Surgical management of chronic thromboembolic pulmonary hypertension

Chronic thromboembolic pulmonary hypertension results from occlusion of the pulmonary vascular bed by non-resolving thromboembolism. This article reviews the pathogenesis, diagnosis and surgical management of chronic thromboembolic pulmonary hypertension with a focus on current literature and surgical management.

Chronic thromboembolic pulmonary hypertension arises from total or partial occlusion of the pulmonary vascular bed by non-resolving thromboembolism. Although pulmonary embolism is one of the more common cardiovascular diseases, chronic thromboembolic pulmonary hypertension remains an under-diagnosed condition. Chronic thromboembolic pulmonary hypertension is defined as precapillary pulmonary hypertension with mean pulmonary artery pressure of more than 25 mmHg, pulmonary capillary wedge pressure of less than 15 mmHg and pulmonary vascular resistance of more than 2 Wood units (Simonneau et al, 2009).

The incidence of chronic thrombotic occlusion in the population depends on the percentage of patients that fail to resolve acute embolic material. Estimates of cumulative incidence of chronic thromboembolic disease developing from clinically recognized acute pulmonary embolism range from 0.8% to 3.8% (Benotti et al, 1983; Pengo et al, 2004). Given that deep vein thrombosis and pulmonary embolism is as common as 1/1000 population/year, the annual incidence of chronic thromboembolic pulmonary hypertension may be of the order of 8–40 cases/million population. However, because some patients diagnosed with chronic thromboembolic disease have no preceding history of acute embolism, the true incidence of this disorder could be much higher.

The majority of cases of deep vein thrombosis and acute pulmonary emboli are managed medically with anticoagulation. Cardiothoracic surgeons rarely become involved in management of acute pulmonary embolism, unless it is in a hospitalized patient who survives a massive embolism that causes life-threatening acute right heart failure and shock. Conversely, the majority of cases of chronic thromboembolic pulmonary hypertension are amenable to surgical treatment by pulmonary endarterectomy. Pulmonary endarterectomy is the definitive and, in most cases, curative treatment for chronic thromboembolic pulmonary hypertension. Surgery aims to normalize pulmonary artery pressure with resultant significant symptomatic and prognostic benefit. Medical management is only palliative, and lung transplantation has an inferior outcome compared to pulmonary endarterectomy and is only relevant for very selected patients with distal disease and extreme pulmonary hypertension.

Pathophysiology

Most cases of chronic thromboembolic pulmonary hypertension result from acute embolic episodes and can be considered as a failure of resolution of the clot burden. Why some patients have unresolved emboli is not certain, but a variety of factors play a role, alone or in combination.

Initially, thrombus resolution probably results from a combination of thrombus fragmentation and endogenous fibrinolysis. In most patients this leads to complete clot resolution. Further resolution relies on clot organization and neovascularization, during which the obstructed vessel becomes recanalized and vessel patency is partially restored.

After the clot becomes wedged in the pulmonary artery, one of two processes occurs (Dibble, 1958):

1. The organization of the clot proceeds to canalization, producing multiple small endothelialized channels separated by fibrous septa (i.e. bands and webs), or
2. Complete fibrous organization of the fibrin clot without canalization may result, leading to a solid mass of dense fibrous connective tissue totally obstructing the arterial lumen.

The generation of pulmonary hypertension in chronic thromboembolic pulmonary hypertension is not just the result of simple obstruction of the pulmonary arterial bed; indeed, there is little rise in pulmonary artery pressure following a pneumonectomy (Cournand et al, 1950). The increased pressure as a result of redirected pulmonary blood flow in the unobstructed pulmonary vascular bed can create an arteriopathy in the small precapillary blood vessels similar to that seen in idiopathic pulmonary arterial hypertension. Hence, the pathogenesis of chronic thromboembolic occlusion in chronic thromboembolic pulmonary hypertension with resultant raised pulmonary vascular resistance is thought to be secondary to obstruction by thromboemboli and remodelling of the previously normal pulmonary vascular bed.

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Clinical presentation and diagnosis

Clinical presentation

There are no symptoms specific for chronic thromboembolism. The most common symptom associated with thromboembolic pulmonary hypertension, as with all other causes of pulmonary hypertension, is exertional dyspnoea. This dyspnoea is out of proportion to any abnormalities found on clinical examination. Syncope or presyncope is another common symptom in severe pulmonary hypertension.

The physical signs of pulmonary hypertension are the same no matter what the underlying pathophysiology. Initially the jugular venous pulse is characterized by a large 'A' wave. As the right heart fails, the 'V' wave becomes predominant. The right ventricle is usually palpable near the lower left sternal border. The second heart sound is often narrowly split and varies normally with respiration. In the later stages of the disease, signs of right heart failure predominate with oedema and ascites. Tricuspid regurgitation can be severe, with a pansystolic murmur and an enlarged pulsatile liver.

Diagnosis

The chest radiograph may be entirely normal. Some show more classical abnormalities with apparent vessel cutoffs at the lobar or segmental pulmonary arteries, or regions of hypovascularity. Central pulmonary arteries may be enlarged, and the right ventricle may also be enlarged (*Figure 1*). Pulmonary function tests reveal minimal changes in lung volume and ventilation; patients generally have normal or slightly restricted pattern as a result of parenchymal scarring. Diffusion capacity is often reduced and may be the only abnormality on pulmonary function testing. Pulmonary arterial pressures are elevated and supra-systemic pulmonary pressures are not uncommon. Resting cardiac outputs are lower than the normal range, and pulmonary arterial oxygen saturations are reduced. Most patients are hypoxic. Dead space ventilation is increased.

The ventilation-perfusion (V/Q) lung scan is the essential test for establishing the diagnosis. An entirely normal lung scan excludes the diagnosis of both acute and chronic thromboembolism.

Transthoracic echocardiography is sensitive for detecting pulmonary hypertension and right ventricular dysfunction but not specific for chronic thromboembolic pulmonary hypertension. Common findings include right ventricular dilatation, hypertrophy and hypokinesis, right atrial enlargement, interventricular septal deviation towards the left ventricle during systole, and tricuspid regurgitation.

Currently, pulmonary angiography is said to be the gold standard imaging test for evaluation of operability in chronic thromboembolic pulmonary hypertension, but experience is essential for the proper interpretation of pulmonary angiograms. Organized thrombi appear as filling defects, webs or bands, or completely thrombosed vessels 'missing' (*Figure 2*). Distal vessels demonstrate the rapid tapering and pruning characteristic of pulmo-

Figure 1. Chest radiograph of a patient with chronic thromboembolic pulmonary disease and evidence of pulmonary hypertension.

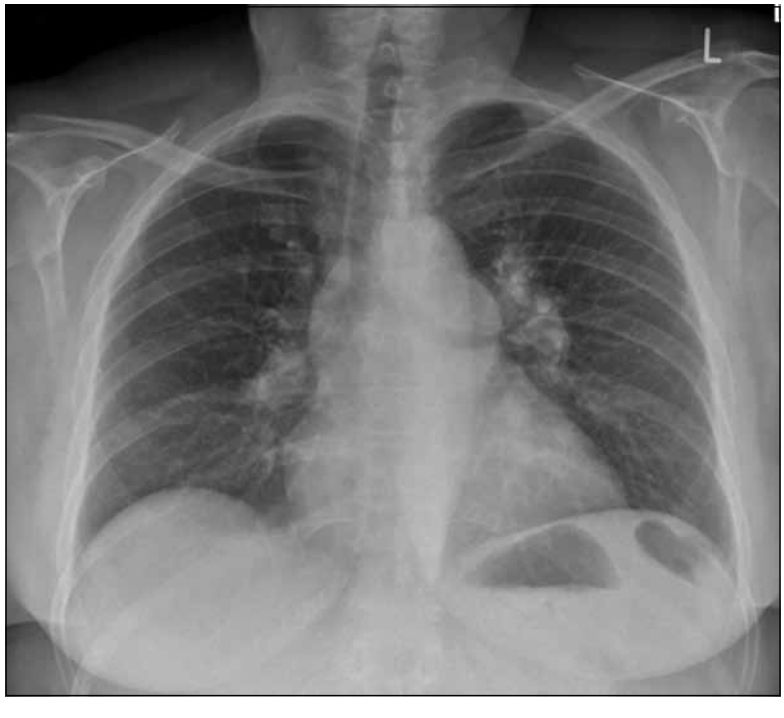
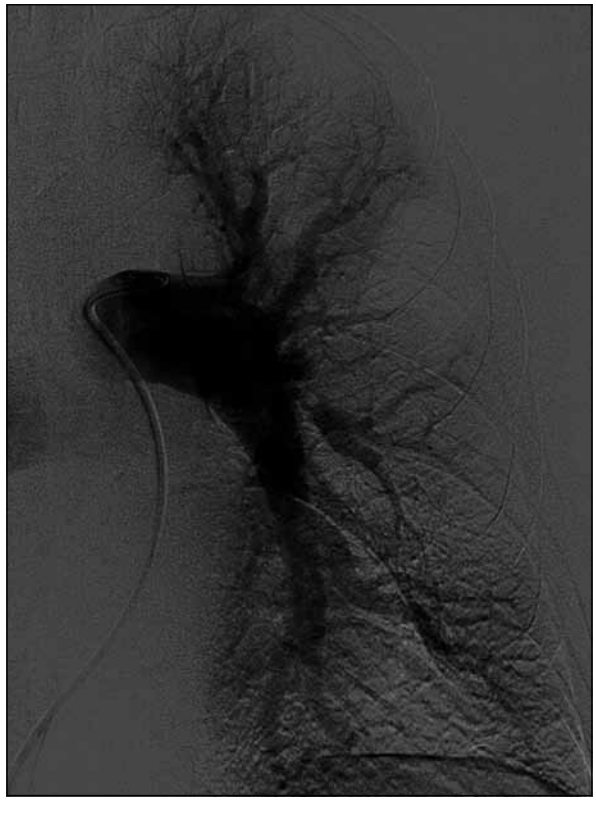


Figure 2. Left pulmonary angiogram demonstrating enlarged pulmonary arteries, post-stenotic dilatation of vessels, lack of filling to the periphery in many areas, and abrupt cutoffs of branches.



nary hypertension. Other modalities of imaging including multi-slice computed tomography pulmonary angiography and magnetic resonance angiography are gaining acceptance and are now favoured over conventional angiography in some centres.

Right heart catheterization is crucial for the diagnosis of pulmonary hypertension, defined as a mean pulmonary artery pressure of >25 mmHg at rest. Right atrial pressure, right ventricular end diastolic pressure, pulmonary artery pressure and mixed venous oxygen saturation are measured directly. Cardiac output and pulmonary vascular resistance can then be calculated. Coronary angiography and other cardiac investigations are recommended for patients over 40–45 years being considered for surgery.

Management

Medical treatment

The main treatment is surgical and all patients with suspected chronic thromboembolic pulmonary hypertension should be referred to an experienced unit able to perform pulmonary endarterectomy. Untreated, the prognosis of chronic thromboembolic pulmonary hypertension is very poor with severe debilitation and premature death from right heart failure. In historical case series, the mean survival is 6.8 years and when the mean pulmonary artery pressure of patients with thromboembolic disease reaches 50 mmHg or more, the 3-year mortality is about 90% (Riedel et al, 1982).

Chronic anticoagulation is the mainstay of the medical regimen. Anticoagulation is primarily used to prevent future embolic episodes, but it also limits the development of thrombus in regions of low flow within the pulmonary vasculature. Inferior vena caval filters are used routinely to prevent recurrent embolization by some centres, but there are few data to support this indication.

Data from clinical drug trials in chronic thromboembolic pulmonary hypertension are also limited. Specific disease-targeted drug therapy is therefore not licensed for patients with chronic thromboembolic pulmonary hypertension, but drugs used for the treatment of idiopathic pulmonary arterial hypertension are sometimes used and may provide symptomatic improvement in some patients (Jais et al, 2008; Toshner et al, 2010).

Pulmonary endarterectomy

History

Most of the surgical experience in pulmonary endarterectomy has been reported from the University of California, San Diego Medical Center by Stuart Jamieson (Jamieson et al, 2003; Madani et al, 2012) with experience totalling more than 2500 cases to date.

The UK experience began in 1997 with John Dunning at Papworth Hospital, Cambridge. In 2000 Papworth Hospital was commissioned to provide this service for all UK patients with more than 900 cases performed to date.

Operative principles

The basis of the operation is the removal of the obstruction of the pulmonary vascular bed by endarterectomy within the superficial media of the arterial wall. Therefore, the reduction in the pulmonary vascular resistance after pulmonary endarterectomy is dependent on the burden of 'clearable' disease as defined on preoperative imaging. The correlation between the degree of clearable disease in imaging studies and pulmonary vascular resistance is the main determinant of operability. The absolute preoperative and resultant postoperative pulmonary vascular resistance are also the main factors that determine outcome after endarterectomy. Mortality following endarterectomy may be 5–10-fold higher in patients with a preoperative pulmonary vascular resistance >1200 dyne/s/cm^5 (Dartevelle et al, 2004). Similarly, a postoperative residual pulmonary vascular resistance of >500 dyne/s/cm^5 is a risk factor for in-hospital mortality (Thistlethwaite et al, 2002).

Although preoperative imaging helps to determine operability, the true extent of the disease can only be determined intraoperatively and has been classified in four types (Thistlethwaite et al, 2002).

- Type 1: central disease where major vessel clots (fresh and/or mature) are present
- Type 2: lobar and segmental disease where thickened intima is present with webs in the lobar and segmental branches
- Type 3: sub-segmental disease where the disease begins distally at the subsegmental branches
- Type 4: distal disease where small vessel disease is present and represents inoperable disease.

Surgery is more successful in patients with type 1 and 2 disease, with a greater reduction in pulmonary vascular resistance and lowest mortality. Surgery in patients with the more distal type 3 disease is more challenging with a smaller reduction in pulmonary vascular resistance and higher risk. However, many patients with type 3 disease still benefit from pulmonary endarterectomy even if there is some residual pulmonary hypertension.

The approach is via a median sternotomy with cardiopulmonary bypass. The patient is cooled systemically to 20°C and right and left pulmonary arteriotomies are performed within the pericardium. Adequate visualization for distal dissection necessitates reduction in bronchial arterial collateral return to the pulmonary arteries. Traditionally this has been achieved by periods of complete deep hypothermic circulatory arrest for up to 20 minutes per side and this remains the standard approach (Jamieson et al, 2003). Deep hypothermic circulatory arrest is the best technique for performing pulmonary endarterectomy and is not associated with cognitive dysfunction post operation (Vuylsteke et al, 2011). The endarterectomy plane is raised and with a sucker-dissector the plane can be extended circumferentially and then distally by careful traction as far as possible into all the affected segmental or subsegmental vessels. A cast of

the inner layer of the pulmonary arterial tree is then dissected free (*Figure 3*).

After completion of the endarterectomies, the patient is rewarmed slowly on full cardiopulmonary bypass. The operation is long because of the time necessary to cool and warm on bypass.

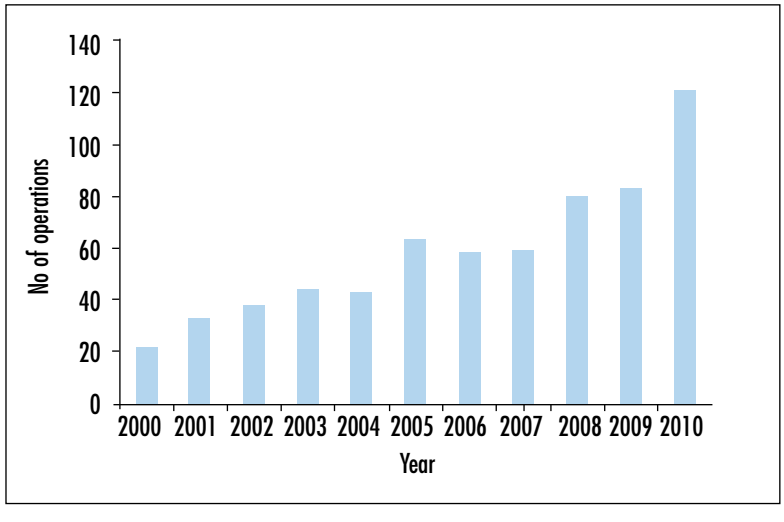
There is early postoperative haemodynamic improvement with an immediate fall in mean pulmonary artery pressure by approximately 50%, and reduction in pulmonary vascular resistance to approximately one third of the preoperative level in majority of patients. Most of the general principles of postoperative cardiac surgical care apply and in addition it is important to avoid any factors that may increase pulmonary vascular resistance.

Complications

Patients are subject to all complications associated with cardiac surgery (e.g. arrhythmias, atelectasis, wound infection, pneumonia and mediastinal bleeding) but also may develop complications specific to this operation. The most serious complications specific to this operation are persistent or residual pulmonary hypertension and reperfusion lung injury. Often both occur in the same patient.

Figure 3. Inner cast of right and left pulmonary arteries following pulmonary endarterectomy.

Figure 4. Number of pulmonary endarterectomy operations in UK.



Persistent pulmonary hypertension: The decrease in pulmonary vascular resistance usually results in an immediate and sustained restoration of pulmonary artery pressure to normal levels. Therefore, cardiac output is often increased and right ventricular function improves. In patients with residual pulmonary hypertension, the postoperative course can be difficult and the risk of death is increased. Pulmonary vasodilators and inotropic support are used in an attempt to reduce pulmonary vascular resistance. If the surgical clearance has been adequate and it is thought there may be some reversibility, veno-arterial extracorporeal membrane oxygenation may allow time for recovery.

Reperfusion lung injury: Reperfusion injury is defined as new radiological opacity in the lungs within 72 hours of pulmonary endarterectomy with associated hypoxia.

Reperfusion injury that directly adversely impacts the clinical course of the patient occurs in approximately 10% of patients. In its most dramatic form, it occurs soon after operation (within a few hours) and is associated with profound desaturation. Early measures should be taken to minimize the development of pulmonary oedema with diuresis, maintenance of haematocrit, and the early use of peak end-expiratory pressure. Once the capillary leak has been established, treatment is supportive because reperfusion pulmonary oedema will eventually resolve if satisfactory haemodynamics and oxygenation can be maintained. Veno-venous extracorporeal membrane oxygenation is sometimes necessary to provide temporary support.

Results

Since 2000, Papworth Hospital has been the sole commissioned centre for pulmonary endarterectomy in the UK and there has been a steady increase in the number of operations and improvement in results over the last 10 years (*Figure 4*).

Over 900 patients have now been operated on at Papworth and the current in-hospital mortality is 2–3%. In a recent cohort, the median age was 60 years (range 15–84 years) with concomitant surgery being carried in 10% of the cases.

Extracorporeal membrane oxygenation has been used to support patients with severe reperfusion lung injury and residual pulmonary hypertension post pulmonary endarterectomy. To date, 33 patients have been supported with successful weaning in 70% and long-term survival in approximately 50%. The period of extracorporeal membrane oxygenation support has ranged from 48 to 1480 hours (Berman et al, 2008).

Long-term follow up

All pulmonary endarterectomy patients in the UK are reviewed at 3 months and 1 year after endarterectomy. A review of 230 patients demonstrated a significant

improvement in New York Heart Association (NYHA) class following surgery (Freed et al, 2008) (*Figure 5*). Five-year survival is nearly 90% even in patients over 70 years of age (Berman et al, 2012).

Conclusions

Pulmonary endarterectomy is now a safe operation with low mortality rate and excellent long-term results. Increased awareness of both the prevalence of this condition and the possibility of a surgical cure should relieve more patients from this debilitating and ultimately fatal disease. BJHM

Conflict of interest: none.

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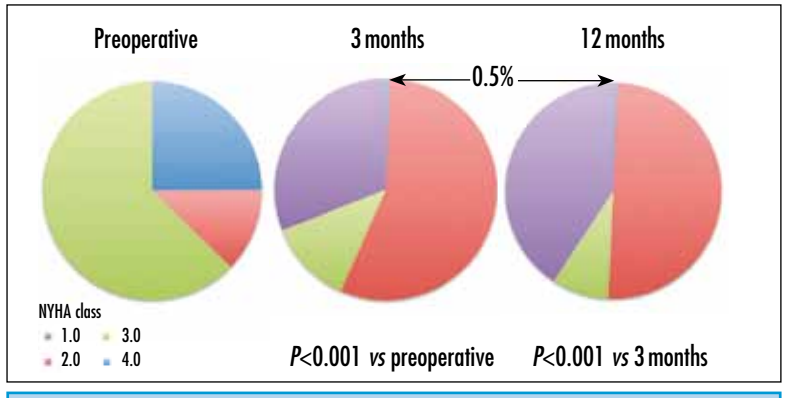
Figure 5. New York Heart Association (NYHA) class – preoperative, at 3 months and 12 months follow up.



KEY POINTS

- Chronic thromboembolic pulmonary hypertension is one of the most prevalent and increasingly recognized forms of pulmonary hypertension and should be considered in all patients with unexplained pulmonary hypertension.
- Patients with persistent breathlessness following pulmonary emboli should be further investigated and referred to an experienced pulmonary hypertension centre.
- Patients with chronic thromboembolic pulmonary hypertension should receive lifelong anticoagulation and be considered for treatment with pulmonary endarterectomy.
- Pulmonary endarterectomy is the treatment of choice in selected cases and may be curative with normalization of pulmonary artery pressures and significant symptomatic and prognostic benefit.
- Current targeted medical therapies in chronic thromboembolic pulmonary hypertension are mainly supportive and have not shown benefit in randomized controlled trials, although drug therapy may improve functional status in some patients.

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