Review Article

Pulmonary Thromboendarterectomy in Chronic Thromboembolic Pulmonary Hypertension

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Key words: **Chronic pulmonary embolism, endarterectomy.**

Manuscript received: June 9, 2005;
Accepted: September 9, 2005.

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Chronic thromboembolic pulmonary hypertension (CTEPH) develops in 1-3% of cases following acute pulmonary embolism. The disease is underdiagnosed and under-treated, as statistical studies have shown.[1] Identification of patients with CTEPH is difficult since 90% of them have no apparent disturbance of the coagulation mechanism.[2]

CTEPH is a progressive disease, the result of the incomplete lysis of large organised thrombus in the main pulmonary artery and secondary branches, leading to obliterative pulmonary hypertension, right ventricular failure and subsequent death.[3-5] Patients with mean pulmonary artery pressure (PAP) >30 mmHg have a five-year survival rate of 30%, while those with PAP >50 mmHg have 10% five-year survival.[6-9]

With surgical treatment (pulmonary thromboendarterectomy, PTE) the organised thromboembolic material is removed, pulmonary hypertension is reduced, right ventricular function and the overall clinical condition are improved in appropriately selected patients. PTE reduces pulmonary hypertension by reducing the ventilation-perfusion ratio, ending right ventricular dysfunction, limiting the retrograde extension of the obstructive thrombus and protecting against arteriopathological changes in the pulmonary vessels that remain patent.[10]

A retrospective[11-20]

The entity of chronic pulmonary artery occlusion was first discovered by Lungdahl in 1928 from post mortem examinations. The first surgical treatment of acute pulmonary embolism was carried out by Trendelenburg in 1908 and the surgical treatment of CTEPH began forty years later. The first procedures were carried out without extracorporeal circulation [Blalock (1948), Boucher (1951), Hollister and Cull (1956), Hurwitt (1958), Hufnagel (1962), Snyder (1963), Houk (1963), Sabinston (1977)], whereas later techniques used median sternotomy with total cardiopulmonary bypass, deep hypothermia and intermittent periods of circulatory arrest [Daily (1980), Chitwood (1984), Braunwald (1970)]. This latter methodology (cardiopulmonary bypass – deep hypothermia – circulatory arrest) has become established as the most effective surgical approach for the treatment of CTEPH. Nowadays, the six-year survival after surgical treatment approaches 75%, with a functional improvement to NYHA classes I-II in more than 90% of cases (Jamieson, University of California at San Diego).

The lungs have a unique feature: embolism rarely causes tissue necrosis because of the bronchial circulation. Thus endarterectomy is therapeutic and with few exceptions it is permanent. The excellent results

nowadays are due to three factors: surgical experience, improvements in surgical technique, and teamwork in postoperative care.

Pathophysiology, classification, clinical appearance, diagnosis

Many patients with CTEPH report no history of previous pulmonary embolism, while those who do report it go through a "honeymoon" period following the initial manifestation and their stabilisation. They progressively exhibit dyspnoea on effort, weakness and syncopal episodes. The clinical findings appear only *after* the right ventricular failure becomes established.[2]

As regards the pathogenesis of CTEPH, some authors maintain that one episode of acute pulmonary embolism is not sufficient to lead to chronic obstruction and that multiple such episodes are necessary. This question has not yet been fully elucidated. There are, however, other factors that contribute to chronic pulmonary occlusion—for example, the pathologoanatomical nature of the emboli that may modify the rate or the extent of fibrinolysis. Some thrombi may be *in situ* in the deep veins of the thigh for a considerable period before embolism occurs. During this time, the significant organisation of the thrombus impedes the expected thrombolysis. In addition, disturbances of the fibrinolytic system may lead to reduced fibrinolysis and subsequent chronic pulmonary occlusion. It is also apparent that a combination of the above factors may lead to the inadequate fibrinolysis of acute pulmonary embolus.[11]

Another important parameter is the speed with which the acute emboli adhere to the pulmonary arterial wall. This can happen in as little as three days, while within a week significant organisation begins on the arterial wall itself. Progressively, the embolic material is replaced by collagen and elastic tissue and becomes adherent to the vascular wall. Simple removal of the obstructive material is no longer feasible and for this reason endarterectomy is required.[12]

In the diagnostic evaluation of patients who are candidates for surgical treatment it is necessary, first, to determine whether the patient has pulmonary hypertension and to assess its severity; second, to establish the aetiology of the pulmonary hypertension; and third, to decide whether the disease is amenable to surgery.[2] The diagnostic evaluation includes the following:

- blood tests, which usually show chronic hypoxia and a low cardiac output;
- ECG, with signs of right ventricular hypertrophy and strain;
- chest X-ray, with reduced or increased vascular signs and central enlargement of the pulmonary arteries;
- respiratory function tests showing the symptoms and disturbances of gas exchange;
- low partial oxygen pressure;
- echocardiogram, with findings indicative of right ventricular failure and probable concomitant tricuspid insufficiency;
- perfusion/ventilation scans, showing segmental or large defects;
- right cardiac catheterisation and pulmonary artery angiography;
- coronary angiographic examination.[13-15]

An important step towards achieving a successful surgical outcome, as mentioned above, is the selection of patients based on the distribution of their pulmonary arterial occlusion. Apart from pulmonary angiography (contrast injection to the right pulmonary artery with recording in the anteroposterior view, and injection to the left pulmonary artery with recording in the left anterior oblique view[23]), spiral vascular tomography of the lungs has been found to be a rather useful diagnostic method. Patients with lesions limited to the segmental or sub-segmental branches are not good candidates for PTE. In such cases the risk of haemorrhage in the airways because of injury to a peripheral pulmonary vessel during PTE is very high. Video angioscopy improves the quality and the degree of PTE in cases with peripheral lesions. PTE is mainly useful in patients with central lesions that extend to peripheral branches.

Patients who have only peripheral lesions are usually treated with lung transplantation.[16-19] An alternative therapeutic approach to inoperable patients is pulmonary angioplasty. Although only a few cases have been reported in the literature so far, the results have been satisfactory and the procedure has a low risk.[24,25]

A recently developed classification system for the anatomical location of thrombi is helpful in the selection of patients for PTE. Type I disease is characterised by a clear central thrombus; type II has thickening of the intima and fibrous reticulum in a main or segmental bronchus, without thrombus in a main vessel; type III is limited to segmental or sub-segmental regions and type IV involves only peripheral vessels and is not a surgical disease.

Indications for surgery

There are three main factors involved in the decision to perform PTE. The first is significant cardiac dysfunction

(NYHA classes III and IV) and the second is that the mean pulmonary arterial pressure (PAP) should not exceed 30 mmHg. Riedel et al have reported that patients with PAP <30 mmHg have a five-year survival rate of 90%, whereas for those with PAP >30 mmHg five-year survival is only 50% and drops further to 10% when PAP is 50 mmHg. In addition, the pulmonary vascular resistances (PVR) at rest or after exercise should be at least 300 dyn.s.cm^{-5}. Patients with occlusion of one or both pulmonary arteries are an exception. In such cases the surgical result will be satisfactory even when the PVR are >300 dyn.s.cm^{-5}. An evaluation of the PVR should rule out primary pulmonary artery thrombosis without embolus, secondary thrombosis due to primary pulmonary hypertension, and pulmonary thrombosis related to the presence of a ventricular septal defect.[11]

The third and most important factor for PTE is the possibility of surgical approach to the thrombi. Types I and II (anatomical classification) are susceptible to endarterectomy, but type III should only be treated by an experienced surgeon in order to avoid rupture of the target vessel, which is extremely difficult to treat (frequent fatal haemorrhage).[21,22]

Patients who are selected for endarterectomy should be relatively free of other health problems. Significant parenchymal pulmonary disease is a risk factor for prolonged respiratory support, inadequate improvement of dyspnoea and for mortality. Peripheral vascular disease is also a contraindication, as are renal dysfunction and age over 80 years.

In many patients with CTEPH who undergo PTE a moderate to severe degree of tricuspid insufficiency is found perioperatively. The main morphological anomaly is right ventricular dilatation, which is accompanied by distension of the tricuspid annulus and by apical and lateral displacement of the papillary muscles. This displacement and the dilation of the annulus diminish the leaflets' coaptation effect. When tricuspid insufficiency develops in CTEPH it is further exacerbated by the increased preload, resulting in a vicious circle that worsens right ventricular function even more.[26,27]

Jamieson et al do not directly recommend tricuspid valve repair unless the valve itself is diseased. As in similar studies concerning the mitral valve in patients with ischaemic heart failure, it is believed that right ventricular remodelling alone is sufficient to restore tricuspid valve function.[24-26]

Postoperative care is similar to that following routine cardiac surgery, apart from aggressive diuresis and fluid removal because of the prolonged cardiopulmonary bypass and hypothermia. Nitric oxide (NO) and other vasodilators of the pulmonary circulation are not used routinely because the cause of the obstructions is supposed to have been removed mechanically.

Postoperatively, subcutaneous heparin is given initially, followed by the usual lifelong anticoagulant regimen with dicoumarol agents.

All patients should have preoperative filter placement in the inferior vena cava (Greenfield) if this is not completely occluded. The filter is extremely important for the prevention of thromboembolic relapse. Patients aged over 45 years should undergo coronary angiography prior to surgery.[2]

Surgical technique

The surgical technique used nowadays has been described by Jamieson et al, the surgical team with the greatest experience worldwide.[20-22]

After a median sternotomy the patient is placed on cardiopulmonary bypass with hypothermia at 20°C. Before the cardiopulmonary bypass the patient's head is wrapped in a blanket with circulating cold water at 4°C. This blanket has a thermometer and a device for regulating the water circulation. After the cardiopulmonary bypass has been started vents are placed in the pulmonary artery and the right superior pulmonary vein. The right pulmonary artery is dissected between the aorta and the superior vena cava and is mobilised within the pericardial reflection. Without opening the pleura, the aorta is clamped and the cardioplegic solution is infused while the heart is cooled locally.

The right pulmonary artery is opened as far as the right lower lobe. Every thrombus that is encountered, whether free or organised, is removed. The endarterectomy cannot proceed unless the thrombi are first removed, because they conceal the surgical field and do not permit contact with the endarterectomised segment. The circulatory arrest starts with the appearance of blood return from the bronchi.

Once the field has been prepared the endarterectomy proceeds with the aid of a microscopic aspirator with a rounded tip. The endarterectomy is carried out towards the periphery from the lobar to the segmental vessels. If the endarterectomised specimen is large and obstructs the optical field it is removed, while the endarterectomy continues for about 20 cm. Although the PVR are not usually reduced to normal levels postoperatively, the residual pulmonary hypertension is due to secondary vascular injury at the arteriole and capillary level and not to residual embolic material.

The circulatory arrest is limited to 20 minutes. Then circulation is restored and the surgeon moves to the left. That side is not usually affected as much as the right and is easier from a technical point of view, apart from the left lower lobe. The duration of circulatory arrest is usually shorter on the left side.

After bilateral endarterectomy has been completed the circulation is restarted and the patient is warmed. During re-warming the interatrial septum is checked for the presence of a *foramen ovalis*, which is quite common (25%) in these patients. If necessary, valvular or aortocoronary bypass are carried out during rewarming.

Postoperative complications[21,24,27-30]

The most frequent cause of death during postoperative hospitalisation (30 days) is pulmonary hypertension that has not been relieved. Other, less common causes are haemorrhage in the mediastinum, intraoperative cardiac arrest and severe pulmonary oedema from the reperfusion. In addition, there may be neurological complications and iatrogenic damage at the insertion points of the cardiopulmonary bypass cannulae.

Complications that are not specific to PTE but also occur in other cardiac surgical procedures are arrhythmias, atelectasis, wound infections, injury to the phrenic nerve (mainly right), delirium and mental disturbances, and pericardial effusions.

Pulmonary oedema from the reperfusion occurs in 10-25% of cases. It is usually of small degree, but may be haemorrhagic and fatal. There are no preoperative factors that predict the occurrence of pulmonary oedema with any certainty. It usually appears 8-12 hours postoperatively, but may be as late as 72 hours. It occurs exclusively in segments that were occluded. Prophylactic measures should be taken to minimise the occurrence of pulmonary oedema. Those measures are diuresis, maintenance of haematocrit levels and the early application of peak end-expiratory pressure (PEEP). If there is leakage into the capillaries the therapy is supplementary, since the pulmonary oedema from reperfusion will be overcome if the haemodynamic and respiratory parameters are preserved. Haematocrit is maintained at levels of 32-36% and diuresis is reinforced even if a filter is needed. The FIO_2 level is maintained so as to achieve a saturation of the order of 90%. The PEEP level is gradually reduced with a progressive change of ventilation from volume to pressure and the acceptance of moderate hypercapnia. Rarely, NO 20-40 parts/ml may be given to improve ventilation. Even more rarely, it is necessary to use an extracorporeal membrane oxygenator until ventilation improves, usually 7-10 days later. Additionally, pulmonary vascular steal syndrome may occur with a rate of 10-15%, accompanied by significant hypoxaemia. The hypoxaemia usually disappears over a few days of continuous mechanical breathing support.

The pulmonary circulation usually recovers after 6-8 weeks.

Clinical experience - long term follow up

PTE is used in a number of important cardiac surgery centres throughout the world,[31,33-36] but the greatest experience of the procedure is to be found in the University of California at San Diego, in the United States of America. At this centre pioneering surgeons (Daily, Utley, Dembitsky, Braunwald) started the surgical treatment of CTEPH in 1975 and in 1990 they published their findings from a series of 187 patients. Mortality was 17%, a rate that dropped to 8.8% in the next published series from the same centre (1994-1998) and according to the latest data (1998-2003) has fallen even further, to 4.4%.[20]

This dramatic improvement in results is due to the distinguished surgeon Stuart Jamieson and his colleagues in the same centre, who set up a special department for patients with CTEPH.[21] The majority of patients had type II disease, followed by type I. The main cause of death was residual elevated PVR and the mortality was 1.3% when PVR were <1000 dyn.s.cm^{-5} but almost ten times higher (10.1%) when PVR were >1000 dyn.s.cm^{-5}. The neurological complications have also gradually been reduced by better brain protection, using a thermoregulatory device to cool the patient's head, and by a reduction in the periods of circulatory arrest as a result of the more accurate selection of patients who are likely to benefit from PTE.

During the long term follow up of 420 patients who survived for more than one year, this centre found that six-year survival was 75%. Even more impressive was those patients' functional recovery. Whereas 95% of them were in NYHA classes III-IV initially, 93% improved to classes I-II after surgery.

Apart from residual pulmonary hypertension, other factors with a negative effect on prognosis are the patient's age, insufficient haemodynamic improvement, and female sex.

Advances in surgical technique, in myocardial and neurological protection, continue to improve the results of PTE in CTEPH. They have made this therapeutic

approach safer than transplantation[32] and have turned it into the method of choice for selected patients.

Conclusions

Surgical treatment with PTE removes organised thromboembolic material, reduces pulmonary hypertension, improves right ventricular function and overall clinical condition in appropriately selected patients. During the diagnostic evaluation (blood tests, ECG, chest X-ray, tests of respiratory function, hypoxaemia, echocardiography, ventilation/perfusion scanning, right cardiac catheterisation, pulmonary angiography/angioscopy) the existence of pulmonary hypertension must be determined, as well as its aetiology if the disease is treatable surgically. Suitable patients are those with thrombus in the central or lobar segments of the pulmonary artery (disease types I and II, respectively), while those with thrombus at a segmental or sub-segmental level are at high risk during surgery. In addition, PVR should not exceed 300 dyn.s.cm^{-5}.

Today, two decades after the first application of PTE, there are surgical methods and techniques (cardiopulmonary bypass, myocardial protection, circulatory arrest, neuroprotection) that guarantee a low rate of surgical and postoperative morbidity and offer a satisfactory long term functional outcome.

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