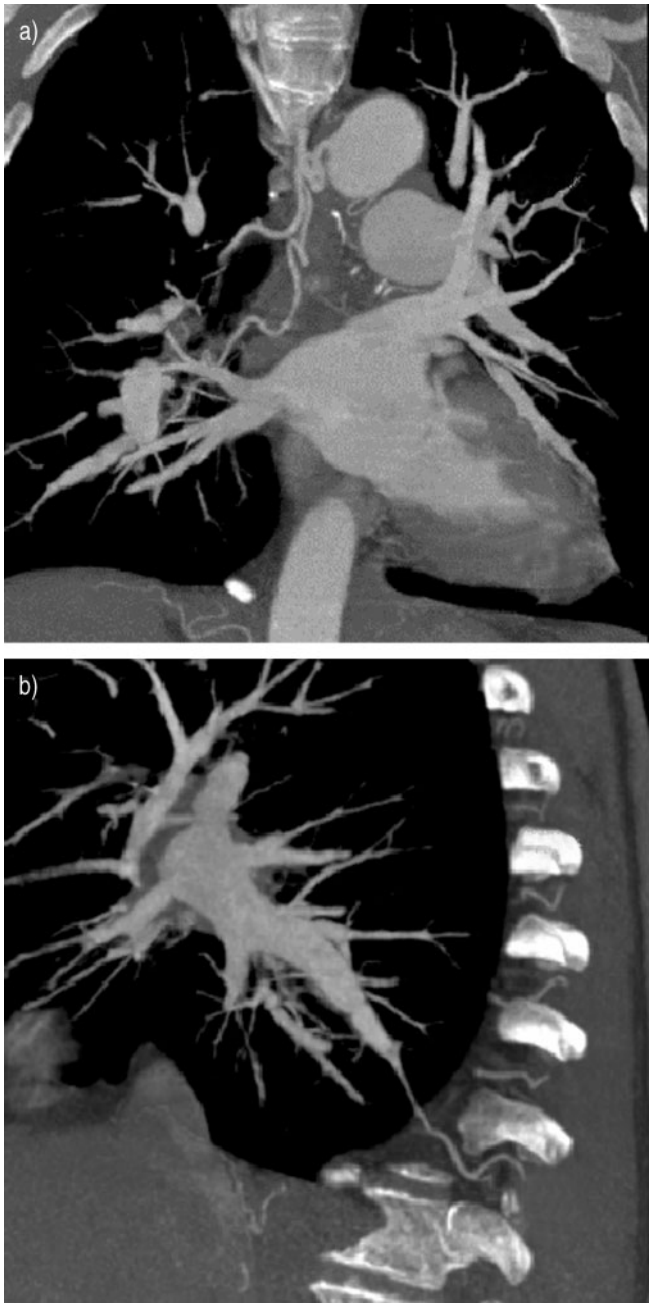

Fig. 4. – Helical computed tomography of a patient with chronic pulmonary hypertension, showing the development of bronchial arteries arising from the aorta (a), and the communication between intercostal arteries and pulmonary arteries through pleural adhesions created after pulmonary embolism (b).

an endarterectomy of each of the pulmonary arteries with a resection of the pulmonary arterial trunk and of the pulmonary valve, followed by the placement of a vascular interposition graft between the right ventricular outflow tract and the pulmonary artery with a valvular homograft or a prosthetic valve (fig. 5).

Tumour emboli into the pulmonary artery

Renal cancer, thyroid cancer, testicular cancer and uterine cancer among others may release emboli to the pulmonary arteries, which become obstructed either by embolisation or

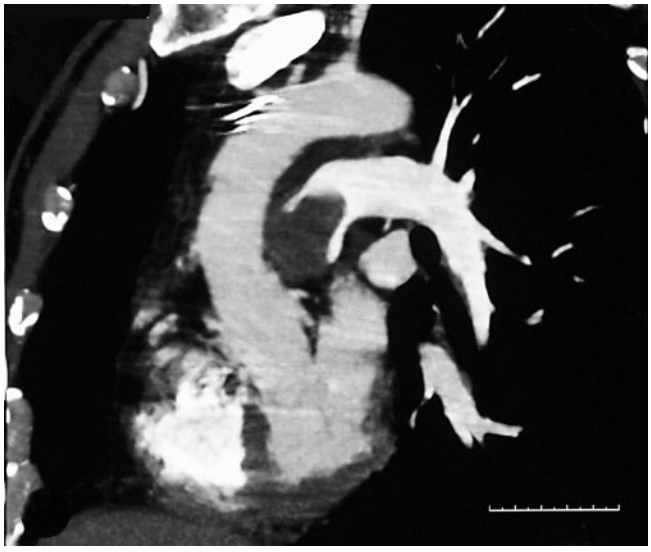

Fig. 5. – Helical computed tomography scale of a patient with an angiosarcoma of the main pulmonary artery involving the pulmonary valves. Scale bar=5 cm.

by direct extension of the tumour through the *vena cava* and right heart chambers. Uterine leiomyomatosis deserves a special mention; a benign tumour with vascular tropism that can lead to invasion of the inferior *vena cava* and obstruction of the pulmonary arteries. Similarly, testicular tumours may continue to grow as a teratoma into the inferior *vena cava* and the pulmonary arteries after response to chemotherapy and normalisation of tumoral markers (fig. 6).

Hydatic emboli

Hydatic cysts of the liver can migrate spontaneously or during hepatic surgery into the inferior *vena cava* and the pulmonary arteries, causing downstream thrombosis and obstruction of a large part of the pulmonary vascular bed. The diagnosis of this form of pulmonary hypertension is aided by the clinical context and positive serology (fig. 7).

Pulmonary arteritis

Pulmonary hypertension secondary to Takayashu′s or Behcet′s arteritis presents typical lesions on angiography with false aneurysm of the pulmonary artery associated with *in situ* thrombosis. These lesions are associated, respectively, with arteritis in the supra-aortic trunks or with cutaneomucosal lesions. They may be improved by dilatation if there is a principal lesion with a gradient.

Fibrous mediastinitis

Fibrous mediastinitis can closely resemble chronic thromboembolic disease on angiography and on CT scan, and can cause severe pulmonary hypertension. The essential difference is that fibrous mediastinitis encases other structures, such as the superior *vena cava*, oesophagus, phrenic and recurrent nerves, pulmonary veins possibly with postcapillary hypertension, and the bronchi. Bronchoscopy plays an important role in the diagnosis by detecting widening of the carinal bifurcations and obstruction of the bronchial ostia. Attempted resection of the perivascular gangue has been unsuccessful and the only currently available treatment of

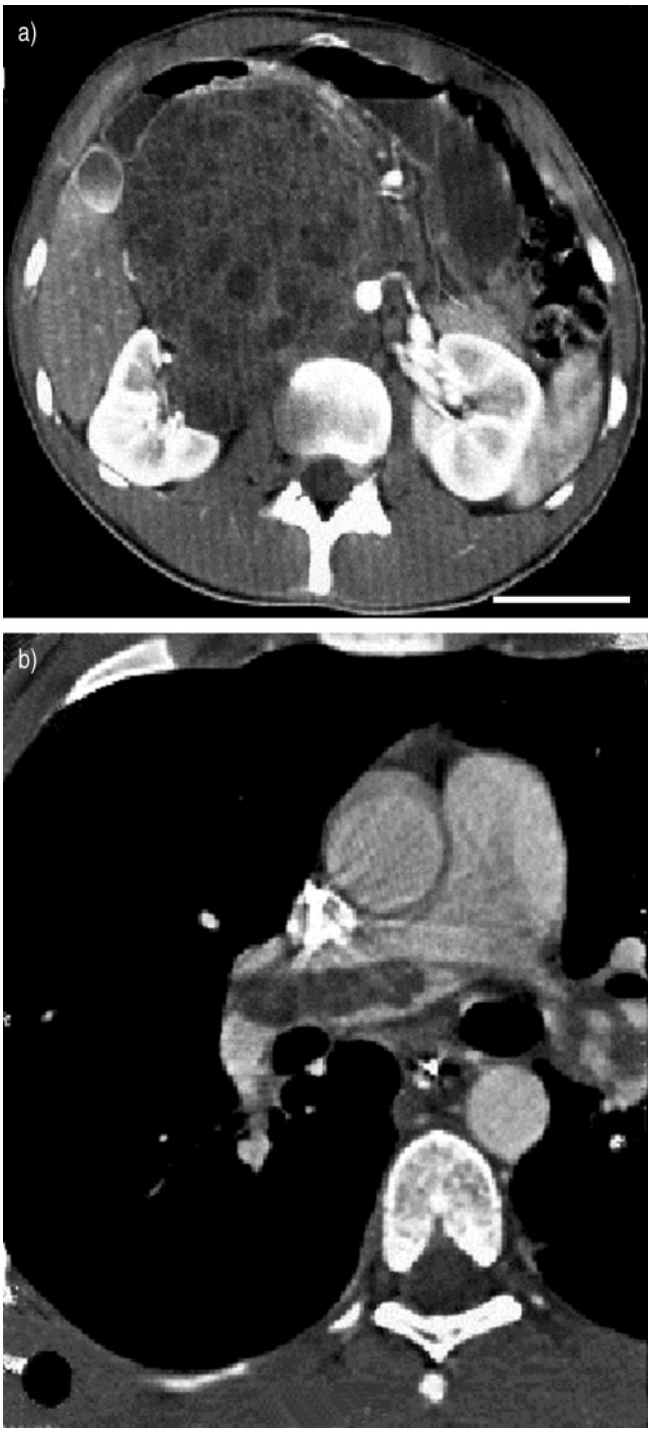

Fig. 6. – Helical computed tomography of a patient with a growing teratoma from a testis cancer after chemotherapy. The tumour arises from retroperitoneal nodes (a) and goes up to both pulmonary arteries throughout the right chambers of the heart (b). Scale bar=5 cm.

fibrous mediastinitis are angioplasty or placement of a vascular shunt between the pulmonary arterial trunk and the distal pulmonary artery beyond the obstruction, within the lung fissure if the distal vascular bed remains patent (fig. 8).

Video-assisted pulmonary endarterectomy

Endarterectomy is the treatment of choice for CTEPH whenever possible, as near-normal cardiopulmonary function

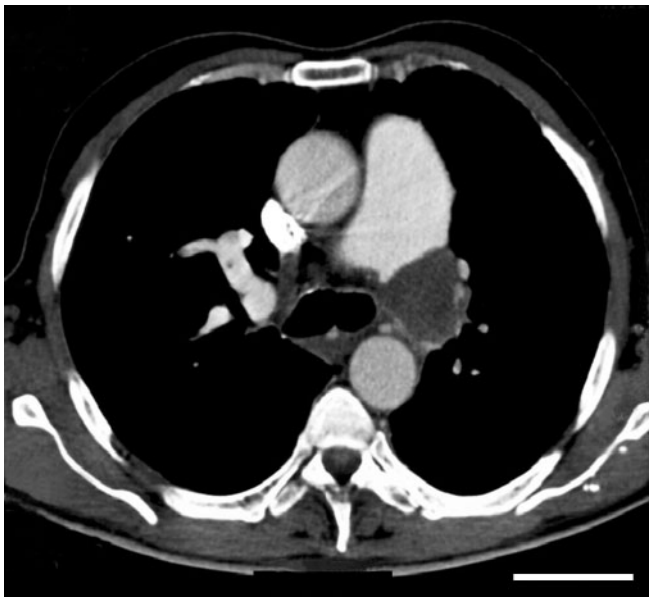

Fig. 7. – Helical computed tomography showing the occlusion of the left pulmonary artery by hydatic cysts which have migrated from the liver. Scale bar=5 mm.

can be restored with anticoagulation as the only long-term therapy.

Technique of pulmonary endarterectomy

Pulmonary endarterectomy is performed during circulatory arrest, removing obstructive material from each pulmonary artery, and its lobar and segmental branches, (20–30 branches in total), and is the only way to reduce pulmonary vascular resistance by at least 50% [2, 5, 30–36]. The intraluminal material is, at this stage, composed of fibrous tissue

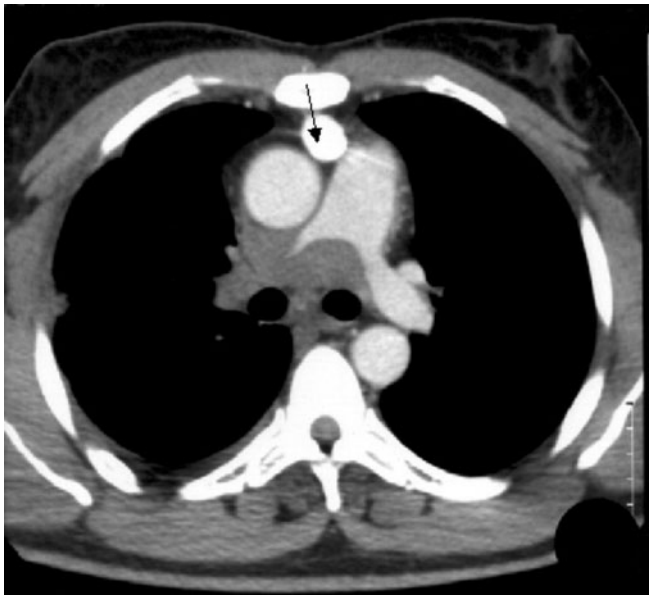

Fig. 8. – Helical computed tomography showing fibrosing mediastinitis involving and obstructing the right pulmonary artery and stenosing the left pulmonary artery. In the anterior mediastinum a polytetrafluorethylene superior vena cava by-pass graft is still apparent in the patient 5 yrs after surgery (arrow).

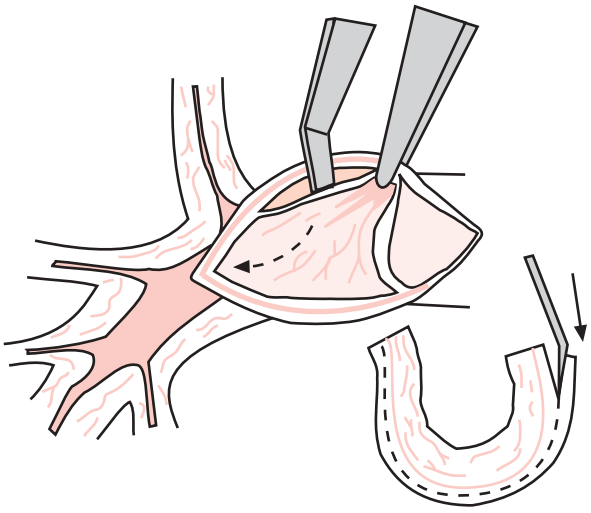

Fig. 9. – Endarterectomy is started by the identification of the correct plane in the media of the posterior surface of the pulmonary artery.

inseparable from the intima and, therefore, inaccessible to thrombectomy or dilatation. Therefore, a true endarterectomy is required, starting at the level of right and left pulmonary arteries inside the pericardium and progressively extended distally into each of the branches of the pulmonary arterial tree (fig. 9).

Patients suffering from this disease quickly develop a systemic hypervascular neovascularisation from bronchial and intercostal arteries through residual adhesions between the chest wall and the visceral pleura due to previous emboli. The development of a systemic-to-pulmonary artery circulation at the precapillary level results in significant back bleeding from the pulmonary artery at the time of endarterectomy. The only way to stop this bleeding, which continuously fills the pulmonary artery and obstructs the surgical field, is to arrest the systemic circulation under conditions of deep hypothermia, between 18–20°C. In order to limit the time of circulatory arrest, the cardiopulmonary bypass is stopped only after identification of the correct plane for endarterectomy. After completion of endarterectomy on the first side, the extra-corporeal circulation is resumed for ~15 min before the contralateral endarterectomy is performed. This sequential technique with intermediate reperfusion limits the cumulated period of circulatory arrest to <55 min.

The operation is performed entirely through a median sternotomy and through the pericardium without having to open the pleura or to dissect the pulmonary artery outside the pericardium. This approach avoids the dissection of highly vascular tissue surrounding blood vessels and pleural adhesions.

Pulmonary endarterectomy is truly an endovascular procedure [29] that can benefit from video technology. The angioscope illuminates the lumen of the pulmonary artery and the videocamera allows the distal arterial divisions to be viewed better, displayed on screen for the surgeon and surgical assistants. The operation is divided into four parts.

First stage. The first stage is to perform a median extrapleural sternotomy, a vertical pericardiotomy, to initiate cardiopulmonary bypass between the superior and inferior vena cava and the aorta. Profound cooling is immediately started and as the patient's temperature is falling, the superior *vena cava* is completely dissected in order to access the right pulmonary artery. A vent is inserted through the right superior pulmonary vein into the left ventricle, decompression of the left heart is essential because of the significant venous return from the hypervascularised bronchial arteries through the pulmonary veins. Once the body temperature has reached 20°C, the ascending aorta is clamped and crystalloid cardioplegia is injected into the aortic root. A longitudinal arteriotomy is performed along the anterior aspect of the right pulmonary artery in the segment between the aorta and the superior *vena cava*. The endarterectomy is started by the identification of the correct plane in the media of the posterior surface of the pulmonary artery. This plane is developed circumferentially in the mediastinal artery and its branches, and then in the intermediary arterial trunk and its branches. Cardiopulmonary bypass is then stopped to work in bloodless vessels and the endarterectomy plane is pursued into the lobar and segmental branches distal to the subsegmental branches of the basilar segments (fig. 10).

Stage two. As the arteriotomy is closed, the patient is reperfused with cardiopulmonary bypass for ~15 min, the time necessary to close the arteriotomy with a back and forth running suture of 6–0 Prolene. Cardioplegia is repeated at this stage.

Stage three. An arciform arteriotomy is made on the left pulmonary artery and the endarterectomy is performed according to the same principles as the right side.

Stage four. The patient is reperfused during closure of the left arteriotomy, the cardiac chambers are de-aired, the aorta is unclamped and the patient is slowly rewarmed to 37°C.

The postoperative course may be complicated by the risk of postreperfusion pulmonary oedema causing hypoxaemia and occasionally requiring prolonged mechanical ventilation. Other complications include right heart failure secondary to persistently high pulmonary pressure, arteriotomy rupture during a spike of pulmonary hypertension, nosocomial pneumonia, haemoptysis, which is easily treated by embolisation, or phrenic nerve palsy, which can prolong dependence on mechanical ventilation. Rethrombosis of an endarterectomised area rarely occurs, particularly in unilateral obstruction, and justifies anticoagulation as soon as possible after surgery. The patients often continue to improve their haemodynamic parameters for several months after the operation.

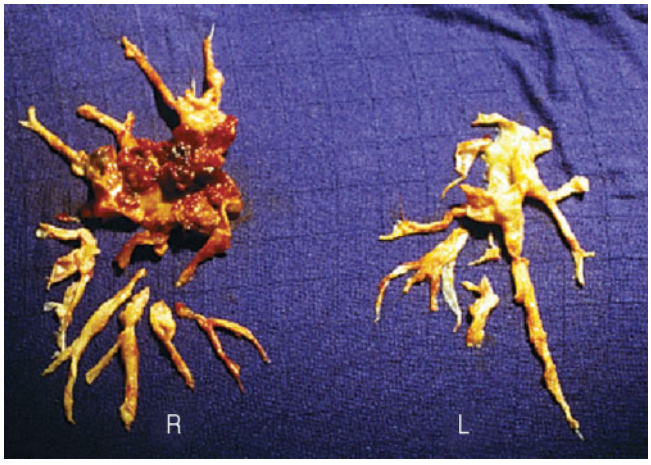

Fig. 10. – Material removed by endarterectomy from the right (R) and left (L) pulmonary artery.

Indications, contraindications and limits of endarterectomy

Indications for this operation are directly related to the technical feasibility (depending on the patient's anatomy) and to the experience of the surgeon. The lesions must start at the level of the pulmonary artery trunks or at the level of the lobar arteries in order to find a suitable endarterectomy plane. Good results are achieved in almost all cases where the haemodynamic compromise corresponds to the degree of vascular obliteration. In contrast, in severe, long-standing cases where resistances are disproportionately high to the degree of anatomic lesions seen on angiography, pulmonary arteritis is usually present in the nonobstructed territories. This group of patients should be selected for endarterectomy only if one predicts that the surgical procedure can reduce the pulmonary resistance by 50% [29, 37]. If that goal is not achieved, a higher postoperative mortality rate occurs (table 1 and 2).

In fact, the most difficult aspect of patient selection is the differentiation between secondary obstruction due to macroscopic pulmonary emboli and primary pulmonary hypertension, with upstream thrombosis in the distal part of the segmental arteries. Pulmonary hypertension by micro-emboli secondary to intravenous catheters appears similar to the latter. Patients presenting with chronic thromboembolic disease should undergo surgery as soon as the diagnosis is made, before the development of an arteritis in the nonobstructed territories and severe pulmonary hypertension. The risk of surgery is low at this early stage of the disease and the future development of arteritis is avoided.

Experience and results of video-assisted pulmonary endarterectomy

Between 1996 and April 2003, 275 video-assisted cases of pulmonary endarterectomy for thromboembolic pulmonary hypertension have been performed at the Marie-Lannelongue Hospital (Le Plessis Robinson, France), with an annual accrual of 20% each year (table 3). This series consists of patients presenting with very high mean pulmonary vascular resistance (table 4) and in whom the short- and mid-term prognosis was poor.

The operative mortality was 10.9% and was due, for the most part, to patients with persistent pulmonary hypertension after endarterectomy. Within this group were those patients who had thromboembolic disease secondary to permanent catheters, pace-maker wires and ventriculo-atrial shunts, and patients with probable primary pulmonary hypertension associated with thrombosis of segmental and sub-segmental branches (table 5).

It is interesting to note that the mortality rate from this operation is closely related to the haemodynamic severity. For pulmonary resistance <900 dynes·s·cm^{-5}, the mortality rate was 4%, and increased to 10% in patients with resistance between 900–1,200 dynes·s·cm^{-5}, and to 20% for higher resistance (fig. 11). More detailed analysis revealed that the mortality is related to the degree of anatomic obstruction rather than to the resistance. Indeed, a patient with very high pulmonary resistance and a low anatomic obstruction is at high risk, whereas one with the same pulmonary resistance but with proximal anatomic obstruction presents with a

Table 1. – Successful predictive factors of pulmonary endarterectomy

Predictive factors
Prior history of pulmonary embolism and/or deep vein thrombosis
"Honeymoon"
Angiographic lesions located proximally in pulmonary arteries or lobar branches
Pulmonary resistance correlated with anatomic obstruction
Developed systemic circulation

Table 2. – Risk factors for pulmonary endarterectomy

Risk Factor
Absence of history of acute thromboembolic event
Presence of indwelling catheter (pace maker, *etc.*)
Distal lesions in angiography and computer tomography scan
Haemodynamics too altered compared to angiographic lesions
Normal bronchial arteries
Myeloproliferative syndrome

Table 3. – Distribution of the 275 patients operated on from 1996 to April 2003

Year	1996	1997	1998	1999	2000	2001	2002	April 2003
Patients n	14	34	30	32	40	46	57	22

Table 4. – Profile of the 275 patients operated on from 1996 to April 2003

Parameter	
Median age yrs	55 (15–80)
Mean PAP mmHg	54±12.3
Cardiac index·mn^{-1}·m^{-2}	2.2±0.61
Total pulmonary resistance dynes·s·cm^{-5}	1206±61

Table 5. – Cause of death for the patients operated on from 1996 to April 2003

Cause of death	Patients n
Persistent pulmonary hypertension	17
Alveolar haemorrhage	1
Pulmonary oedema	3
Pneumopathy	3
Other	4

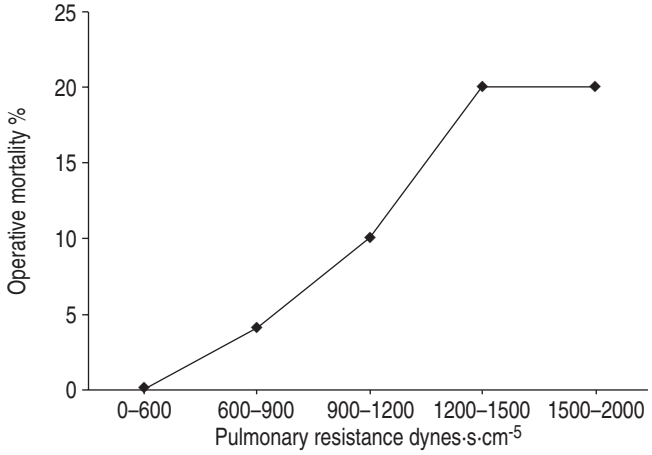

Fig. 11. – Operative mortality according to the pulmonary resistance.

low risk (table 1 and 2). For the last 40 patients of the series, the authors excluded operating on patients with the very distal form of thomboembolism associated with severe haemodynamic alterations, and the mortality rate dropped to 5%.

After surgery, considerable diminution of pulmonary resistance is usually seen, with a significant improvement in the functional state of the patient.

Pulmonary transplantation

The number of pulmonary transplantations performed is markedly lower than liver, kidney or heart transplantations. The lungs, in contrast to other transplantable organs, are in contact with the external milieu through the tracheobronchial tree and are at risk of pneumonia during donor resuscitation.

Recipient selection criteria

Recipient selection criteria at the Marie-Lannelongue Hospital currently includes: age <55 yrs; the absence of mechanical respiratory insufficiency due to scoliosis; absence of phrenic paralysis; and absence of recent neoplastic disease or other potentially life-threatening diseases.

Transplantation for pulmonary arterial hypertension is indicated for patients with a life expectancy of <1 yr, consistent with a functional status of NYHA stage III or IV. Recent worsening of dyspnoea and haemodynamic parameters, such as a right atrial pressure of >12 mmHg, pulmonary arterial pressure >60 mmHg, a cardiac index <2.2 $L \cdot min^{-1} \cdot m^{-2}$ or indexed pulmonary resistance >30 UI are indications for transplant.

Types of pulmonary transplantation

Single lung, bilateral lung or heart-lung transplantations have been performed in patients suffering from end-stage pulmonary hypertension. The latter is the current authors' preferred approach, because it gives greater pulmonary reserve to the patients who may suffer bronchiolitis obliterans and infection. The transplanted heart is adapted to the pulmonary circulation, which helps to avoid left ventricular dysfunction or right ventricular outflow tract obstruction secondary to hypertrophic cardiomyopathy, both of which may be seen after bilateral lung transplantation performed for pulmonary hypertension.

An advantage of bilateral lung transplantation is that the donor heart can be transplanted into another recipient awaiting heart transplantation alone. Compared to heart-lung transplantation, however, bilateral lung transplantation patients can potentially develop bronchial ischaemia extending into the distal bronchial tree and leading to anastomotic dehiscence or stenosis. Lung and heart-lung transplantation for CTEPH is often associated with severe bleeding due to the multiple neovascularised pleural adhesions and to the development of significant bronchial arterial circulation from the intercostal and bronchial arteries [38].

Regardless of the operation, pulmonary transplantation is always associated with: 1) low donor rate that will never match the number of patients awaiting transplantation; 2) postoperative mortality rate of ~20%; 3) life-long immunosuppression; 4) succeptibility to bacterial, viral and fungal infections, and post-transplant lymphoproliferative disease associated with prolonged immunosuppression; and 5) episodes of acute and, even more worrisome, chronic rejection leading to bronchiolitis obliterans and respiratory failure.

Results of pulmonary transplantation

In the series of 101 pulmonary transplants performed for pulmonary hypertension at the Marie-Lannelongue Hospital between 1986–2002, 18 were for CTEPH. There were 70 heart-lung, 28 bilateral and only three single lung transplants. The perioperative mortality was ~20% and was not significantly different between the operation performed (table 6).

A total of 35 patients developed bronchiolitis obliterans of whom 18 died. Seven patients developed a malignancy, five of which were lymphomas. Two patients underwent re-transplantation: one patient had a single lung transplant 10 yrs after heart-lung transplantation; and the other underwent heart-lung transplant 14 yrs after single left lung transplantation. The actuarial 5-yr survival is 52% and 12 patients are currently alive >10 yrs after transplantation (fig. 12).

Conclusions

Pulmonary endarterectomy in chronic thromboembolic pulmonary hypertension is more than just an alternative to lung transplantation, it is the treatment of choice whenever it is possible. Pulmonary endarterectomy has the advantage of a lower operative risk and long-term cure with only anticoagulation therapy required in the long term. The complications of immnosuppression are avoided, as is the risk of developing bronchiolitis obliterans and respiratory failure associated with lung transplantation.

Pulmonary endarterectomy is a complex operation requiring considerable experience. The results depend on the experience of the surgical team as well as on the location of the obstruction and the severity of the disease. When performed at an early stage of the disease, before severe pulmonary arteritis occurs, the operative risk is relatively low.

Table 6. – Operative mortality after heart-lung, double lung and single lung transplantation for pulmonary hypertension

	Transplantation			Totals	Mortality %
	Heart-lung	Double lung	Single lung		
Patients n	70	28	3	101	
Primary pulmonary arterial hypertension					20.5
Patients n	59	21	3	83	
Death	10	6	1	17	
Postembolic pulmonary arterial hypertension					16.7
Patients n	11	7		18	
Deaths	3	0		3	
Mortality %	18.6	21.4	33		Global 19.8

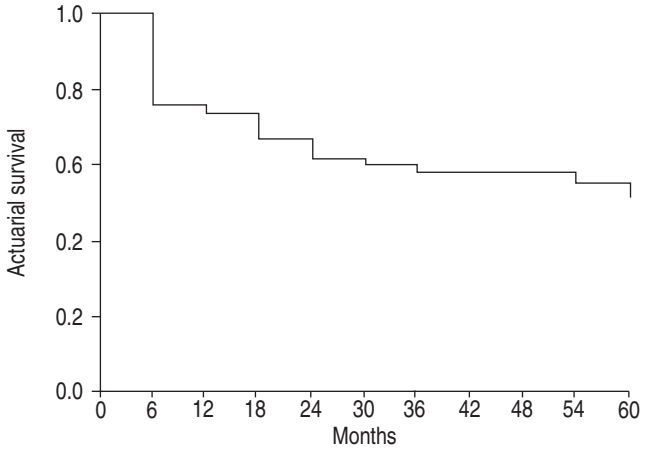

Fig. 12. – Actuarial survival in a series of 101 patients transplanted for pulmonary hypertension.

Improvement in the quality of radiological imaging is likely to allow improvement in the selection of candidates for this operation in the near future.

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