

***Pulmonary thromboendarterectomy for
chronic thromboembolic pulmonary
hypertension***

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MSAC Reference 05

Assessment report

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The Medicare Services Advisory Committee is an independent committee which has been established to provide advice to the Commonwealth Minister for Health and Aged Care on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform Government decisions about which medical services should attract funding under Medicare.

This report was prepared by the Medicare Services Advisory Committee (MSAC) with the assistance of Dr Elmer Villanueva and Ms Alexandra Raulli, Australasian Cochrane Centre, and Mr Anthony Harris, Health Economics Unit, Monash Institute of Public Health, Monash University, Melbourne. The report was endorsed by the Commonwealth Minister for Health and Aged Care on 27 March 2001.

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MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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Executive summary

The procedure

Pulmonary thromboendarterectomy (PTE) involves the surgical removal of organised thrombi along with a thin lining of intima from the pulmonary artery and its distal branches to improve functional and haemodynamic outcomes in patients with chronic thromboembolic pulmonary hypertension.

Medicare Services Advisory Committee – role and approach

The Medicare Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health and Aged Care on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. The medical literature available on the technology is searched and the evidence is assessed and classified according to the National Health and Medical Research Council (NHMRC) four-point hierarchy of evidence. A supporting committee with expertise in this area then evaluates the evidence and provides advice to MSAC.

MSAC's assessment of pulmonary thromboendarterectomy

Clinical studies currently available on pulmonary thromboendarterectomy in the management of chronic thromboembolic pulmonary hypertension are limited to case series (NHMRC Level IV) or small comparative studies using internal comparison groups defined by survival (NHMRC Level III-2).

Clinical need

Chronic thromboembolic pulmonary hypertension is thought to arise from repeated or untreated pulmonary embolism. Although there are no reliable estimates of the prevalence or incidence of chronic thromboembolic pulmonary hypertension, expert opinion suggests a total of four to six patients per year is a reasonable estimate for Australia.

Safety

The lack of rigorous studies prevents the proper assessment of the safety profile of the procedure. The available information suggests significant mortality and morbidity that varies with the surgical centre where the operation was performed, possibly reflecting differences in skill and surgical technique, patient factors, and system-wide differences.

The most common causes of death are ventricular failure and reperfusion oedema. The most common causes of morbidity are similar to those found in cardiac surgery.

Effectiveness

There have been no studies of rigorous methodology that have focused on the effectiveness of pulmonary thromboendarterectomy. None considered direct comparisons between PTE and either current best medical therapy or lung transplantation. Nevertheless, marked improvements are evident in survival, functional status (as measured using the New York Heart Association Functional Classification and scales measuring ability to perform activities of daily living), quality of life and haemodynamic outcomes.

Cost effectiveness

There are currently three patients each year on average subsidised under the Australian Government Medical Treatment Overseas (MTO) program to receive PTE at the University of California at San Diego (UCSD) Medical Centre, USA. If restricted to those who would have travelled overseas for treatment, and PTE treatment in Australia can achieve similar results to the best of the facilities overseas, there is the possibility of a substantial improvement in convenience for patients and their families and a potential health care cost saving. If the non-randomised evidence on effectiveness is accepted, there may be gains in survival and quality of life associated with PTE compared to medical management of patients currently treated in Australia. Based on the evidence presented, and an indicative model of cost effectiveness, it would seem that if six patients a year were treated, PTE may cost less than \$13,500 per quality-adjusted life year (QALY) gained compared to medical management only. A facility in Australia that treated at least three patients per year would probably be regarded as cost effective if it could achieve the effectiveness suggested by the current evidence. It would also have to be demonstrated that there were no capacity constraints on current cardiovascular facilities, that potential patients were as suitable for treatment as those cases in the published literature, and that a training program was able to achieve and maintain the same quality of treatment and consequent effectiveness within a reasonable time period.

Recommendation

MSAC recommended that, on the strength of evidence pertaining to the efficacy and relative safety of pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension, and the life threatening nature of this condition, public funding should be supported for this procedure to be performed in Australia.

- The Minister for Health and Aged Care accepted this recommendation on 27 March 2001 -

Introduction

The Medicare Services Advisory Committee (MSAC) has reviewed the use of pulmonary thromboendarterectomy (PTE), a surgical technique for the treatment of chronic thromboembolic pulmonary hypertension (CTEPH).

MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer affairs and health administration.

This report summarises the assessment of current evidence for pulmonary thromboendarterectomy.

Background

Chronic thrombotic pulmonary hypertension

Pulmonary hypertension is defined as a mean pulmonary artery pressure (PAP) of at least 25 mm Hg at rest or 30 mm Hg during exercise.^{1,2} Some of the causes of pulmonary hypertension are listed in Table 1.

Table 1 Selected etiologic conditions giving rise to pulmonary hypertension (adapted from classification and nomenclature proposed by the WHO World Symposium on Primary Pulmonary Hypertension).³

| | |
|------|--|
| 1. | Pulmonary arterial hypertension |
| 2. | Pulmonary venous hypertension |
| 3. | Pulmonary hypertension associated with disorders of the respiratory system and/or hypoxaemia |
| 4. | Pulmonary hypertension due to chronic thrombotic and/or embolic disease |
| 4.1. | Thromboembolic obstruction of proximal pulmonary arteries |
| 4.2. | Obstruction of distal pulmonary arteries |
| a. | Pulmonary embolism (thrombus, tumour, ova and/or parasites, foreign material) |
| b. | In-situ thrombosis |
| c. | Sickle cell disease |
| 5. | Pulmonary hypertension due to disorders directly affecting the pulmonary vasculature. |

Chronic thromboembolic pulmonary hypertension (CTEPH) is a progressive disease characterised by unresolved thromboembolic material in the pulmonary artery bed. The chronic presence of thrombi in the pulmonary vasculature was previously thought to be a rare occurrence following an episode of acute pulmonary embolism. Previous opinion held that acute thromboembolic events resolved without long-term haemodynamic sequelae.⁴ It is now known that a minority of individuals surviving an acute thromboembolic event are unable to clear thromboemboli in the pulmonary circulation.⁵ Chronic thromboembolic pulmonary hypertension is now viewed as the logical progression of a series of physiological processes that arise from untreated or repeated pulmonary embolism (PE).^{4,6,7}

Hartz⁶ and Presti, Berthrong & Sherwin⁷ propose the following cascade of events as leading to CTEPH: the occurrence of endothelial proliferation in the margins of thrombi already incorporated into the walls of pulmonary arterial vessels is exacerbated by inadequate anticoagulation (due to ineffective management, missed diagnoses, or silent cases). The deposition of fresh thrombi from distal sources leads to either fresh thrombosis in previously unaffected vessels or to further fibrovascular organisation and recanalisation in other vessels.^{8,9} Cyclical insults to the pulmonary vascular bed are postulated to lead to pulmonary hypertension and right heart failure. Feied, Miller et al⁴ and Lang¹⁰ propose four changes stemming from the presence of chronic pulmonary thromboemboli: the creation of alveolar dead space and impaired gas exchange, altered haemodynamics of pulmonary flow resulting in segmental underperfusion, abnormalities of the pleura and pulmonary parenchyma, and cor pulmonale.

The initiation of adequate anticoagulation therapy for acute episodes of PE is associated with reduced risk for the development of the complete condition due to the interruption

of the thrombosis-recanalisation cycle. However, surgical procedures are required to resolve the obstructions caused by fibrous tissue adherent to the vessel wall. Even then, more distally affected arteries of the pulmonary circulation are inaccessible by current techniques.

Predisposing factors

Patients prone to developing CTEPH are thought to have defective fibrinolytic systems, have partially organised emboli that are less likely to undergo fibrinolysis, a chronic and unrecognised source of recurrent embolisation, or a hypercoagulable state.¹¹ The presence of lupus-like anticoagulant was prevalent in 10 to 30 percent of patients seen in two case series.^{12,13} Other coagulation abnormalities include protein C, protein S, and antithrombin III deficiency.^{2,6,13} For a majority of patients with CTEPH, however, no defects can be demonstrated.^{11,14}

There is also some association between CTEPH and malignancy, the presence of indwelling venous catheters, and atrial septal defects.^{15,16}

Clinical presentation, diagnosis and natural history

The clinical presentation of CTEPH is that of right-sided heart failure.² The most common presenting symptom is progressive dyspnoea on exertion.^{17,18} Patients may also complain of chronic cough, chronic fatigue, excessive daytime sleepiness, and restriction of activities.^{4,19,20}

Given the necessity of repeated cycles of thrombosis and recanalisation required to bring about significant obstruction, onset is often insidious. Moser, Auger & Fedullo²¹ have proposed the existence of a “honeymoon period” during which time pulmonary hypertension is present but the subject exhibits few symptoms, if any. It is during this time that compensatory hypertrophy of the right ventricle occurs in an effort to maintain cardiac output in the presence of increased pulmonary vascular resistance (PVR). However, compensatory mechanisms fail swiftly after a threshold is reached (ie compromise of about 50 percent of the pulmonary circulation), resulting in rapidly increasing PAP (pulmonary hypertension), loss of right ventricular functional capacity leading to right heart failure, and impaired pulmonary gas exchange leading to hypoxaemia.^{6,20} Once cardiac output is severely depressed, chest pain mimicking that of coronary artery disease may develop. Exercise-related syncope may occur.^{4,17}

The clinical history of a patient is usually of little assistance in the diagnosis of CTEPH. Physical examination findings are indicative of pulmonary hypertension and right heart failure: a prominent right ventricular impulse or heave, a loud second heart sound, tricuspid regurgitation murmurs, engorged liver and neck veins, elevated jugular pressure with a positive hepatojugular reflex, the presence of peripheral oedema, and peripheral and central cyanosis. Auscultatory findings suggestive of right ventricular dysfunction include a right ventricular, S₃, S₄, or summation gallop. Flow murmurs over the major pulmonary arteries rather than over the normal cardiac auscultatory areas are characteristic of CTEPH.^{11,22} A chest x-ray will usually show hilar fullness attributable to the engorgement of the central pulmonary arteries, clear lung fields, and right ventricular enlargement. An electrocardiogram will often indicate right ventricular hypertrophy and

strain. Spirometry is often normal. At rest, arterial blood gases may also be within normal limits.²

Ventilation perfusion (V/Q) scans and pulmonary arteriograms are advocated as providing the most useful information in the diagnosis of, and subsequent decisions about, the operability of cases of CTEPH.^{6,14,23} Ventilation perfusion scans allow the distinction to be made between primary pulmonary hypertension and obstructive causes of pulmonary hypertension such as CTEPH. When V/Q scan results are inconclusive, or in cases where information about the technical operability is required, pulmonary arteriography is the procedure of choice. The collection of haemodynamic data such as PAP, PVR, and cardiac output (CO) through right heart catheterisation during the process of pulmonary arteriography is useful in the final determination of the feasibility of surgery. Generally, patients with no other life threatening illnesses and with obstructions of the central pulmonary arteries resulting in a PVR greater than 300 dynes/s/cm⁵ are good candidates for PTE, although various centres employ variations of these selection criteria.

The procedure

Pulmonary thromboendarterectomy as a surgical option for CTEPH was first proposed by Hollister and Cull in 1956.²⁴ A year later the procedure was carried out by Hurwitt, Shein & Rifkin.²⁵ Further work in the early 1960s by Snyder, Kent & Baisch²⁶ and Houk, Hufnagel & McClenathan²⁷ further established the technique as the treatment of choice for PTE.

The surgical approach to the patient with CTEPH has changed considerably since its first application. The surgical procedure has been described elsewhere.^{6,11,12,18} The current practice is generally the one developed at the UCSD Medical Centre involving median sternotomy with cardiopulmonary bypass and periods of cardioplegia, hypothermia, and circulatory arrest. The surgical technique involves removing organised thrombi along with a thin lining of intima while leaving the media intact (Figure 1). Because CTEPH is a bilateral disease in all but a few cases, sternotomy is used to gain access to both pulmonary arteries to facilitate the complete removal of the thrombi. Surgical success depends on having a bloodless field so cardiopulmonary bypass with periods of circulatory arrest is essential to prevent bronchial arterial flow flooding the surgical field. During the procedure, patients are cooled to 17-20°C.^{19,28} to avoid injury to the myocardium and the brain.

At present, the procedure is performed at a limited number of centres because of the skill and complexity involved. Lack of adequate experience has led to incomplete thromboendarterectomies in some cases resulting in inadequate postoperative pulmonary haemodynamic outcomes.¹¹

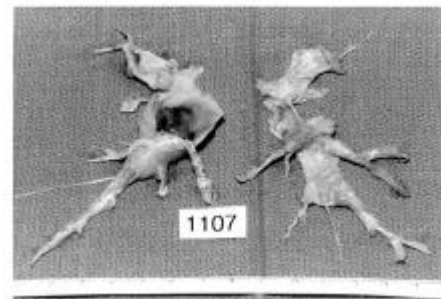


Figure 1 *In situ* surgical specimen of chronic thrombi showing organised fibrotic material.

The postoperative management of patients is complicated. Apart from the usual difficulties seen with open heart surgery (ie arrhythmias, haemodynamic instability, electrolyte imbalance, pericardial effusion, pericarditis, and infection), patients may also suffer from persistence of pulmonary hypertension (probably due to the inability to remove a sufficient amount of thrombus during the procedure) and reperfusion pulmonary oedema.

Anticoagulant therapy is started immediately after surgery, unless major bleeding problems are present.

Intended purpose

Pulmonary thromboendarterectomy is intended for patients suffering from CTEPH. Candidates for surgery are chosen after fulfilling specific criteria developed by specialist centres currently adopted worldwide. Most patients referred to surgery have significant functional disability as evidenced by the New York Heart Association (NYHA) functional classification III or IV; calculated pulmonary vascular resistance at rest of greater than 300 dynes/s/cm⁵ (values above 1,000 dynes/s/cm⁵ are usual in this patient group); chronic thrombus location in the main, lobar, or segmental arteries; absence of severe associated diseases such as coronary artery and valvular disease; and willingness to accept surgical risk.^{6, 11, 12, 29-31} In units with greater surgical experience, more liberal patient selection criteria have been used⁶. These include patients with more distal thromboembolic disease, those with severe elevation of pulmonary vascular resistance (greater than 1200 dyne/sec per cm⁵) and those with advanced hepatic and renal dysfunction due to right-sided heart failure. Occasionally, patients with a pulmonary vascular resistance less than 300 dyne/sec per cm⁵ have been accepted for surgery. These have been young people with total unilateral pulmonary artery occlusion and unacceptable exertional dyspnoea.

Clinical need

To date there are no reliable data on the prevalence or incidence rates of CTEPH. Estimates from three different sources of information are given below.

Although there are no Australian data pertaining to CTEPH, there is information regarding pulmonary embolism, its initial disease state. In 1995-1996 the total number of hospital separations for pulmonary embolism was 5,178. The number of pulmonary embolism patients experiencing progression to CTEPH, while unknown, has been estimated by experts to range from 0.01percent to 4.0percent.^{21,32} Based on these estimates, the potential number of patients with pulmonary embolism who may go on to develop CTEPH ranges from approximately 0.3 to 104 per year. From 1,100 pulmonary thromboendarterectomies performed between 1990 and 1999 at UCSD³³, the estimated annual case load is about 110 cases per year.

Between 1998 and the third quarter of 2000, seven patients received subsidy under the Commonwealth Medical Treatment Overseas (MTO) Program for PTE performed at UCSD. Expert opinion suggests this represents one half to one third of eligible patients in Australia (ie. a total of four to six patients per year).

Existing procedures and comparators

Pulmonary thromboendarterectomy is currently the treatment of choice for CTEPH. Medical therapy is an option for those who are ineligible for surgery or in patients awaiting surgery. While it fails to correct the underlying pathology of pulmonary vascular obstructions, medical therapy attempts to prevent further clot embolisation and endeavours to treat existing cor pulmonale and right ventricular failure.^{4, 11, 34}

Anticoagulation is usually initiated immediately and maintained for life. It is used to reduce the likelihood of recurrent deep venous thrombosis and pulmonary embolism. Thrombolytic therapy is often ineffective because thrombosed material is fibrotic and organised. However, its use might be indicated for acute occurrences of pulmonary thromboembolism.

The insertion of an inferior vena caval (IVC) filter prevents recurrent large emboli from reaching the pulmonary vasculature.

Angioplasty is ineffective as a treatment for this condition because arteries are totally obstructed. Also, the fibrous consistency of thrombi causes them to withstand considerable compression and retain their original arrangement.

The administration of oxygen and the recommendation of a diet low in salt are mainstays of adjuvant therapy.

CTEPH may be an indication for lung transplantation. Lung transplants decrease pulmonary vascular resistance, improve right ventricular ejection fraction and give good symptomatic relief. Single lung transplantation for pulmonary vascular disease can be complicated and hazardous.^{35, 36} Bilateral sequential lung transplant and heart/lung transplant are also feasible. Large centres should achieve 80 percent one-year and 50-55 percent five-year survival rates.^{37, 38} This compares unfavourably with the results for PTE, with an 88 percent one-year and 76 percent five year survival rate.⁵¹ Furthermore, many patients with pulmonary vascular disease would die on waiting lists for transplant because of the lack of suitable donors.

Current reimbursement arrangement

There is currently no specific MBS item number for PTE, which has rarely been performed in Australia. Access to the procedure for Australian patients is available through the MTO Program administered by the Australian Department of Health and Aged Care. This Program provides financial assistance for Australian patients requiring a life-saving medical treatment, which is not available in Australia. Patients approved for a PTE under the Program are referred to the UCSD Medical Centre for treatment.

Approach to assessment

Review of literature

A team from the Australasian Cochrane Centre and the Health Economics Unit, Monash University, was engaged to conduct a systematic review of literature on pulmonary thromboendarterectomy. The review follows methods outlined in the Cochrane Collaboration Handbook,³⁹ appropriately modified to deal with observational studies.

Literature search

The medical literature was searched to identify relevant studies and reviews for the period between 1966 to 2000. Table 2 lists the electronic databases used in the search.

Table 2 Electronic databases (including edition) used in the review.

| Database | Period Covered |
|--|-----------------------------|
| Best Evidence (Ovid) | 1991 to March/April 2000 |
| Biological Abstracts (Ovid) | 1980 to March 2000 |
| CINAHL (Ovid) | 1982 to March 2000 |
| Cochrane Library including: the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effectiveness, the Cochrane Controlled Trials Register, Health Technology Assessment Database, and the NHS Economic Evaluation Database | Issue 2, 2000 |
| Current Contents (Ovid) | 1993 Week 26 to 2000 Week 9 |
| HealthSTAR | 1975 to March 2000 |
| Journals@Ovid (Ovid) | March 2000 |
| Medline (Ovid) | 1966 to March 2000 |
| National Guidelines Clearinghouse | March 2000 |

The following concepts were applied: pulmonary hypertension (chronic), thromb(o)endarterectomy and surgery. Expansions of the search were made to increase the sensitivity of the process.^{40,41} The peripheral concepts used included: pulmonary embolism, deep venous thrombosis, lung transplantation, anticoagulation, thromboembolism, embolectomy and thrombectomy.

Electronic searching included the Internet sites of the following health technology assessment groups: International Society of Technology Assessment in Health Care, International Network of Agencies for Health Technology Assessment (and 28 member organizations), British Columbia Office of Health Technology Assessment (Canada), German Health Technology Assessment Project, Center for Medical Technology Assessment (Sweden), Scottish Health Purchasing Information Centre (Scotland), Medical Technology and Practice Patterns Institute (USA), NIH Office of Medical Applications of Research (USA), Office of Technology Assessment Archive (USA), RAND Corporation (USA), University HealthSystems Consortium (USA) and the Veterans Affairs Technology Assessment Program (USA).

Textbooks and book chapters were assessed. Reference lists of publications were scanned and relevant citations retrieved.

Entry criteria

Collected citations were filtered through a multi-level review involving a team with skills in clinical medicine, public health, health information, basic science, clinical epidemiology and biostatistics. Articles were excluded if they met the following criteria:

- Basic experimental or animal studies;
- Focus was not on PTE for CTEPH;
- Studies enrolling less than 10 subjects;
- Articles that included data published in later studies; and
- Publications in a language other than English

Data extraction

The review extracted data from the included articles using a standardised instrument created for this assessment. Two independent reviewers examined each article. Discrepancies in evaluation were discussed and resolved through consensus.

The review assessed evidence presented in the selected studies and classified it according to the National Health and Medical Research Council (NHMRC) revised hierarchy of evidence (Table 3).

Table 3 Designation of levels of evidence.

| | |
|-------|---|
| I | Evidence obtained from a systematic review of all relevant randomised controlled trials. |
| II | Evidence obtained from at least one properly designed randomised controlled trial. |
| III-1 | Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method). |
| III-2 | Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies or interrupted time series with control group. |
| III-3 | Evidence obtained from comparative studies with historical control, two and more single arm studies or interrupted time series without a parallel control group. |
| IV | Evidence obtained from case series, either post-test or pre-test and post-test. |

Source: NHMRC⁴²

Expert advice

A supporting committee with expertise in cardiothoracic surgery, thoracic medicine, cardiology, intensive care medicine, and public health was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for supporting committees, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the supporting committee is provided at Appendix B.

Results of assessment

Is it safe?

The complications arising from PTE are mainly those that take place due to cardiac surgery. These include arrhythmias, bleeding complications, pericarditis, pericardial effusion, wound infections, and electrolyte imbalances. Multiple comorbidities are often present in the population likely to benefit from the procedure and in spite of severe limitation and accompanying disease, few have been debarred.¹¹

Three additional complications are distinctive to PTE and affect gas exchange during the immediate postoperative period: persistent pulmonary hypertension, reperfusion lung injury and pulmonary vascular steal.^{2, 12, 43} Reperfusion oedema is due to the overperfusion of blood in the endarterectomized portions of the lung causing capillary leakage. Radiographically, it is seen to affect portions of the lung distal to the thrombotic insult and is associated with normal pulmonary capillary wedge pressures. It may appear as a radiographic infiltrate as early as two hours after surgery but usually takes up to 72 hours to develop. Severity can vary from a mild 'radiographic oedema' with hypoxaemia to a fatal acute haemorrhagic event. Levinson, Shure & Moser have suggested pathophysiologic mechanisms involving inflammatory responses from the pulmonary vessels.⁴⁴ Mechanical ventilatory support and careful management of fluid balance are required until resolution.^{11, 28, 45} There is some evidence to suggest corticosteroids provide some benefit.⁹

Pulmonary vascular steal is characterised by reduced perfusion in areas of the lung where thrombi were absent and greater perfusion in areas of the lung from which thrombi were removed. The cause of this phenomenon is not fully understood although it is known to resolve itself over time.²⁸

One of the most serious problems affecting subjects is the persistence of pulmonary hypertension due to the inability to remove enough organised material at the time of surgery.¹¹

Transient delirium in the postoperative period is associated with hypothermia and total circulatory arrest times of 55 minutes or more.^{6, 31, 46} To avoid this complication circulatory arrest is generally limited to a maximum of 20 minutes per side. Where transient delirium occurs, supportive management is recommended until it resolves, which is usually within 48 hours.^{12, 31}

Mortality

Published reports of mortality following PTE are summarised in Table 4. Mortality rate varied from about two percent to 24 percent.^{13, 47} Overall, about 85 percent of subjects undergoing PTE survived the in-hospital period. Variations in centres (possibly reflecting differences in skill and surgical technique, patient factors and throughput) accounted for a large proportion of the heterogeneity among results. A large proportion of deaths was due to ventricular failure and reperfusion oedema.^{13, 43, 47-50} Other reported causes include pulmonary haemorrhage, respiratory failure, cardiac tamponade and pneumonia.

Table 4 Reports of in-hospital mortality following pulmonary thromboendarterectomy in published series.

| First Author and Year of Publication | Total Number of Subjects | Frequency (%) | Causes of Death | Proportional Mortality Frequency (Rate,%) |
|--------------------------------------|--------------------------|------------------|--|---|
| Archibald 1999 ⁵¹ | 308 | 54 (17.5) | Not specified | --- |
| Dartevelle 1999 ⁴⁸ | 68 | 9 (13.2) | Right ventricular failure | 5 (55.6) |
| | | | Reperfusion oedema | 2 (22.2) |
| | | | Pulmonary haemorrhage | 1 (11.1) |
| | | | Cardiac tamponade | 1 (11.1) |
| Mayer 1999 ⁵² | 47 | 4 (8.5) | Residual pulmonary hypertension | 2 (50.0) |
| | | | Reocclusion of pulmonary arteries | 1 (25.0) |
| | | | Unclear | 1 (25.0) |
| Gilbert 1998 ⁴⁹ | 17 | 4 (23.5) | Heart failure or reperfusion oedema | 2 (50.0) |
| | | | Hypoxemia and ventricular arrhythmia | 2 (50.0) |
| Miller 1998 ⁴⁷ | 25 | 6 (24.0) | Progressive cardiac and respiratory failure with persistent pulmonary hypertension | 2 (33.3) |
| | | | Numerous postoperative complications Pneumonia and respiratory failure | 2 (33.3) |
| | | | Unexplained | 1 (16.7) |
| | | | | 1 (16.7) |
| Tanabe 1997 ⁵⁰ | 25 | 4 (16.0) | Right ventricular failure | 2 (50.0) |
| | | | Could not be weaned from extracorporeal circulation | 2 (50.0) |
| Hartz 1996 ⁴³ | 34 | 8 (23.5) | Reperfusion oedema | 3 (37.5) |
| | | | Respiratory failure | 2 (25.0) |
| | | | Right ventricular failure | 2 (25.0) |
| | | | Multiorgan system failure | 1 (12.5) |
| Simonneau 1995 ¹³ | 11 | 2 (18.2) | Reperfusion oedema | 1 (50.0) |
| | | | Pulmonary hypertensive lesions | 1 (50.0) |
| Totals | 596 | 91 (15.3) | | |

In spite of the mortality rate, there is evidence that improvements in technology and skill are translating into improved patient survival. Chitwood, Sabiston & Wechsler reviewed the literature of the surgical results for CTEPH from 1960 to 1983.⁵³ During this period they report a mortality rate of 22 percent. Since then, mortality rates have declined with increasing surgical skill and experience. The UCSD is identified as having the lowest reported mortality of 6.6 percent from 1993 to 1995.³⁰

Several studies have attempted to describe predictors of mortality in this population. A study by Hartz, Byrne et al suggested preoperative PAP and PVR was associated with survival.⁴³ In their study population, patients who died had higher PAP and PVR compared to those who survived (PAP, 62.1 compared to 49.5 mm Hg; PVR, 1,512 versus 949 dynes/s/cm⁵). When specific cut-off points were identified, 41 percent of patients with PVR's of greater than 1,100 dynes/s/cm⁵ died compared to six percent with values less than 1,100 dynes/s/cm⁵ ($p < 0.01$). A similar relationship was observed for PAP: mortality was 37 percent for subjects with average preoperative values of more than 50 mm Hg compared to eight percent ($p < 0.01$). Daily, Dembitsky et al found in-hospital mortality was statistically significantly related to failure to achieve at least a 50 percent decrease in preoperative PVR (odds ratio (OR)=3.31; $p < 0.001$), total number of minutes on cardiopulmonary bypass (OR=1.13 per 10 minutes; $p = 0.002$), and baseline preoperative PVR ($p = 0.002$).⁵⁴ However, Gilbert, Gaine et al did not find any relationship between pre-surgical haemodynamic or clinical variables and subsequent survival.⁴⁹

Morbidity

The most common causes of morbidity following PTE are similar to those found in cardiac surgery and other procedures requiring cardiopulmonary bypass. Published reports, summarised in Table 5, indicate that some of the leading causes of death identified in the previous section are present in milder instances. Darteville, Fadel et al reports about a third of subjects undergoing PTE experienced reperfusion oedema and about one in every five patients experienced pneumonia.⁴⁸ The figures reported by Hartz, Byrne et al. are only slightly different.⁴³ Predictors of morbidity have not been found. Levinson, Shure & Moser found no specific associations between preoperative patient characteristics and the development of reperfusion oedema following PTE.⁴⁴

Table 5 Adverse events following pulmonary thromboendarterectomy in published series.

| First Author and Year of Publication | Total number of subjects | Maximum length of follow up | Adverse Event | Number of Subjects (%) |
|--------------------------------------|--------------------------|-----------------------------|------------------------------------|------------------------|
| Darteville 1999 ⁴⁸ | 68 | 3 months† | Reperfusion pulmonary oedema | 23 (33.8) |
| | | | Pneumonia | 13 (19.1) |
| | | | Cardiac tamponade | 4 (5.9) |
| | | | Transient neurologic complications | 4 (5.9) |
| | | | Bilateral phrenic nerve injury | 4 (5.9) |
| | | | Bronchial bleeding | 3 (4.4) |
| | | | Renal failure | 3 (4.4) |
| Miller 1998 ⁴⁷ | 25 | 2 months | Bilateral diaphragmatic paralysis | 1 (4.0) |
| Tanabe 1997 ⁵⁰ | 25 | 2 years | Postoperative cerebral infection | 1 (4.0) |
| Hartz 1996 ⁴³ | 34 | ?‡ | Reperfusion pulmonary oedema | 7 (20.6) |
| | | | Pulmonary haemorrhage | 6 (17.6) |
| | | | Bilateral phrenic nerve injury | 5 (14.7) |
| | | | Respiratory failure | 4 (11.8) |
| | | | Recurrent laryngeal nerve injury | 4 (11.8) |
| | | | Right ventricular failure | 3 (8.8) |
| | | | Pneumonia | 3 (8.8) |
| | | | Postoperative bleeding | 3 (8.8) |
| | | | Cardiac tamponade | 2 (5.9) |
| | | | Delirium | 1 (2.9) |
| | | | Renal failure | 1 (2.9) |
| | | | Sternal wound infection | 1 (2.9) |
| | | | Stroke | 1 (2.9) |
| Sepsis | 1 (2.9) | | | |

* Abbreviations: NYHA=New York Heart Association

† Results are at three months of follow-up. Total length of follow-up is unclear.

‡ Unstated or unknown.

Is it effective?

The ideal study design for assessing the clinical effectiveness of a therapeutic procedure is a randomised controlled trial (RCT). The literature search did not retrieve RCTs examining the use of PTE for CTEPH. None of the studies considered direct comparisons between PTE and either current best medical therapy or lung transplantation.

Eight studies were retrieved from the primary literature. These studies represented the most recent published experience of specific patient groups defined by the location of the surgical centre or hospital. The presence of multiple publications from the same research group and examining the same pool of subjects introduces considerable bias if not detected. As stated previously, this report examines only the most recent publications produced by particular research groups where particular outcomes were examined. Table 6 summarises general characteristics of the collected studies. The most recent reports have been published in the latter half of 1990s, five being published between 1998 and 1999. Half of all studies were conducted in the United States. Most were descriptive case series. Two were comparative studies utilising internal comparison groups defined by survival.^{43,49}

Table 6 General characteristics of studies meeting entry criteria.*

| First Author and Year of Publication | NHMRC Level and Study Design | Location | Enrolment Period | Maximum Length of Follow-up | Study Population | | | |
|--------------------------------------|------------------------------|------------------|--------------------------|-----------------------------|------------------|------------|----------------------|--|
| | | | | | N | Male n (%) | Age, years mean (SD) | NYHA Class n (%) |
| Archibald 1999 ⁵¹ | IV Case series | California USA | 1970 - '94 | 16 yrs | 308 | 181 (58.8) | 56.2 (15.6) | ?† |
| Darteville 1999 ⁴⁸ | IV Case series | France | 1996 - '98 | 3 mths‡ | 68 | 35 (51.5) | 54.3 (13.5)# | I or II: 2 (2.9) III or IV: 66 (97.1) |
| Mayer 1999 ⁵² | IV Case series | Germany | 1989 - '97 in two series | 6 yrs | 47 | ? (56.3)§ | 51 (18)§# | I or II: 3 (3.8) III or IV: 77 (96.2) |
| Gilbert 1998 ⁴⁹ | III-2 Comparative Study | Maryland USA | 1994 - '97 | ? | 17 | ? | 49.4 (11.6)¶ | ? |
| Miller 1998 ⁴⁷ | IV Case series | Pennsylvania USA | 1985 - '95 | 2 mths | 25 | 21 (84.0) | 46 (23-74)** | ? |
| Tanabe 1997 ⁵⁰ | IV Case series | Japan | 1985 - '96 | 2 yrs | 25 | 9 (36.0) | 51 (13) | I or II: 2 (8.0) III or IV: 23 (92.0) |
| Hartz 1996 ⁴³ | III-2 Comparative Study | Illinois USA | 1983 - '95 | ? | 34 | 16 (47.1) | 49 (23-84)** | ? |
| Simonneau 1995 ¹³ | IV Case series | France | 1984 - '93 | 5 yrs | 11†† | ? | ? | I or II: 4 (44.4) III or IV: 5 (55.6) |

Abbreviations: NHMRC = National Health and Medical Research Council; NYHA = New York Heart Association; SD = standard deviation.

† Unstated or unknown.

‡ Results at three months of follow-up. Total length of follow-up is unclear.

§ Result for subgroup. Result for total population is unclear.

Value is assumed to be the standard deviation.

¶ Calculated from data.

** Values in parentheses are ranges.

†† Total eligible population was 72. The characteristics of two patients who died postoperatively are not reported.

Archibald, Auger et al described the experience of 308 patients followed for a maximum of 16 years.⁵¹ All other studies examined much smaller patient numbers for shorter periods post-operatively. Most of the later studies report a greater proportion of males. All studies examined patient groups with mean ages over 45 years, although with varying ranges. Most patients were graded under the NYHA classification as being of Classes III or IV, reflective of accepted criteria for determining operability. In spite of this, Simonneau, Azarian et al report that four of nine subjects (44%) undergoing PTE in their institution were in Classes I and II.¹³

Survival

No studies compared the estimated cumulative survival of patients undergoing PTE with those receiving different therapies. A study published by Riedel, Stanek et al⁵⁵ and widely cited by experts as providing data on the survival of medically treated CTEPH patients^{13, 18, 43} estimates survival probabilities according to mean PAP (Table 7). Median survival for PAP values reported by the various case series range from between less than one year (for PAP greater than 50 mm Hg) to about five years (for a PAP of 31-40 mm Hg). The survival experience of 532 subjects undergoing PTE, as summarised by Archibald, Auger et al., points to increased survival times and probabilities.⁵¹

Table 7 Estimated survival times and cumulative survival probabilities from two separate single-arm survival studies following medically- and PTE-treated CTEPH patients.*

| Sample size | Medically-treated subjects (Riedel 1982 ⁵³) | | | PTE-treated subjects (Archibald 1999 ^{8, 49}) |
|---|--|---------|------|--|
| | 10 | 19 | 35 | 532 |
| PAP, mm Hg | 31 - 40 | 41 - 50 | > 50 | 47.9† |
| Approximate median survival time, years‡ | 4.5 - 5 | 2.5 - 3 | < 1 | 17 |
| Approximate cumulative survival probability, %‡ | | | | |
| 1 year | 90 | 70 | 40 | 88 |
| 2 years | 70 | 60 | 20 | 82 |
| 3 years | 70 | 45 | 15 | 80 |
| 5 years | 50 | 30 | 10 | 76 |
| 10 years | --- | 20 | --- | 75 |

* Abbreviations: PAP = pulmonary artery pressure; PTE = pulmonary thromboendarterectomy.

† Mean for entire study population.

‡ Approximated from published Kaplan-Meier curves.

Functional status

Improvements in functional status as measured by changes in NYHA Functional Classifications are evident in a majority of cases (Table 8). Group summaries point to significant improvements in survivors. Prior to surgery, Darteville, Fadel et al,⁴⁸ Mayer, Kramm et al⁵² and Tanabe, Okada et al⁵⁰ report that more than 90 percent of their patients were in either Class III or IV. After surgery, the proportions were 5.0 percent, 5.1 percent, and 23.8 percent respectively.

Table 8 Reported changes in functional status (NYHA Classification) following pulmonary thromboendarterectomy.*

| NYHA Functional Classification | Archibald 1999 ⁵¹ | | Darteville 1999 ⁴⁸ | | Mayer 1999 ⁵² | | Tanabe 1997 ⁵⁰ | | Simonneau 1995 ¹³ | |
|--------------------------------|------------------------------|---------------|-------------------------------|--------------|--------------------------|--------------|---------------------------|--------------|------------------------------|--------------|
| | Pre-PTE | Post-PTE | Pre-PTE | Post-PTE | Pre-PTE | Post-PTE | Pre-PTE | Post-PTE | Pre-PTE | Post-PTE |
| I | ?† | 170 (55.6) | --- | 42 (71.2) | --- | 56 (70.0) | --- | 16 (76.2) | 4 (44.4) | 9 (100.0) |
| II | | 112 (36.6) | 2 (2.9) | 14 (23.7) | 3 (3.8) | 20 (25.0) | 2 (8.0) | | | |
| III | | 20 (6.5) | 43 (63.2) | 3 (5.1) | 48 (60.0) | 4 (5.0) | 18 (72.0) | 5 (23.8) | 5 (55.6) | --- |
| IV | | 4 (1.3) | 23 (33.8) | --- | 29 (36.2) | --- | 5 (20.0) | | | |

* Abbreviations: NYHA = New York Heart Association; PTE = pulmonary thromboendarterectomy.

† Unstated or unknown.

Archibald, Auger et al described the use of a validated Shortness of Breath Questionnaire (SOBQ) developed at the UCSD.⁵¹ It estimates the severity of dyspnoea in 23 activities of daily living. A six-point scale is used (0=no dyspnoea, 5=inability to perform activity due to dyspnoea). The mean (\pm SD) SOBQ score post-surgery for all 23 activities was 0.64 ± 0.71 (median, 0.41; range, 0-3.95). Of 303 patients, 191 (63.0%) had no shortness of breath when walking on a level surface and 76 (25.1%) reported sometimes experiencing dyspnoea.

The general occurrence of dyspnoea was tested by asking subjects “How would you rate your shortness of breath since surgery?” and applying Likert-like ratings. Of 306 patients, 224 (73.2%) reported “much improvement”, 70 (22.9%) reported “improvement”, eight (2.6%) reported no change, and two (0.6%) reported worsening of shortness of breath. Self-reported ability to climb flights of stairs indicated that 7.2 percent could climb stairs “indefinitely” with only 4.8 percent climbing less than one flight. The mean duration of oxygen use for patients discharged on oxygen was 7.1 weeks. The mean time before returning to work was 16.6 ± 18.3 weeks.⁵¹

Use of supplemental oxygen

Archibald, Auger et al stated that a large majority of patients (89.6%) reported not using supplemental oxygen, 7.2 percent use oxygen during exertion, 5.0 percent at rest and 9.4 percent during sleep.⁵¹ Twenty-six patients out of 68 (38.2%) required oxygen prior to surgery in the Darteville, Fadel et al series. After surgery, only three out of 59 (5.1%) needed oxygen therapy at reassessment three months later.⁴⁸

Quality of life

Only the study by Archibald, Auger et al looked at quality of life (QoL).⁵¹ The authors used Likert-ratings and the SF-36 to measure general QoL domains. When compared to a group of non-diseased subjects, patients who underwent PTE scored statistically significantly lower in four of eight domains (physical function, role limitations due to physical function, general health, and emotional well-being), reported lower scores for bodily pain and higher scores in energy, and had similar scores for social functioning and role limitations due to emotional causes. When compared to a separate group of patients with CTEPH prior to surgery, the post-PTE group showed improvement in all domains except emotional well-being.

Two additional questions were asked. For the first (“In general, would you say your health is excellent, very good, good, fair, or poor?”), 53 of 298 (17.8%) reported excellent health, 92 (30.9%) reported very good health, and seven (2.3%) reported poor health. The second question was posed in the following manner: “How do you feel about the quality of your life since the surgery?” of which five choices were available (much worse, worse, same, improved, much improved). Of 302 responders, 232 (76.8%) reported they were much improved, 61 (20.2%) improved, and nine (3.0%) were the same as before.

Haemodynamic outcomes

Studies reporting haemodynamic outcomes unanimously observed statistically significant improvements in these variables (Table 9).

Table 9 Reported changes in haemodynamic variables following pulmonary thromboendarterectomy.

| Variable | First Author and Year of Publication | Pre-PTE | Post-PTE | P value |
|------------------------------|--------------------------------------|--------------|-------------|---------|
| PAP, mm Hg | Dartevelle 1999 ⁴⁸ | 53.1 (13.0) | 30.2 (11.8) | <0.001 |
| | Mayer 1999 ⁵² | 50.0 (13) | 26.0 (11) | <0.001 |
| | Tanabe 1997 ⁵⁰ | 44.0 (4) | 30.0 (8) | <0.001 |
| | Simonneau 1995 ¹³ | 39.0 (11) | 26.0 (8) | <0.05 |
| CI, l/min/m ² | Dartevelle 1999 ⁴⁸ | 2.1 (0.5) | 2.8 (0.6) | <0.001 |
| | Tanabe 1997 ⁵⁰ | 2.6 (0.6) | 3.3 (0.4) | <0.001 |
| | Simonneau 1995 ¹³ | 2.6 (0.9) | 3.3 (0.8) | <0.05 |
| CO, l/min | Dartevelle 1999 ⁴⁸ | 3.8 (0.9) | 5.0 (1.3) | <0.001 |
| SVO ₂ , % | Dartevelle 1999 ⁴⁸ | 55.0 (8) | 63.0 (9) | <0.01 |
| TPR, dynes/s/cm ⁵ | Dartevelle 1999 ⁴⁸ | 1174.0 (416) | 519.0 (250) | <0.001 |
| PVR, dynes/s/cm ⁵ | Mayer 1999 ⁵² | 1018.0 (234) | 319.0 (143) | <0.01 |
| | Gilbert 1998 ⁴⁹ | ?† | ? | <0.05 |
| | Tanabe 1997 ⁵⁰ | 778.0 (313) | 410.0 (197) | <0.001 |
| | Simonneau 1995 ¹³ | 823.0 (505) | 393.0 (161) | <0.05 |

* Abbreviations: CI = cardiac index; CO = cardiac output; PAP = pulmonary artery pressure; PTE = pulmonary thromboendarterectomy; PVR = pulmonary vascular resistance; SVO₂ = venous oxygen saturation.

† Unstated or unknown.

What are the economic considerations?

General cost effectiveness framework

The framework for the economic evaluation of any medical technology considered by MSAC is the comparison of the social costs and benefits of that technology compared with the current alternative treatment for patients. Cost effectiveness analysis involves the calculation of an incremental cost effectiveness ratio $(C_i - C_c) / (O_i - O_c)$ where C_i is the total cost of resources used associated with the intervention, C_c is the total cost of resources used associated with the comparator, O_i is the outcome associated with the intervention and O_c is the outcome associated with the comparator. Where there are two comparators, a weighted average of cost and outcome can be calculated where the weights are the proportion of patients who are likely to receive each of the comparator treatments. Given the uncertainty surrounding the effectiveness of PTE and the cost of setting up treatment in Australia, we have only been able to undertake an exploratory analysis of its cost effectiveness. We have calculated an indicative incremental cost effectiveness ratio using data on effectiveness from the previous section, and cost data taken from a number of sources to predict the cost of PTE in Australia and estimate the cost of alternative treatments.

Comparator

In the case of PTE there are two main issues in deciding the appropriate comparator. First, the next best alternative to PTE is commonly accepted as medical management. Double lung transplant is an option for some patients if otherwise suitable but this is usually only offered to those under 60 years of age – not the typical age group of CTEPH patients. Second, since some Australian patients are currently treated by PTE overseas the appropriate comparator for patients who could be treated by PTE in Australia is a mixture of medical treatment for those currently treated here and PTE treatment overseas.

Costs

Pulmonary thromboendarterectomy

The cost of treatment includes the diagnostic work up, the procedure itself, insertion of an IVC filter, intensive and other in-patient care, cardiac rehabilitation, oxygen therapy and maintenance drugs and monitoring. The direct medical costs of PTE in Australia are unknown. However, the procedure is likely to be similar in resource intensity to a complex cardiovascular procedure. As a conservative estimate of the cost of the procedure, we have used the hospital cost of heart transplant. The post-acute treatment costs of those successfully treated are unknown but not likely to be high. There will be some rehabilitation, drug and monitoring costs. We assume patients will visit a specialist doctor four times a year. We assume they will take anticoagulant drugs such as warfarin indefinitely. In the case of patients who travel overseas, the total cost of PTE includes the cost of treatment, rehabilitation and travel overseas for themselves and their families and any subsequent lifetime medical costs in Australia on their return.

Medical management

Medical management is not resource intensive and is likely to involve the use of cardiac medications such as diuretics and digoxin. However, expert opinion suggests patients on medical management need intensive hospital care as the disease progresses and in the final year of life may be admitted to hospital on a number of occasions most likely with a diagnosis of heart failure.

Table 10 shows the estimated resources and unit costs associated with PTE and medical treatment over a five-year period.

Table 10 Resources used for PTE and medical management over five years.*

| Resource | Cost per unit (\$) | Source |
|---|------------------------|---|
| PTE Overseas | | |
| Procedure | 190,000.00 | Cost to MTO program |
| PTE in Australia | | |
| Procedure and cardiac rehabilitation | 35,686.00 | Equivalent to DRG 008 heart transplant ⁶⁴ |
| Doctor visits | 65.80 | MBS specialists visit |
| Anti-coagulant therapy per month | 8.45 | |
| Training cost | | |
| Initial training of a surgeon and physician | 75,000 each for 6 mths | Opportunity cost of a surgeon/physician |
| Ongoing staff training | 75,000 per annum | Opportunity cost of medical staff |
| Medical management | | |
| Oxygen therapy (per week) | 20.00 | Expert opinion |
| Cardiovascular drugs | 30.00 | PBS monthly cost of 2 typical heart disease medications |
| Doctor visits | 65.80 | MBS specialists visit |
| Hospital admissions for heart failure | 3,500.00 | DRG 252 heart failure ⁶⁴ |

* Abbreviations: DRG=diagnosis related group; MBS=Medicare Benefits Scheme; MTO=Medical Treatment Overseas Program; PBS=Pharmaceutical Benefits Scheme; PTE=pulmonary thromboendarterectomy.

Outcomes

The potential benefits to patients with PTE in Australia are the possible increase in the length and quality of life associated with treatment. For those who would have travelled overseas, removing the dislocation for patients and their families is likely to be of considerable personal value.

Incremental cost effectiveness

The cost effectiveness of PTE could be calculated as the difference between the average cost of PTE and medical treatment divided by the expected extra survival per patient adjusted for quality of life.

This would give an incremental cost per quality-adjusted life year (QALY). However, if we are concerned with gains to be made from reallocation of current health resources, it is legitimate to take into account resources and outcomes associated with PTE overseas, either funded privately or subsidised under the MTO Program. Consequently, we have also calculated a weighted average cost per life year gained taking into account the prior decision to reimburse cost of travel and treatment overseas.

Modelled cost effectiveness – assumptions

There are a number of issues in estimating the incremental cost effectiveness ratio for PTE:

- There is considerable uncertainty about the number of patients each year suitable for the procedure. Between 1998 and the third quarter of 2000, seven patients received subsidy under the MTO program to undergo PTE at the UCSD Medical Centre. It may be that others were treated with funds raised privately. It has been suggested those treated overseas represent one half to one third of eligible patients in Australia (ie. a total of four to six patients per year).
- The efficacy of PTE as reported in published papers has been discussed above. The effectiveness of PTE even in established centres is not well demonstrated in randomised controlled trials. None of the published studies makes a direct comparison between PTE and current best medical management. If one or more facilities were established in Australia it may take some time to develop the expertise to achieve the results of the best in the published literature even with a subsidised training program.
- The literature does not allow an accurate estimate of increased survival from PTE compared to medical treatment. Table 11 shows an extrapolation of the survival data in Table 7 to calculate the expected years of life for PTE and medical management over ten and twenty year time horizons. The data suggest that for those with PAP in the 41 to 50 mm Hg range in the medical management group, there would be 3.6 expected years of life after 10 years; for PTE, 7.8 years is expected. Applying a five percent discount rate, the expected life years per patient are 2.6 for medical management and 5.6 for PTE over a ten-year period. Extending the horizon to 20 years suggests a greater gain from PTE given the low survival of medically managed patients beyond five years. However, extrapolating to 20 years on limited data is unreliable. We have, thus, restricted the cost effectiveness analysis to a 10-year horizon.

Table 11 Estimated expected years of life over a 10- and 20-year period.*†

| | Medical management | PTE | Difference | Discounted difference at 5% |
|-----------------|--------------------|------|------------|-----------------------------|
| 10 year horizon | 3.6 | 7.8 | 4.2 | 3.0 |
| 20 year horizon | 4.5 | 12.6 | 8.1 | 6.1 |

Abbreviations: PAP=pulmonary artery pressure; PTE=pulmonary thromboendarterectomy.

† Projections based on data from table 7 with PAP in the 41 to 50 mm Hg range with no survivors at 20 years for medical management and 25 percent survival for PTE.

- The quality of life measures used in the published literature are not consistent across studies and are subject to the same biases as the clinical measures. Therefore, their psychometric properties make them unsuitable for calculating quality adjusted life years. Because of this, we have restricted the cost effectiveness analysis to a cost per life year gained. However, it must be acknowledged the quality of life measures that do exist suggest a substantial improvement in the quality of life of survivors associated with PTE compared to medical management.

- The cost of the PTE procedure in Australia is unknown but is likely to be similar to other complex cardiovascular procedures. The cost of a heart transplant is estimated to be \$35,686.⁵⁶ Expert opinion suggests the procedure can be performed in existing cardiovascular surgical units and there is no need for additional investment in equipment or facilities. The only cost in addition to the recurrent cost of the procedure is the cost of training staff. The typical cost to the Commonwealth of sending a patient to the USA for treatment in the last three years has been about \$175-200,000. The cost in the future is in part dependent on the exchange rate fluctuations. Patients who pay for the treatment themselves may pay more.
- The downstream costs of treatment for CTEPH with PTE are not well established. It has been suggested the maintenance costs for successful patients following PTE are low and limited to three or four doctor visits per annum and anticoagulant drugs. We have attributed a cost of four specialists visits a year and warfarin treatment to PTE patients in Australia.
- For those who fail PTE treatment or remain on medical management survival is low and the cost of treatment in the final year of life could be high. It has been suggested such patients are likely to be on continuous oxygen therapy and admitted to hospital on at least two occasions with a diagnosis of heart failure in the final year of life. Home oxygen therapy typically costs about \$80 per month. Based on the public hospital cost of heart failure (DRG 252⁵⁴), we assume the cost of an admission with heart failure is approximately \$3,500. The annual per-patient cost of medical management in Australia is not known but is likely to consist of a range of cardiovascular drugs. Drugs used in cardiovascular drug maintenance therapy typically have a PBS price of around \$10-15 each per month. We assume a total cost of \$30 per month per patient.
- If a unit or units were established in Australia to perform PTE, there would be additional establishment and training costs. On the assumption that the public opportunity cost of a surgeon was of the order of \$150,000 per annum with six months of training for two people per facility in the first year, this would add the annual equivalent of a \$35,000 investment per annum to the program cost over five years (with a five percent discount rate). There would be additional training cost in Australia thereafter. This might involve training one person a year for six months at a cost of \$75,000 per annum or an annual equivalent. All long-term expected costs were estimated by adjusting for survival over five years with mortality assumed to occur in mid-year. The *present value* of the stream of costs and outcomes was calculated using a five percent discount rate and its annual equivalent attributed to patients in the first year. Costs were assumed to accrue at the beginning of each year. The present value of a stream of costs is the investment, which would return an equivalent stream of income over the five-year period. The annual equivalent stream of costs is a constant annual cost with the same present value as that investment.

Results of the analysis

Table 12 shows a summary of the results of the exploratory cost effectiveness analysis. If six patients were treated each year with PTE in Australia the analysis suggested we would expect a total annual cost saving equivalent to about \$297,000. However, if the number of patients were to rise above 17 there would be an additional cost. The cost saving is largely attributable to the cost of treatment overseas at \$190,000 per patient. If no patients were treated overseas then setting up a PTE facility in Australia for six patients per annum would incur an annual cost with a present value of \$239,000 compared to medical treatment only. On the assumptions of effectiveness and extrapolated survival given above, the incremental cost per life year gained would be less than \$13,500 (\$239,000/18). It is possible the predicted incremental cost per QALY would be less than this, given the apparent comparatively high quality of life of survivors of the procedure and the apparently low quality of life of those on medical management.

Table 12 Results of indicative cost effectiveness analysis for PTE for six patients per year in Australia compared to current practice and medical management.*

| | Cost of program (\$) | Life years | Incremental cost per life year gained |
|--|----------------------|------------|---------------------------------------|
| Current practice (3 overseas, 3 medical) | 605,157.00 | 24.7 | |
| Six domestic PTE procedures | 307,327.00 | 33.6 | |
| Six medical treatments | 68,069.00 | 15.8 | |
| PTE minus current practice | -297,831.00 | 8.9 | PTE dominant |
| PTE minus medical management | 239,258.00 | 17.8 | \$13,461 |

* Abbreviation: PTE=pulmonary thromboendarterectomy.

Sensitivity analysis

No formal analysis of the sensitivity of results to the assumptions in the exploratory cost effectiveness analysis has been carried out. It is clear however that the predicted savings associated with reduced overseas treatments and the estimated cost effectiveness ratio compared to medical management for all patients are sensitive to the assumed potential efficacy of PTE in Australia. Predicted cost savings are sensitive to the comparative cost of treatment in Australia and the USA. Training costs, as estimated, are not a major determinant of the cost effectiveness of treatment especially if throughput is higher than modelled here. If training costs were four times as high as estimated for a throughput of six patients, the cost effectiveness ratio for PTE versus medical management would double and the savings compared to current practice would be close to zero.

Considering the limitations of the evidence available, it is not possible to provide a definitive estimate of the cost effectiveness of PTE compared to current medical management in the treatment of CTEPH. The recurrent cost of PTE performed in Australia is likely to be substantially less than the cost of sending patients to the USA, even with the additional costs associated with training for a period of years. An estimate of the likely annual cost per patient of performing PTE in Australia over five years suggests savings of \$297,000 per annum, compared to treating three eligible patients by medical management and sending three patients overseas for surgery each year. However, it must be emphasised the estimated incremental cost per patient is based on the assumption of the existence of a similar level of unmet demand for the procedure in Australia from a cohort of patients with a similar degree of disease and suitability for

surgery as those subjects treated in current facilities overseas. We do not have direct evidence such an unmet need exists nor do we have evidence indicating Australian facilities would have a success rate with the procedure similar to the results in the published literature. There is a well-established need to acquire expertise over time and this may take a number of years. The learning curve in a surgical procedure with low numbers of patients may be comparatively long and proficiency of local surgeons may never achieve the level found in facilities with a higher throughput of patients. If patients are recruited into the program with a different level of disease and the expertise of the local practitioners is not able to match that of overseas experts, the cost effectiveness of setting up a unit in Australia becomes less clear. If no overseas treatment were offered, then PTE facilities would have a total additional cost of \$239,000 per annum compared to medical treatment alone for six patients. Any additional cost must be weighed against the expected benefit per patient from treatment in terms of survival and quality of life.

Published evidence suggests considerable survival gains and improved quality of life but these results come from uncontrolled studies and are subject to considerable potential bias. The exploratory analysis suggested a possible total gain of 18 discounted years of life in a 10-year horizon compared to medical management of the same six patients. Given the expected net cost of the technology, the cost per life year gained may be less than \$13,500. Any estimated incremental cost per QALY is likely to be less than the incremental cost per life year gained given the low quality of life associated with the disease and the apparently large improvement associated with PTE. With a lower rate of discount, the cost effectiveness ratio would look more attractive for PTE. Once again, however, we would emphasise that the reliability of these cost effectiveness estimates are constrained by the need to establish that the local provision of PTE in an environment of low patient throughput could achieve the levels of effectiveness reported in the literature even with high quality training. Our confidence in those levels is further limited by the non-experimental nature of the evidence.

Conclusions

Safety

The lack of rigorous studies prevents the proper assessment of the safety profile of the procedure. The available information suggests significant mortality and morbidity that varies with the surgical centre where the operation was performed, possibly reflecting differences in surgical experience and technique, patient selection and system-wide differences. The most common causes of death are right ventricular failure and reperfusion oedema. The most common causes of morbidity are similar to those found in cardiac surgery.

An Australian unit would be expected to achieve an operative mortality of 20 percent or less within the first 10 patients and 15 percent or less within the first 20 patients. Median post-operative intensive care and total hospital stays of three and 10 days should be achievable within the first 10 patients. Patients discharged following surgery should ultimately achieve independence from oxygen and NYHA Class I or II status.

Effectiveness

The procedure is associated with increased survival, improvements in functional status (as measured using the New York Heart Association Functional Classification, and scales measuring ability to perform activities of daily living), quality of life, and haemodynamic outcomes when post-surgical status is compared to preoperative levels. There is no strong evidence to determine whether the advantages of this procedure are significantly different from other treatment alternatives (or no treatment) in individuals. Clinical expertise suggest that high-level evidence (Level II or higher) is not likely to be available given the widespread acceptance of PTE as an established procedure in the management of CTEPH.

Cost-effectiveness

There may be gains in survival and quality of life associated with PTE compared to medical management of patients currently treated in Australia. If six patients a year were treated, PTE may cost less than \$13,500 per QALY gained compared to medical management only. A local facility treating at least three patients per year would probably be regarded as cost effective subject to the following:

- Achievement of effectiveness suggested by the current evidence;
- Absence of capacity constraints on current cardiovascular facilities;
- Suitability and comparability of potential patients for treatment as those cases in the published literature; and
- Development and maintenance of a training program that achieves the same quality of treatment and consequent effectiveness within a reasonable time period.

Recommendation

MSAC recommended that, on the strength of evidence pertaining to the efficacy and relative safety of pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension, and the life threatening nature of this condition, public funding should be supported for this procedure to be performed in Australia.

- The Minister for Health and Aged Care accepted this recommendation on 27 March 2001 -

Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Commonwealth Minister for Health and Aged Care on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Commonwealth Minister for Health and Aged Care on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Commonwealth Minister for Health and Aged Care on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to the AHMAC.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

| Member | Expertise |
|-----------------------------------|--|
| Professor David Weedon (Chair) | pathology |
| Ms Hilda Bastian | consumer health issues |
| Dr Ross Blair | vascular surgery (New Zealand) |
| Mr Stephen Blamey | general surgery |
| Dr Paul Hemming | general practice |
| Dr Terri Jackson | health economics |
| Professor Brendon Kearney | health administration and planning |
| Mr Alan Keith | Assistant Secretary, Diagnostics and Technology Branch, Commonwealth Department of Health and Aged Care |
| Associate Professor Richard King | internal medicine |
| Dr Michael Kitchener | nuclear medicine |
| Professor Peter Phelan | paediatrics |
| Dr David Robinson | plastic surgery |
| Professor John Simes | clinical epidemiology and clinical trials |
| Associate Professor Bryant Stokes | neurological surgery, representing the Australian Health Ministers' Advisory Council |

Appendix B Supporting committee

Supporting committee for MSAC reference 05 Pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension

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|---|---|
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Appendix C Studies included in the review

General characteristics of studies meeting entry criteria.*

| First Author and Year of Publication | NHMRC Level and Study Design | Location | Enrolment Period | Maximum Length of Follow-up | Study Population | | | |
|--------------------------------------|------------------------------|------------------|----------------------------|-----------------------------|------------------|------------|----------------------|--|
| | | | | | N | Male n (%) | Age, years mean (SD) | NYHA Class n (%) |
| Archibald 1999 ⁵¹ | IV Case series | California USA | 1970 to 1994 | 16 years | 308 | 181 (58.8) | 56.2 (15.6) | ?† |
| Dartevelle 1999 ⁴⁸ | IV Case series | France | 1996 to 1998 | 3 months‡ | 68 | 35 (51.5) | 54.3 (13.5)# | I or II: 2 (2.9) III or IV: 66 (97.1) |
| Mayer 1999 ⁵² | IV Case series | Germany | 1989 to 1997 in two series | 6 years | 47 | ? (56.3)§ | 51 (18)§# | I or II: 3 (3.8) III or IV: 77 (96.2) |
| Gilbert 1998 ⁴⁹ | III-2 Comparative Study | Maryland USA | 1994 to 1997 | ? | 17 | ? | 49.4 (11.6)¶ | ? |
| Miller 1998 ⁴⁷ | IV Case series | Pennsylvania USA | 1985 to 1995 | 2 months | 25 | 21 (84.0) | 46 (23 to 74)** | ? |
| Tanabe 1997 ⁵⁰ | IV Case series | Japan | 1985 to 1996 | 2 years | 25 | 9 (36.0) | 51 (13) | I or II: 2 (8.0) III or IV: 23 (92.0) |
| Hartz 1996 ⁴³ | III-2 Comparative Study | Illinois USA | 1983 to 1995 | ? | 34 | 16 (47.1) | 49 (23 to 84)** | ? |
| Simonneau 1995 ¹³ | IV Case series | France | 1984 to 1993 | 5 years | 11†† | ? | ? | I or II: 4 (44.4) III or IV: 5 (55.6) |

* Abbreviations: NHMRC = National Health and Medical Research Council; NYHA = New York Heart Association; SD = standard deviation.

† Unstated or unknown.

‡ Results at three months of follow-up. Total length of follow-up is unclear.

§ Result for subgroup. Result for total population is unclear.

Value is assumed to be the standard deviation.

¶ Calculated from data.

** Values in parentheses are ranges.

†† Total eligible population was 72. The characteristics of two patients who died postoperatively are not reported.

Abbreviations

| | |
|------------------|---|
| CI | cardiac index |
| CO | cardiac output |
| CTEPH | chronic thromboembolic pulmonary hypertension |
| DRG | diagnosis related group |
| IVC filter | inferior vena caval filter |
| MBS | Medicare Benefits Scheme |
| MTO | Medical Treatment Overseas Program |
| NHMRC | National Health and Medical Research Council |
| NYHA | New York Heart Association |
| OR | odds ratio |
| PAP | pulmonary artery pressure |
| PBS | Pharmaceutical Benefits Scheme |
| PE | pulmonary embolism |
| PTE | pulmonary thromboendarterectomy |
| PVR | pulmonary vascular resistance |
| QALY | quality-adjusted life year |
| QoL | quality of life |
| RCT | randomised controlled trial |
| SOBQ | Shortness of Breath Questionnaire |
| SVO ₂ | venous oxygen saturation |
| TPR | total pulmonary resistance |
| UCSD | University of California at San Diego |
| V/Q scan | ventilation perfusion scan |

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