Anaesthesia management for pulmonary endarterectomy
Roland Demeyere, Marion Delcroix and Willem Daenen

Purpose of review
Options for the surgical treatment of chronic thromboembolic pulmonary hypertension are either lung transplantation or pulmonary endarterectomy. Pulmonary endarterectomy is considered permanently curative and the treatment of choice. The procedure dramatically improves functional status and provides an excellent immediate and long-term survival, much better than transplantation. Pulmonary endarterectomy, until recently performed in only a few highly specialized centres, is now spreading worldwide with good results. This review will focus on the understanding of the pathophysiology of the disease and on recent advances in assessment and treatment strategies.

Recent findings
Recent data reinforce the thromboembolic nature of chronic thromboembolic pulmonary hypertension, and have shown that the disorder is more common than was thought and remains underdiagnosed. There has recently been a remarkable surge in the understanding of the mechanisms involved in the pathogenesis of pulmonary hypertension. Advances in diagnosis, surgical techniques, preoperative treatment, and perioperative management have improved the prognosis of this debilitating disease. New information about pretreatment and medical treatment with prostanoids and endothelin receptor antagonists is now available.

Summary
Pulmonary endarterectomy can be successfully performed in selected centres using a multidisciplinary approach involving the specialties of surgery, pulmonary medicine, cardiology, radiology, anaesthesiology and critical care medicine. The largest risk factor remains the degree of operability related to a high pulmonary vascular resistance caused by permanent changes in the pulmonary vascular bed. Early operation is now recommended to prevent these irreversible changes. Further investigations are warranted to establish the role of new drugs in surgical patients with chronic thromboembolic pulmonary hypertension.

Keywords
anaesthesia management, chronic thromboembolic pulmonary hypertension, pulmonary embolism, pulmonary hypertension, pulmonary thromboendarterectomy

Introduction
Chronic thromboembolic pulmonary hypertension (CTEPH) is a term that has been proposed by Kenneth Moser from the University of California, San Diego (UCSD). It is an insidious and often unrecognized disease that has been ignored for a long time. Diagnosis is often delayed or overlooked. CTEPH is associated with considerable morbidity and mortality. In general, prognosis is poor: the 5-year survival in patients with a mean pulmonary artery pressure (mPAP) of more than 40 mmHg is only 30%, and that in patients with a mPAP exceeding 50 mmHg is only 10% [1–3,4,5].

CTEPH is no longer an autopsy curiosity, and the disease is being recognized with increasing frequency largely as a result of the pioneering work of the group at UCSD. Patients with CTEPH may be asymptomatic for several years (the 'honeymoon period’) before they present with recurrent acute or progressive exertional dyspnoea, chronic non-productive cough, atypical chest pain, tachycardia, syncope and even cor pulmonale.

Important advances in diagnosis, surgical techniques, and postoperative management have greatly improved the prognosis of this debilitating disease.

In selected patients, pulmonary endarterectomy (PEA) offers the possibility for a substantial improvement in symptoms, haemodynamics and prognosis. The optimal reduction in pulmonary vascular resistance caused by chronic pulmonary embolism is obtained by bilateral pulmonary thromboendarterectomy (PTE) with the removal of occlusive material in all bronchopulmonary
segmental arteries that are partly or completely obstructed.

Although the operation historically has been described as ‘pulmonary thromboendarterectomy’, it is better termed ‘pulmonary endarterectomy’ [2**,6**].

At the third World Symposium on Pulmonary Arterial Hypertension, held in 2003 in Venice, Italy, there was a clear consensus that patients with pulmonary hypertension caused by chronic thromboembolic disease should be assessed for thromboendarterectomy, and it was proposed that the name of this operation should be changed to ‘pulmonary endarterectomy’ because by the time of surgery thrombi are found in few cases.

Successive improvements in operative techniques have been developed over the past few decades. Since 1990 probably more than 2500 PTE procedures have been reported worldwide. UCSD has the greatest experience. More experienced centres worldwide are now carrying out successful surgery in patients with severe distal disease as well as proximal disease, a technically more challenging procedure. The surgical mortality rate for the procedure ranges from less than 5% (UCSD) to 24% at the relatively few institutes who perform this procedure.

Some patients are still not referred for operation because of a lack of awareness both of the prevalence of the disease and the effectiveness of surgical therapy [7**]. Over the past few years chest physicians, cardiologists, cardiothoracic surgeons and cardiac anaesthesiologists have shown increasing interest in this disease because of the development of new techniques and therapies that have improved the outcome and quality of life of patients and because of the challenging approach.

Classification of pulmonary hypertension

Traditionally, pulmonary hypertension has been classified as being primary or secondary. The nomenclature and a clinical diagnosis classification of pulmonary hypertension, proposed at the World Health Organization Symposium on Primary Pulmonary Hypertension in 1998 in Evian, France, divides pulmonary hypertension into five distinct categories. According to these criteria CTEPH was classified as class 4: pulmonary hypertension caused by chronic thrombotic or embolic disease. This category includes either CTEPH caused by proximal organized clot in the major pulmonary arteries, which can benefit from PEA, or more peripheral emboli or thrombi that are indistinguishable from thrombotic lesions observed in primary pulmonary hypertension (PPH) and can be treated with chronic pulmonary vasodilator therapy.

A revised clinical classification with some minor modifications was proposed at the third World Symposium on Pulmonary Arterial Hypertension held in Venice in 2003 [6**]. This diagnostic classification of the various forms of pulmonary hypertension was found to be helpful in communicating about individual patients and in standardizing diagnosis and treatment.

A functional classification with four classes of functional assessment (classes I–IV) established by the World Health Organization and the New York Heart Association (NYHA) was also proposed to quantitate exertional intolerance [6**].

Incidence

The incidence of CTEPH is very difficult to determine. This disease, initially considered to be rare, is being diagnosed more and more frequently and is clearly more common than was previously thought.

Its incidence after pulmonary embolism is not well documented. After acute pulmonary embolism, most thrombi resolve spontaneously or with thrombolytic therapy, and most patients are treated with warfarin afterwards [8]. An article in the New England Journal of Medicine by Fedullo et al. [9] estimated that CTEPH occurs in 0.1–0.5% of cases of acute non-fatal embolism, but in a recent article [10**], the cumulative incidence of symptomatic CTEPH after an acute episode of pulmonary embolism without previous venous thromboembolism was found to be 1% at 6 months, 3.1% at one year, and 3.8% at 2 years of follow-up [11**]. Women are affected more frequently than men. Most patients have bilateral involvement. Unilateral disease is only rarely observed.

In a recent study, Blauwet et al. [12**] evaluated surgical specimens from PEA and reviewed the medical histories from 54 patients (2003): 52% had a history of deep venous thrombosis (DVT), 78% had a history of pulmonary embolus, 44% had both, 28% had coagulation abnormalities, and 15% had autoimmune or haematological disorders.

Pathogenesis

The pathogenesis of CTEPH is still unclear, but the third World Symposium on Pulmonary Arterial Hypertension in 2003 was prompted by a remarkable surge in the understanding of the mechanisms involved in the pathogenesis of pulmonary hypertension (Table 1).

After massive acute pulmonary embolus, most survivors resolve their emboli. However, in some individuals, thromboemboli do not resolve and the thrombus becomes organized and forms endothelialized, fibrotic obstructions of the pulmonary vascular bed, including the major branches. Areas unaffected by occlusive thrombi
Table 1. Possible causes of chronic thromboembolic pulmonary hypertension

<table>
<thead>
<tr>
<th>Possible Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of DVT</td>
</tr>
<tr>
<td>Evidence of pulmonary embolus</td>
</tr>
<tr>
<td>Evidence of both DVT and pulmonary embolus</td>
</tr>
<tr>
<td>Pulmonary arteriopathy – pulmonary vascular remodelling in the vascular bed</td>
</tr>
<tr>
<td>Decreased expression of prostacyclin synthase leading to impaired prostacyclin biosynthesis</td>
</tr>
<tr>
<td>Coagulation abnormalities – thrombophilia</td>
</tr>
<tr>
<td>Autoimmune or hematological disease</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
</tr>
<tr>
<td>Previous splenectomy, permanent IV catheters, ventriculo-atrial shunts, chronic inflammation</td>
</tr>
<tr>
<td>Antiphospholipid syndrome (anticardiolipin antibodies, lupus anticoagulant)</td>
</tr>
<tr>
<td>Elevated plasma levels of factor VIII</td>
</tr>
<tr>
<td>Decreased plasma thrombomodulin concentration</td>
</tr>
<tr>
<td>Increased lipoprotein (a)</td>
</tr>
<tr>
<td>Increased readiness of circulating neutrophils to respond with inflammatory mediators generation</td>
</tr>
</tbody>
</table>

DVT, deep venous thrombosis; IV, intravenous.

may develop secondary pulmonary hypertension changes of the pulmonary vascular bed.

After a period of months to years, during which the patient has no clinical symptoms (‘honeymoon period’), dyspnoea at exertion starts to develop and the clinical deterioration parallels the loss of right ventricular functional capacity.

The strong association between DVT and pulmonary embolism supports the assumption that CTEPH develops when acute pulmonary emboli fail to resolve. However, a majority of patients with CTEPH lack a clear history of either DVT or pulmonary embolism.

A prospective, long-term follow-up study was recently conducted to assess the incidence of symptomatic CTEPH in consecutive patients with an adequately treated episode of pulmonary embolism but without previous venous thromboembolism, and this was found to be ‘not so rare after all’ [10**,11**].

Repeated periods of embolism that do not resolve may eventually occlude enough pulmonary vasculature to cause hypertension. Pathologically, these cases are marked by such characteristic lesions as eccentric intimal thickening and webs and septa within the arterial lumen. Pulmonary vascular remodelling occurs in the vascular bed of patients with CTEPH and contributes to the prognosis of the disease. The pathogenesis and molecular mechanisms of vascular remodelling causing CTEPH have so far not been well clarified.

It has been hypothesized that in-situ thrombosis and pulmonary arteriopathy are common causes of vascular occlusion leading to CTEPH, and that (acute) pulmonary embolism is unlikely to be a common cause of this disease. A decreased plasma thrombomodulin concentration may reflect pulmonary vascular endothelial dysfunction, leading to altered anticoagulant and fibrinolytic function in CTEPH [13]. Coagulation abnormalities are often present, as well as autoimmune (lupus anticoagulant) or various haematological disorders.

CTEPH has been associated with the presence of congenital or acquired thrombotic risk factors. According to a large series [6**], 15–30% of patients with a diagnosis of CTEPH present a positive result for thrombophilia, the presence of lupus anticoagulant being the abnormality most frequently found. Colorio et al. [14] recently determined the prevalence of thrombophilic factors in a prospective study in 24 consecutive patients.

In contrast to what was previously published, 75% of the patients were found to have at least one thrombophilic risk factor, which was antiphospholipid antibodies in 50% of cases. The presence of antiphospholipid antibodies (lupus anticoagulant or anticalidolipin antibodies) and elevated plasma factor VIII was the abnormality most frequently found [15]. Hyperhomocysteinemia, true protein S deficiency, protein C deficiency, activated protein C resistance, antithrombin III deficiency, prothrombin gene G 20210A mutation, and the factor V Leiden mutation were also found. Some had clinical evidence of heparin-induced thrombocytopenia (HIT), although no HIT is reported in CTEPH without lupus anticoagulant. Some patients disclosed more than one thrombophilic abnormality.

Mechanisms leading to a vasculopathy (endothelial dysfunction, vascular remodelling) similar to that seen in PPH are not well understood at present but provide a rationale for the consideration of medical therapy with prostaglandins and endothelin-antagonists in some patients before some definitive surgery [16**].

Heart failure caused by CTEPH appears to generate a pronounced inflammatory response with a release of pro-inflammatory and anti-inflammatory cytokines (IL-6, IL-10 and TNF-α) [17]. Increased IL-6 levels may be responsible for the severe vasoplegia during the early postoperative course.

Postoperatively pulmonary vasculopathy may regress after revascularization of the chronically obstructed pulmonary artery, as shown by Fadel et al. [18] in a piglet model of chronic pulmonary artery obstruction.

The pathogenesis and molecular mechanisms of vascular remodelling causing CTEPH have so far not been well clarified, but current studies in laboratories may provide insight into the molecular pathogenesis of CTEPH.
The biosynthesis of prostacyclin may be impaired, with a decreased expression of prostacyclin synthase observed in the lung vasculature of patients with pulmonary arterial hypertension (PAH) and the biosynthesis of prostacyclin was found to be impaired in CTEPH, but this seems not to be genetically determined by the PGIS gene [19].

A recent study by Rose et al. [20] demonstrated that the circulating neutrophils from patients with PPH and CTEPH possess an enhanced readiness to respond with inflammatory mediator generation (respiratory burst, elastase secretion, lipid mediator synthesis).

Increased levels of plasma lipoprotein(a), a genetically determinant risk factor for atherosclerosis and thrombosis, have been found in patients with CTEPH.

In CTEPH, plasma monocyte chemoattractant protein 1 is upregulated in response to increased pulmonary vascular resistance (PVR), resulting in large and small vessel remodelling of the pulmonary arteries [21].

Circulating levels of endothelin 1 are increased, but ETB receptor gene expression also seems to be affected by selective upregulation [22]. Human angiopoietin gene expression is upregulated and correlates with the severity of pulmonary hypertension in these patients [23].

**Diagnostic evaluation of patients with chronic thromboembolic pulmonary hypertension**

The diagnostic process is now more clearly defined than before, with consensus reached on an algorithm of various investigational tests and procedures to ensure that an accurate diagnosis of CTEPH can be reached and to exclude other causes of PAH (Fig. 1) [24].

**Clinical manifestations**

CTEPH can be a difficult diagnosis to establish, typically requiring a high index of suspicion on the part of the clinician when challenged with a patient reporting exertional dyspnoea. CTEPH is usually diagnosed during an assessment for exertional dyspnoea, right heart failure, syncopal episodes during effort, stress angina, haemoptysis or chest pain. In a fair number of patients, the past medical history is not relevant [7**,25].

The diagnostic evaluation of pulmonary hypertension serves three purposes: (1) to confirm the presence and to determine the severity of pulmonary hypertension; (2) to determine its etiology; and (3) to determine if a surgical correction is possible. The diagnostic evaluation of patients with CTEPH includes echocardiography, chest radiographs, pulmonary function tests, ventilation/perfusion scanning, right heart catheterization, pulmonary angiography, spiral computed tomography, coagulation testing, and eventually magnetic resonance imaging (MRI) (Table 2).

**Electrocardiography**

Electrocardiography sometimes presents no specific features, but may consist of right ventricular hypertrophy or strain with right axis deviation greater than 90°, complete or incomplete right bundle branch block pattern, and ST-segment abnormalities. Signs of right ventricular overload appear to have the potential to aid in diagnosing CTEPH in patients who underwent an acute embolic event in the past [26].

**Chest radiography (X-ray)**

The chest radiograph is often normal in the early stages, but may show abnormalities later on: an enlarged right heart, filling of the aortopulmonary window, suggestive of pulmonary hypertension, clear lung fields with paucity of vascularization in some areas and enlarged central pulmonary vessels.
Table 2. Recommended evaluation (screening) examinations before anaesthesia in patients with chronic thromboembolic pulmonary hypertension: diagnostic strategies

<table>
<thead>
<tr>
<th>Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>Chest radiography</td>
</tr>
<tr>
<td>Arterial blood gases</td>
</tr>
<tr>
<td>Blood analysis (clotting diathesis)</td>
</tr>
<tr>
<td>Pulmonary function tests (mechanics – diffusion capacity – 6 min walking capacity)</td>
</tr>
<tr>
<td>Ventilation–perfusion (V/Q) lung scintigraphy</td>
</tr>
<tr>
<td>Echocardiography</td>
</tr>
<tr>
<td>Examination for DVT (contrast venography, venous ultrasonography)</td>
</tr>
<tr>
<td>Pulmonary angiography</td>
</tr>
<tr>
<td>Pulmonary angiography</td>
</tr>
<tr>
<td>Chest CT scanning (helical contrast-enhanced – spiral CT)</td>
</tr>
<tr>
<td>(high-resolution CT scan)</td>
</tr>
<tr>
<td>MRI (magnetic resonance angiography – cine magnetic resonance – phase contrast magnetic resonance)</td>
</tr>
<tr>
<td>Coronary angiography</td>
</tr>
</tbody>
</table>

CT, Computed tomography; DVT, deep venous thrombosis; MRI, magnetic resonance imaging.

Pulmonary function tests

Patients generally have normal or slightly restricted pulmonary mechanics. The diffusion capacity is often reduced and may be the only abnormality, but pulmonary function tests are also necessary to exclude obstructive or restrictive intrinsic pulmonary parenchymal disease as the cause of pulmonary hypertension. They include a spirometry, lung volumes and diffusing capacity, arterial blood gas determinations, exercise oximetry and an assessment of the functional status (6-min walk test, NYHA/World Health Organization functional status).

Echocardiography

Transthoracic echocardiography is usually one of the first tests to show abnormalities in the right ventricular–pulmonary vascular coupling: right ventricular dilatation and hypertrophy, right atrial enlargement, septal hypertrophy or flattening of the interventricular septum or paradoxical movement, moderate to severe tricuspid regurgitation as a sign of increased pulmonary artery pressure, and an interventricular septum shift with compression of the left ventricle [27]. Continuous wave Doppler of the tricuspid regurgitant jet allows an estimation of the degree of pulmonary hypertension by the measurement of the reverse gradient across the tricuspid valve [28]. A non-invasive estimation of right ventricular systolic pressure (RVSP) can be obtained from the Doppler flow profile of tricuspid valve regurgitation using peak jet velocity (TRVP) measured by continuous wave Doppler and right atrial pressure (RAP). The simplified Bernouilli equation, $\Delta P = 4V^2$, is used to obtain the right ventricular to right atrial pressure difference.

$$RVSP = 4(\text{TRVP})^2 + \text{RAP}$$

A right to left shunt through a reopening of the foramen ovale is sought by intravenous injection of microbubbles.

CTEPH may lead to left ventricular diastolic dysfunction despite the absence of previous intrinsic left ventricular disease. A systolic pulmonary artery pressure of 60 mmHg or greater is needed to induce changes in the left ventricular diastolic filling pattern. Transmural flow is consistently abnormal in patients with severe CTEPH. The E/A ratio is also increased post-PEA and varies inversely with mean pulmonary hypertension and directly with cardiac output [29,30].

The right ventricle chamber size can be determined with excellent precision using three-dimensional transthoracic echocardiography [31].

Radionuclide ventilation/perfusion (V/Q) lung scan

This is the essential test for establishing the diagnosis of CTEPH and makes the differential diagnosis with other causes of pulmonary hypertension possible. In idiopathic PAH the radioisotopic ventilation/perfusion scan is usually normal or has a patchy and mottled appearance, in contrast to the multiple punched-out lobar and segmental perfusion defects of CTEPH. The pulmonary perfusion scan reveals segmental, large and usually bilateral defects, whereas the ventilation scan is mostly homogenous. Although very helpful, the V/Q scan may underestimate the degree of vascular occlusion.

In patients with severe unoperated CTEPH, the perfusion scan shows an apparent decrease of segmental flow abnormalities over time, paralleling right ventricular decline, probably because of the progression of secondary vascular changes [32]. A positive V/Q scan, suggestive of CTEPH, should always lead to an additional evaluation.

Cardiac catheterization

Right heart catheterization is usually performed in combination with a pulmonary angiography and provides a direct measurement of the degree of pulmonary hypertension by measuring pulmonary artery pressures and cardiac output. This allows a calculation of the PVR, which is an important measure of operative risk. Blood samples for oxygen saturation are also obtained. The pulmonary artery pressure waveform also contains much more diagnostic information than expected [33–36].

Pulmonary angiography

Pulmonary angiography remains the gold standard for the diagnosis and preoperative evaluation of patients with CTEPH by showing the exact localization and type of pulmonary artery obstructions. Multiple arterial obstructions are seen, showing changes characteristic of chronic embolism, including wells, bands, webs, filling defects, pouches and intimal irregularities, as well as abrupt
‘cut-off’ and narrowed and occluded vessels in the main, lobar or segmental pulmonary arteries.

Five angiographic features are characteristic of CTEPH: sacciform stops from obstruction of the pulmonary artery, transverse bands tethering the arterial lumen, irregularities of the arterial wall, an abrupt change in the calibre of the artery, and the absence of segmental or lobar branches.

In selected patients, pulmonary fibreoptic angioscopy is used to supplement the information obtained from pulmonary angiography, especially with unclear angiographic findings or disproportionately severe PAH with mild angiographic obstructions.

Right and left lateral views are better compared with the anterior–posterior view. Intravascular sonography has also been used.

The combination of right heart catheterization and selective pulmonary angiography is still regarded as the standard of reference with respect to establishing the diagnosis, assessing the severity of disease, and determining the technical feasibility of surgery for CTEPH.

The analysis of pulmonary artery reflection was found to be useful in the differential diagnosis of CTEPH and idiopathic PAH [33,34]. The fractional pulmonary artery pulse pressure in addition to PVR was found to be useful in predicting the outcome of surgery, especially in patients with severe haemodynamic impairment [35].

In 2000, Menzel et al. [27] presented the results of measurements using right heart catheterization and echocardiography in 39 patients before and after undergoing thromboendarterectomy.

Pulmonary artery occlusion pressure waveform analysis may identify CTEPH patients at risk of persistent pulmonary hypertension and poor outcome after PTE. Patients with CTEPH and an upstream resistance value of less than 60% appear to be at highest risk [36].

Pulmonary angiography remains the gold standard for the diagnosis and preoperative evaluation of patients with CTEPH by showing the exact localization and type of pulmonary artery obstructions. Patients over 45 years old must also undergo coronary angiography.

**Computed tomography scanning**

Computed tomography (CT) scanning shows the distribution of typical obstructive pulmonary artery lesions at the main, lobar, and segmental levels and a mosaic pattern of lung attenuation because of regional perfusion differences [37,38]. If negative, it should not obviate the use of pulmonary angiography.

**Helical (spiral) computed tomography scanning**

This is highly sensitive for detecting proximal and sub-segmental thrombi, but fails to yield sufficient quantitative information about the severity of functional impairment. Distal lesions are also poorly visible. Helical CT is more interesting in patients with unilateral obstruction.

CT angiographic evidence of extensive central vessel disease and limited small vessel involvement indicates a favourable surgical outcome after PEA [39].

Cross-sectional imaging modalities such as single or multisector helical CT are becoming increasingly important because they also display the extent of central thromboembolic material.

**Magnetic resonance imaging**

MRI seems to be promising for overcoming the restrictions of CT and digital subtraction angiography [39].

Magnetic resonance angiography using high-field technology and fast imaging techniques is now becoming a helpful non-invasive investigation in CTEPH because the lumen as well as the organized tissue in the wall of the pulmonary artery branches can be depicted, as well as enabling an evaluation of right heart function.

Cine magnetic resonance (functional imaging) and velocity-precoded magnetic resonance assessing maximal peak velocity in the pulmonary artery provide additional information in a non-invasive way. Breath-hold magnetic resonance techniques enable a morphological non-invasive semi-quantitative assessment of pulmonary haemodynamics [40]. This optimized contrast-enhanced magnetic resonance angiographic technique has been proved to be superior even to selective digital subtraction angiography for the assessment and delineation of the proximal extent of organized thrombotic material.

Both CT and MRI are additive to the angiogram. New tools may also enhance predictive accuracy when used in combination with standard testing modalities.

Tests for non-invasive haemodynamic evaluation include transthoracic echocardiography with Doppler, radionuclide or MRI scan and CT scan. Invasive haemodynamic evaluations are right heart catheterization, vasodilator trials, and left heart catheterization (if left heart function is in doubt or coronary artery disease is suggested). Oral anticoagulants must be replaced by heparin for invasive tests. Coronary angiography has to be performed in all
patients more than 45 years old. All patients must be examined for DVT by contrast venography or venous ultrasonography.

**Laboratory tests**

Laboratory tests are generally normal and abnormalities are occasionally encountered. They include routine tests (arterial blood gases and mixed venous oxygen saturation). A search for hyperhomocystinemia and increased uric acid levels is also useful. A thorough screening for thrombophilia in all patients with a diagnosis of CTEPH is recommended.

The following coagulation tests are usually performed: lupus anticoagulant, deficiencies in protein C, protein S, and antithrombin III, the presence of factor V Leiden mutation, HIT test, and antiphospholipid syndrome. A real procoagulant state may be present: 10–20% of patients with CTEPH have a lupus anticoagulant, 5% have inherited deficiencies in protein C, S and antithrombin III. A decreased plasma thrombomodulin level is also found. A connective tissue screen is performed and blood analysed for anticardiolipin antibodies.

**Definition of chronic thromboembolic pulmonary hypertension**

Patients are diagnosed as having CTEPH if they meet the following criteria: a resting mPAP of 25 mmHg or greater with a normal wedge pressure (<12 mmHg) during right heart catheterization and a calculated resting PVR of 300 dynes per s/cm\(^{-5}\), or greater, having symptoms for more than 6 months and with significant changes in lung perfusion scan and pulmonary angiography. Signs of the severity of the disease are listed in Table 3.

**Differential diagnosis**

A differential diagnosis is made with CTEPH and PPH (now replaced with the term ‘idiopathic’ PAH) by means of the ventilation/perfusion scan and by means of an analysis of characteristics of the pulmonary artery pressure waveform and normalized pulse pressures estimated from Doppler ultrasound measurements [33].

Other differential diagnoses have sometimes to be established with an angiosarcoma of the pulmonary artery, tumour emboli into the pulmonary artery (neoplastic embolic pulmonary hypertension), pulmonary arteritis and fibrous mediastinitis.

**Treatment**

The options for surgical treatment are either lung transplantation (which is considered as inappropriate) or PEA (which is permanently curative). Lung transplantation has a significant mortality on the waiting list, and has an inferior prognosis because of continued immunosuppressive therapy (antirejection medication) with associated side-effects (risk of infection and rejection).

The prognosis for untreated pulmonary hypertension is poor, with a 5-year mortality rate of 90% if the mPAP is higher than 50 mmHg. Lung perfusion scintigrams in patients with severe unoperated CTEPH show an apparent decrease in segmental flow abnormalities over time, paralleling right ventricular decline [32].

**Medical therapy**

Some patients are not suitable candidates for definitive surgical therapy and thus have to be treated with medical means only (continuous anticoagulation and pulmonary vasodilators). The benefit of medical therapy is restricted and the prognosis of these medically treated patients is unfavourable. Survival with continued medical therapy is poor.

It was found that pulmonary artery pressure was the most important risk factor in CTEPH. The mPAP proved to be an independent risk factor. Riedel et al. [4] recorded a 20% survival rate over a period of 2 years for patients with mPAPs greater than 50 mmHg. Lewczuk et al. [5], in a study of 49 unselected patients with CTEPH who did not fulfill the criteria or had contraindications for PEA and who were given pharmacological treatment exclusively, found that during a follow-up period ranging from 6 to 72 months (18.7 months on average) 32% of the patients died.

Considerable advances have been achieved in the medical therapy of PAH, but medical therapy is only supportive; surgical therapy is curative. The medical treatment mainly consists of the prevention and treatment of right heart failure and the administration of oxygen. Anticoagulation is indicated in all patients (warfarin: full-dose anticoagulation international normalized ratio: 2.5–3.5). Some patients receive a continuous infusion of epoprostenol [41**–44**]. Iloprost, a prostacyclin analogue, can be administered by nebulization [45,46,47†]. Other drugs such as beraprost, an oral prostacyclin analogue, are still under investigation [41**].
Bosentan, a non-selective endothelin receptor antagonist [48], and sitaxsentan, an endothelin-A selective inhibitor, have been used in patients, but the long-term effects of prostacyclin analogues (iloprost, treprostinil), endothelin-receptor antagonists (bosentan, sitaxsentan), sildenafil and other investigational agents has yet to be determined [41**].

Pretreatment
Some authors have recently suggested a role for the medical therapy of patients awaiting PEA.

Nagaya et al. [42**] reported their experience using continuous intravenous epoprostenol before PEA in patients with severe CTEPH, as defined by a PVR of more than 1200 dynes per s/cm⁵. A 28% decrease in PVR was described, with a decrease in brain natriuretic peptide [42**]. Bresser et al. [44**] found that the most severely impaired patients appeared to derive the greatest benefit.

Olschewski and colleagues [45,46] studied the effects of iloprost, a prostacyclin analogue, in patients with PAH. One study by Kramm et al. [47] found that in patients with CTEPH, the inhalation of iloprost elicited no significant pulmonary vasodilatation before surgery, and even had detrimental effects on systemic haemodynamics. Postoperatively, it significantly reduced mPAP and PVR, and enhanced cardiac index. The inhalation of iloprost was found to be useful to improve early postoperative haemodynamics [48].

A preoperative period of at least 3 months of adequate anticoagulation is advisable and the preoperative placement of an inferior vena cava filter is mandatory [49].

Surgical treatment
The PEA procedure must be distinguished from an acute pulmonary embolectomy for massive pulmonary embolism. PEA, in fact, involves a true endarterectomy [49,50**,51*]. The presence of concomitant microvascularopathy (small-vessel pulmonary vascular disease) or inaccessible distal disease may limit the response to PEA.

The goal of pulmonary (thrombo)endarterectomy is to decrease the extent of pulmonary vascular obstruction, thereby reducing pulmonary arterial pressure and improving cardiac function. PEA results in a significant symptomatic and haemodynamic improvement. Selection for surgery is made on the basis of the degree of incapacity and the degree of pulmonary hypertension.

The indications for surgery are severe pulmonary hypertension (mPAP at least ≥40mmHg), a pulmonary vascular resistance higher than 300 dynes per s/cm⁵, surgically accessible thrombus (the term is no longer appropriate) [49]. The contraindications for surgery are severe co-morbid conditions. The only absolute contraindication to PEA for the UCSD group is the presence of severe underlying lung disease, either obstructive or restrictive.

In 2000, Jamieson and Kapelanski [49] proposed a surgical intraoperative classification system of thromboembolism. They described a method of classification based on the localization and morphology of thromboembolic and vascular wall disease found at the time of operation, with an intraoperative assessment of thrombi and intimal vascular changes encountered. The four distinct types of thromboembolic disease as defined at UCSD are type 1: fresh thrombus in the main-loobar pulmonary arteries; type 2: intimal thickening and fibrosis proximal to the segmental arteries; type 3: occlusions within distal segmental and subsegmental arteries only; and type 4: distal arteriolar vasculopathy without visible thromboembolic disease [49,52]. This classification is useful for predicting patient outcomes after PEA. The operative results correlate with this classification type, and the intraoperative location of thromboembolic disease was found to be a predictor of the postoperative haemodynamic outcome, short-term mortality, and an improvement in tricuspid valve regurgitation [52].

Concomitant surgical procedures that have been performed include closure of patent foramen ovale or atrial septal defect, coronary artery bypass grafting surgery, tricuspid annuloplasty, and thrombus removal.

The operative PEA is considered to be curative and greatly superior to transplantation. PEA can be performed in selected centres with a multidisciplinary approach. In fact, few centres have extensive experience with this procedure. There is undoubtedly also a learning curve for this operation.

PEA is a classic bilateral endarterectomy in which the thrombus, the intimal and part of the adjacent medial layers are carefully dissected with dedicated surgical instruments. PEA is truly an endovascular procedure that can benefit from video technology (video-assisted surgery, video angiography) [1**,2**,49,50**,51*].

PEA is a major cardiovascular procedure requiring full cardiopulmonary bypass (CPB) with two caval cannulae with two periods of deep hypothermic circulatory arrest. Anticoagulation is achieved with the use of porcine intestinal heparin 400 U/kg. CPB is used to cool the patient to allow two periods of circulatory arrest at 20°C, because good visibility is required in a bloodless field without the inconvenience of a copious bronchial blood flow. This allows a complete true endarterectomy
defining an adequate endarterectomy plane in the plane of the media deep into the subsegmental vessels. Surface cooling, the head packed in ice, topical cooling of the heart, and a cooling blanket is also used. Retrograde cerebral perfusion has been advocated in a few centres during total circulatory arrest.

The operation is always bilateral, because most of the time both pulmonary arteries are substantially involved, the approach being performed through a median sternotomy incision avoiding entry into the pleural cavities. PEA is a true endarterectomy and bears little resemblance to pulmonary embolectomy. The surgical techniques have been well described by the UCSD group [2**,9,49].

First an incision is made in the right pulmonary artery. The endarterectomy procedure on one side is usually possible with a 20-min period of circulatory arrest followed by a period of reperfusion and another period of circulatory arrest on the contralateral side via a left-sided pulmonary arteriotomy. Careful dissection and removal of the thromboembolic material leads to significant reductions in pulmonary artery pressure and vascular resistance and a consistent improvement in functional status.

After completion of the endarterectomy, CPB is reinstated and warming is started. Methylprednisolone is administrated and mannitol 20% is given at reperfusion. During the rewarming period a 10% infusion of mannitol and warming is started. Methylprednisolone is continued and warming is started. Methylprednisolone is given at rewarming.

After completion of the endarterectomy, CPB is reinstated and warming is started. Methylprednisolone is administrated and mannitol 20% is given at reperfusion. During the rewarming period a 10°C gradient is maintained between the perfusate and the body temperature. Haemofiltration during bypass is routinely performed in many centres. Other cardiac procedures, such as coronary artery surgery, can be performed during the rewarming period.

Tricuspid annuloplasty is not performed, even when severe tricuspid regurgitation has been documented preoperatively. Right ventricular remodelling occurs in the days after the operation with the return of tricuspid competence [53].

Hagl et al. [54**] recently developed some technical modifications of the originally described PEA. Thirty patients were operated using a modified technique including moderate hypothermic (28–32°C), total CPB and simultaneous selective antegrade cerebral perfusion and balloon occlusion of the bronchial arteries. These technical advances may improve the neurological outcome, control back-bleeding from bronchial arteries, and avoid prolonged rewarming phases [54**]. In some centres retrograde hypothermic cerebral perfusion ('cerebroplegia') is used for brain protection. During the operation the presence of a person familiar with angiographic and CT scan data will be appreciated.

### Anaesthetic management

Before anaesthesia, chronic medical treatment already being administered for pulmonary hypertension and right-sided heart failure should be continued. If already being given, continuous intravenous epoprostenol therapy should be maintained at the same dose. Oxygen therapy by mask is useful for transport to the operating room after premedication, especially in patients with hypoxemia (oxygen saturation <90%) because hypoxemia causes pulmonary vasoconstriction increasing PVR (Table 4).

<table>
<thead>
<tr>
<th>Table 4. Anaesthetic considerations in patient with chronic thromboembolic pulmonary hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preoperative management</strong></td>
</tr>
<tr>
<td>Inferior vena cava filter</td>
</tr>
<tr>
<td>Coumadin stopped and replaced by heparin</td>
</tr>
<tr>
<td><em>Oxygen for transport to the operating room</em></td>
</tr>
<tr>
<td><strong>Induction agents</strong></td>
</tr>
<tr>
<td>Opioids, such as fentanyl and sufentanil</td>
</tr>
<tr>
<td>Muscle relaxant</td>
</tr>
<tr>
<td><strong>Maintenance of anaesthesia</strong></td>
</tr>
<tr>
<td>Opioids</td>
</tr>
<tr>
<td>Muscle relaxant</td>
</tr>
<tr>
<td><strong>Intraoperative medication: management</strong></td>
</tr>
<tr>
<td>Pulmonary vasodilators (nitric oxide, epoprostenol, prostaglandin E1)</td>
</tr>
<tr>
<td>Potentially neuroprotective drugs (thiopentone, diphenylhydantoin, steroids, mannitol 20%)</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
</tr>
<tr>
<td>Two arterial lines, CVP line, volumetric oximetric thermodilution pulmonary artery catheter</td>
</tr>
<tr>
<td>Arterial blood gases, carbon dioxide monitoring (capnography), blood sugar</td>
</tr>
<tr>
<td>Electroencephalogram – SSEPs</td>
</tr>
<tr>
<td><strong>Postoperative management</strong></td>
</tr>
<tr>
<td>Lowest inotropic support and pulmonary artery end-diastolic pressure to maintain adequate cardiac output</td>
</tr>
<tr>
<td>Fluid restriction: aggressive diuresis</td>
</tr>
<tr>
<td>Mechanical ventilation at <em>F</em>&lt;sub&gt;IO2&lt;/sub&gt; to maintain <em>SaO</em>&lt;sub&gt;2&lt;/sub&gt; &gt; 95% and <em>Paco</em>&lt;sub&gt;2&lt;/sub&gt; &lt; 35 mmHg</td>
</tr>
<tr>
<td>Heparin restarted (aPTT 50–60 s)</td>
</tr>
<tr>
<td>Coumadin restarted and heparin stopped at INR 2.5–3.5</td>
</tr>
<tr>
<td>Anticoagulation for life (target INR 2.8–3.5)</td>
</tr>
</tbody>
</table>
| aPTT, activated partial thromboplastin time; CVP, central venous pressure; DVT, deep venous thrombosis; *F*<sub>IO2</sub>, fractional inspired oxygen; INR, international normalization ratio; *Paco*<sub>2</sub>, arterial carbon dioxide tension; *SaO*<sub>2</sub>, arterial oxygen saturation; SSEP, somatosensory evoked potential.
Premedication is performed when necessary with midazolam or lorazepam. Under lorazepam sedation catheters are placed in both radial arteries and in the jugular vein.

The induction of anaesthesia can be risky; cardiac output is generally fixed and low. Most general anaesthetic agents and sedative drugs reduce systemic vascular resistance, which may lead particularly in fixed cardiac output states to decreased systemic arterial pressures and coronary perfusion [55]. After induction, a volumetric flow-directed pulmonary artery thermodilution catheter is advanced with caution into the proximal pulmonary artery for continuous monitoring of cardiac output, pulmonary artery pressure and mixed venous oxygen saturation before CPB. It is then withdrawn into the superior caval vein and later refloated before stopping CPB. Difficulties may be encountered in passing the catheter through the tricuspid valve into the pulmonary artery in some patients with severe pulmonary hypertension. Wedging is avoided.

Insufflation of the pulmonary artery catheter (Swan–Ganz) catheter balloon is contraindicated after PEA because of the risk of suture disruption.

All factors that increase PVR should be avoided (such as hypoxia and hypercarbia), and ventilation and oxygenation should be controlled carefully. The electrocardiogram, electroencephalogram, oesophageal, nasopharyngeal or tympanic, and rectal temperature are monitored. Transoesophageal echocardiography is useful for the diagnosis of patent foramen ovale and for the assessment of right ventricular function. Anaesthesia is induced with etomidate and sufentanil and maintained with a low dose of a continuous infusion of propofol. Other medications include a full dose of aprotinin, cefazolin, prostaglandin E1 and nitric oxide (NO) in some patients. Phenylephrine, ephedrine, or norepinephrine may be needed to sustain systemic blood pressure and the coronary perfusion pressure of the right ventricle. Cooling and warming blankets are placed around the body of the patient.

The operation is performed through a midline sternotomy with deep hypothermia and circulatory arrest. The aorta is cannulated and a bicaval cannulation is performed after heparin 300–400 IU/kg. With the activated clotting time over 400 s, CPB is started, and the patient is slowly cooled to a nasopharyngeal temperature of 15°C. Before the heart arrests, a catheter is inserted to vent the left heart; the aorta is clamped, and the heart is arrested with cold antegrade crystalloid cardioplegia or cold blood retrograde cardioplegia. The myocardial temperature is monitored and the heart is kept at a temperature between 10 and 15°C with intermittent cardioplegia. After reaching 15–20°C, the circulation is arrested, and venous blood is drained into the bypass circuit. The utilization of extracranial cooling by packing the patient’s head in ice or with a special head wrap (the head jacket) is an excellent adjunct to this deep core cooling. Pharmacological interventions for brain protection with barbiturates (thiopentone 500–1000 mg) or phenytoin 15 mg/kg will help to ensure the cessation of electrocerebral activity before circulatory arrest.

Steroids such as methylprednisolone and dexamethasone may help to prevent cerebral oedema, and osmotic agents such as mannitol also help to reduce oedema and are free radical scavengers.

**Surgical technique**

The surgical technique has been described extensively elsewhere [2**,3**,49,50**,51*,56,57]. The whole operation is performed from the pericardium and the pleural space is not entered. A true endarterectomy in the plane of the media is performed. Very good visibility is required in a bloodless field to define an adequate endarterectomy plane, and periods of circulatory arrest are necessary because of excessive bronchial blood flow that is usually present. Dendritically organized thrombi are removed.

Although tricuspid valve regurgitation is often severe, tricuspid valve repair is not performed. Remodelling of the right ventricle occurs within days, with the return of tricuspid competence.

Rewarming takes approximately one hour. During warming a 10°C temperature gradient is maintained between the perfusate and the body temperature and haemofiltration is usually performed. Temporary atrial and ventricular pacing wires and a left atrial catheter are placed. Eventually the infusion of prostaglandin E1 is restarted. The administration of NO at 20–40 parts/million may also be helpful in patients with elevated pulmonary artery pressures. After rewarming, CPB is discontinued. Attention is paid to the ratio of pulmonary and systemic arterial pressures, to cardiac output and to arterial oxygen tension. The arterial carbon dioxide tension is kept below 35 mmHg.

Dobutamine, dopamine and norepinephrine are used for inotropic support if needed. Norepinephrine is preferentially administered via the left atrial catheter. Many patients receive norepinephrine (0.1–0.2 μg/kg per minute through a left atrial catheter) to maintain adequate coronary perfusion pressure for the right ventricle.

The avoidance of positive inotropic catecholamines in combination with non-aggressive mechanical ventilation was associated with a low incidence of reperfusion pulmonary oedema or right heart failure after PTE [58].
Haemostasis is readily achieved and the administration of platelets is generally unnecessary. Some patients who have received previous warfarin therapy need the administration of fresh frozen plasma or coagulation factors.

In the post-bypass period attention must be paid to a careful manipulation of the cardiac loading condition (especially the right heart). A balance is sought between too much and too little preload, a reduction in right ventricular afterload with selective pulmonary vasodilators such as NO, epoprostenol and iloprost. Aggressive diuresis is instituted in the post-bypass period (Table 5).

Postoperative care
In the majority of patients, the postoperative course is characterized by a marked increase in cardiac output, with a concomitant decrease in pulmonary artery pressures and PVR both immediate and sustained.

Patients are generally mechanically ventilated for at least 24 h with a maximal inspiratory pressure maintained below 30 cm of water. The fractional inspired oxygen level is kept as low as possible ensuring an oxygen saturation of over 90%, and the haematocrit is kept high (30–32%) [59,60].

Increased platelet aggregation has been demonstrated postoperatively in CTEPH patients, and the administration of antiplatelet drugs should help to prevent re-thrombosis of the pulmonary arteries after surgery.

Investigators have tried to define the predictors of operative mortality of which the most important were severe pulmonary hypertension (PVR >1100 dynes per s/cm²), pulmonary artery systolic pressure greater than 50 mmHg, and a reduction in PVR of less than 50% after surgery.

Anticoagulation for postoperative venous thrombosis and re-occlusion prophylaxis is started within 4–8 h after surgery using intravenous heparin infusion, with subcutaneous low molecular-weight heparin on the evening of surgery followed by anticoagulation with warfarin (target international normalization ratio 2.5–3.0) as soon as the pacing wires and mediastinal drainage tubes are removed. A life-long anticoagulation is mandatory.

Perioperative mortality occurs almost exclusively during the early postoperative period and still ranges between 5 and 10%, even in centres with a large experience. Specific risk factors that contribute to this early morbidity and mortality are persistent postoperative pulmonary hypertension as a result of inadequate endarterectomy, non-accessible peripheral obstructions or unrecognized small vessel disease, with subsequent right heart failure as well as reperfusion oedema.

Persistent (residual) postoperative pulmonary hypertension can be a major problem. Low-dose inhaled NO therapy can be a major and safe contribution to the management of acute persistent pulmonary hypertension in the postoperative period.

There are only a few studies and only one prospective placebo-controlled trial of NO inhalation after PEA [61,62].

Several clinical trials have demonstrated that medical therapy with intravenous epoprostenol and inhaled iloprost can improve cardiopulmonary functional status in patients with different types of pulmonary hypertension, including those with CTEPH not amenable to surgery [41**,44**,45,46,47*]. The administration of iloprost is six to eight times a day, with a single dose up to 25 μg. Iloprost seems to have a better response rate than NO or prostacyclin. Compared with inhaled NO, iloprost has been described as more potent in selective pulmonary vasodilation, with superior improvement in gas exchange.

Reperfusion pulmonary oedema develops in the majority of patients, but to variable degrees of severity [63,64]. Reperfusion lung injury after PEA is typically a high-permeability lung injury, previously being demonstrated to be neutrophil mediated. Cylexin, an analogue of the carbohydrate structure sialyl-Lewis X, which is expressed on the surface glycoprotein of neutrophils and serving as the ligand for E and P-selectins was found to reduce the incidence of reperfusion lung injury in patients after PTE [65].

Recruitment manoeuvres and high positive end-expiratory pressure have been used in this situation. In some rare cases extracorporeal membrane oxygenation or extracorporeal carbon dioxide removal has been used to overcome this period of life-threatening pulmonary oedema.
arrest may be present in the postoperative period. In the early days of PTE there was a substantial incidence of postoperative delirium [66]. Postoperative confusion is now no more common than with ordinary heart surgery.

Pulmonary haemorrhage may occur. Some case reports have recently been reported [67].

The risk of recurrence after PEA is low, because patients generally have a preoperative placement of an inferior vena cava filter and are treated indefinitely with oral anticoagulants once surgery has been performed. Preoperative PEA can be performed with a perioperative risk comparable with primary PEA, although the improvement in pulmonary haemodynamics seems not to be as favourable [68]. Bilateral primary operation, carefully effectuated, effective caval filtration, and vigilant anticoagulant management would prevent the need for most reoperative PTEs.

Patients of all ages have undergone the surgical procedure with success. PTE for CTEPH may be performed safely in conjunction with other cardiac operations such as coronary artery bypass grafting surgery, foramen ovale closure, mitral valve repair and valve replacement surgery [69].

Short-term results
Successfully performed PTE leads to a significant reduction of right ventricular chamber size and an improvement in systolic function. Brain natriuretic peptide and atrial natriuretic peptide may be considered as markers for the efficacy of PEA [70,71].

The mortality rate for the operation has been reduced steadily and was 4.4% at its lowest in the last 400 patients operated at UCSD.

Long-term results after pulmonary endarterectomy
Long-term follow-up information regarding improvement after PTE was reported by several authors [9]. The most recent update from UCSD of inhospital mortality after PTE was reported in 2004.

Survival was 75% at 6 years or more and 93% were in NYHA class I or II. The mortality rate was 30.6% when the residual PVR was higher than 500 dynes per s/cm⁻5 but only 0.9% when it was below this level. Neither the preoperative severity of pulmonary hypertension nor the degree of cardiac failure influenced the outcome of the operation. PEA resulted in good haemodynamic recovery even in severely compromised patients. Whereas preoperatively 95% of the patients at UCSD were in NYHA functional classes III–IV, postoperatively 95% were in classes I–II [2**].

The efficacy of PEA on haemodynamics and long-term gas exchange has been analysed in some centres. The early postoperative efficacy of PEA was mainly achieved as a result of the reduction in pulmonary hypertension, whereas an improvement in gas exchange was obtained over the longer term [72].

There are three potential options for patients who are deemed non-surgical or high-risk surgical candidates: medical therapy, balloon pulmonary angioplasty, and lung transplantation.

Patients who are not candidates for thromboendarterectomy, and those who suffer from significant pulmonary hypertension after surgery should be considered for lung or heart–lung transplantation.

In individuals with CTEPH who are not surgical candidates, a small number of patients have undergone balloon pulmonary angioplasty, possibly a promising interventional technique, with a long-term improvement in NYHA class and 6-min walking distances [73,74].

Conclusion
Physicians should increase their awareness of the potential for CTEPH in patients who present with dyspnoea after a recent period of pulmonary embolism.

The prevention of recurrent pulmonary embolism would most likely help prevent CTEPH. This could be achieved by proper diagnosis and prompt, adequate treatment of patients with pulmonary emboli, risk-factor modification (e.g. aggressive prophylaxis) and the use of secondary prevention.

Adequate preoperative patient evaluation, selection and pre-treatment, surgical and anaesthetic technique and experience, meticulous postoperative management, and a multidisciplinary approach are the basic prerequisites for a successful PEA.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
** of outstanding interest

Number 10 of the series ‘Advances in pathobiology, diagnosis, and treatment of pulmonary hypertension’. An excellent article concerning many aspects of CTEPH, including pathophysiological mechanisms, diagnostic tools, evaluation and surgical selection. It also presents unique data on 275 video-assisted pulmonary endarterectomy cases performed at the Marie Lannelongue Hospital.

In this paper the authors from the centre with the greatest and best experience in this field have described their single institution experience, and have demonstrated progressive excellence in outcomes of PEA, establishing the gold standard for both surgical mortality and haemodynamic outcomes.
An excellent update on the state of art of the use of new pharmacological therapies in the treatment of PAH.


An excellent update on the state of art of the use of new pharmacological therapies in the treatment of PAH.

In this non-randomized trial the authors report their experience using continuous intravenous epoprostenol as a 'medical bridge' to stabilize high-risk patients before PEA. The idea for this pretreatment was based on the observation that epoprostenol is used to treat other forms of pulmonary hypertension.


A short editorial comment on the article by Nagaya et al. [42] suggesting the necessity for a randomized trial to determine the role of preoperative epoprostenol therapy to improve mortality in high-risk patients undergoing PEA. The authors also suggest the possibility of using new pharmacological therapies, such as prostanoid analogues and endothelin receptor antagonists in the preoperative management of CTEPH.


In this retrospective study in a limited number of nine selected patients out of 246 patients who had to undergo PEA, the clinical and haemodynamic benefit of continuous intravenous epoprostenol treatment before PEA, observed by Nagaya et al. [42], was confirmed. It was also suggested that continuous intravenous treatment with epoprostenol should merit further evaluation for inoperable patients as a medical bridge to transplantation, and in postoperative PEA patients with severe residual postoperative hypertension.


This open-label, observational trial was carried out in 10 patients undergoing PEA. Aerosolized iloprost was administered before surgery and after PEA. Before surgery, no significant pulmonary vasodilation was obtained and there was even a deterioration of systemic haemodynamics. After PEA, iloprost was found to be useful to improve early postoperative haemodynamics.


This paper provides evidence-based recommendations from the American College of Physicians for the selection and timing of surgical and interventional treatments for PAH.


An overview of different interventional and surgical approaches for the treatment of PAH: arterial septostomy, PEA and lung or heart–lung transplantation. Postoperative and long-term follow-up haemodynamic changes in 50 patients after PEA are reported from the University Hospital of Mainz.


This review analyses the factors responsible for tricuspid valve regurgitation after PEA and provides a strategy to predict the small numbers of patients who will not show an improvement in tricuspid valve function after the operation.


The authors describe their experience in 20 patients with some technical modifications of the originally described PEA. It includes moderate hypothermic, total CPB without circulatory arrest and selective antegrade cerebral perfusion and occlusion of the bronchial circulation by an occlusive balloon catheter in the descending aorta. These technical advances have been shown to improve neurological outcomes and to control back-bleeding from bronchial arteries.


In this report from UCSD of three cases of massive pulmonary hemorrhage after PEA, the diagnosis, clinical course, and possible treatments of this potentially fatal complication are discussed.


74 Dillon MB, Herber S, Mayer E, Thelen M. Pulmonary balloon angioplasty of chronic thromboembolic pulmonary hypertension (CTEPH) in surgically inaccessible cases. Rofo Fortschr Rontgenstr 2003; 175:631–634.

This paper presents two surgically inaccessible cases of CTEPH that were successfully treated with balloon pulmonary angioplasty, possibly a promising interventional technique.