Functional and haemodynamic outcome 1 year after pulmonary thromboendarterectomy

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Received 3 September 2007; received in revised form 7 April 2008; accepted 8 April 2008; Available online 22 May 2008

Abstract

Objective: Chronic thromboembolic pulmonary hypertension (CTEPH) results in severe symptoms and impaired survival. Pulmonary thromboendarterectomy (PTE) is considered the gold standard treatment. Many units have reported excellent early results post PTE, but there is less information on whether benefit is sustained. We sought to determine the medium-term functional and haemodynamic outcome for patients following PTE and the longer-term survival after discharge from hospital.

Methods: Data were collected prospectively on all patients who underwent PTE in the UK between 1997 and June 2006. Patients were reassessed at 3 and 12 months after operation. Follow-up over time was assessed using repeated measures ANOVA, the Friedman test or Wilcoxon signed ranks test as appropriate. Results: Two hundred and twenty-nine patients underwent PTE, survived to hospital discharge, and completed follow-up. At 3 months following operation, there was a significant reduction in mean pulmonary artery pressure ($47 \pm 14$ to $25 \pm 14$ mmHg, $p < 0.001$), a significant increase in cardiac index ($1.9 \pm 0.7$ to $2.5 \pm 0.6$ l/min m$^2$, $p < 0.001$) and a significant increase in 6-min walk distance ($269 \pm 123$ to $375 \pm 104$ m, $p < 0.001$). At 12-month follow-up, the haemodynamic improvements were sustained and there was a further increase in 6-min walk distance ($375 \pm 104$ to $392 \pm 108$ m, $p = 0.004$). NYHA class was significantly reduced at 3 months, with the improvement sustained at 12 months. Conditional survival following discharge from hospital was 92.5% at 5 years and 88.3% at 10 years. Conclusions: PTE is a very effective therapy for CTEPH. This is the first report from a continuous national series to fully characterise haemodynamic and functional outcome 1 year after PTE. Patients enjoy continued improvement in haemodynamic status that translates into better exercise capacity, reduced symptoms and excellent survival.

Keywords: Pulmonary thromboendarterectomy; Pulmonary endarterectomy; Pulmonary hypertension; Survival; Surgical outcomes

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is associated with poor clinical status and historically poor survival. Patients with a mean pulmonary artery pressure (mPAP) over 50 mmHg have a 5-year survival of less than 10% [1,2]. Medical management of these patients has been disappointing because there is a poor response to vasodilator therapy [3–5], although newer therapies may provide some benefit [6–9]. Pulmonary thromboendarterectomy (PTE) was developed as a surgical strategy to relieve pulmonary artery obstruction in CTEPH and has been remarkably successful. This procedure has been pioneered primarily by Jamieson’s group at the University of California, San Diego (UCSD), and is now associated with acceptable operative risk [10,11]. In the postoperative period, patients enjoy a reduction in pulmonary pressure and an improvement in cardiac function.

Although to date there have been over 3000 operations performed worldwide, and many case series have been published, lead by the extensive experience and excellent results of Jamieson’s group, documentation of haemodynamic and functional outcome after discharge from hospital is minimal. In 1999 the UCSD group reported the results of a mail-out questionnaire survey of their patients. This revealed a substantial improvement in symptom class in patients who responded to the survey [12]. In a more recent study from the Netherlands, the 6-min walk test was found to be improved at 1 year after PTE in 35 patients and the degree of improvement correlated with the reduction in pulmonary artery pressure (PAP) obtained in the perioperative period [13]. Matsuda et al. reported the outcomes of 102 patients who underwent PTE. The peak oxygen consumption (VO$_2$) and 6-min walk test (SMWT) were found to be improved at 1 month and again at 1 year. There was no significant improvement between 1 and 2 years. They had an actuarial survival rate of 90.9% at 3 years and 84.0% at 5 years [14]. In
2000, D’Armini et al. reported haemodynamic improvements at 3 months and 2 years following PTE in 23 and 10 patients, respectively. These patients also experienced an improvement in New York Heart Association (NYHA) functional class [15]. Mellemkjaer et al. observed a similar result in their 38 patients [16]. In 1996, Mayer et al. demonstrated improvement of NYHA class and haemodynamics in 65 of 90 long-term survivors. They showed reduced pulmonary vascular resistance (PVR), improved cardiac index (CI) and reduced right ventricular (RV) size at 27 months. The remaining 25 patients were not re-investigated [17]. Because of the way PTE services have evolved, longer-term survival after discharge from hospital has been even more difficult to quantify. Selected patients often travelled vast distances for surgery in the pioneering centres and therefore comprehensive follow-up has not been possible. However, the CTEPH disease process is complex and it is known that patients with operable (so called proximal) disease in the segmental pulmonary artery branches can also develop a peripheral vasculopathy in the non-obstructed vascular beds with histological changes similar to those in idiopathic pulmonary hypertension. This may explain why some patients have a degree of persisting pulmonary hypertension even after apparently successful surgical clearance of all visible disease. The impact of this process in the longer-term is not understood.

The objective of this study was to determine the outcome in all patients following hospital discharge after PTE surgery in the United Kingdom (UK). This procedure was first performed at Papworth hospital in 1997, and in 2000 the hospital was commissioned to provide the UK PTE service. Since that time, nearly 400 operations have been performed. From 2001, the medical management of patients with pulmonary hypertension in the UK was designated to five specialist pulmonary hypertension centres. In addition to concentrating the experience with CTEPH and PTE, this provides a unique opportunity to study the natural history of this disease process by careful follow-up of all patients with this illness in the UK.

2. Patients and methods

All patients with CTEPH and suspected operability were discussed preoperatively at a weekly multidisciplinary team meeting with pulmonary hypertension physicians, specialist radiologists and PTE surgeons. Patients with other diseases causing the radiological appearance of CTEPH, for example sarcoma and vasculitis, were excluded from the current follow-up study. PTE was performed using principles similar to that employed by the UCSD group [18,19]. Early in our experience, all operations were done using deep hypothermia and circulatory arrest (DHCA). In the later half of our experience, we have used deep hypothermia with selective antegrade cerebral perfusion wherever possible, although DHCA was still employed if visualisation proved difficult due to excessive collateral blood flow [20].

Our standard follow-up protocol for all patients returning to Papworth hospital includes assessment of NYHA class, a 6-min walk test and right heart catheterisation (RHC) at 3 months following PTE. At 12 months, the NYHA class is recorded and a walk test is repeated. Early in our experience, all patients underwent RHC at 12 months as well, although this was found to be unnecessary and practice has changed so that only those with persistent pulmonary hypertension (mPAP ≥ 25 mmHg) at 3-month RHC underwent 12-month RHC. Perioperative patient data was entered prospectively into a dedicated surgical database and postoperative data was recorded on the Papworth pulmonary hypertension database. The recent merger of these databases has given the opportunity for verifying all data, and any missing fields were cross-checked with original case notes. All patients continue life-long follow-up at one of the five specialist pulmonary hypertension centres. The patient survival data was verified by a recent visit (completed January 2007) to all the national pulmonary hypertension centres with examination of all records and individual case notes.

2.1. Statistics

Analysis was performed using the SPSS v13.0 statistical package. Continuous variables are described as the mean (± standard deviation) or median (interquartile range) and compared using a paired Student’s t-test. Categorical data are expressed as proportions, and compared using the χ² test. Follow-up over time was assessed using repeated measures ANOVA, the Friedman test or Wilcoxon signed ranks test for variables within subjects as appropriate. Estimation of cumulative survival was performed using the Kaplan–Meier method. A p value of < 0.05 was considered significant.

3. Results

Between the start of the program in 1997 and June 2006, 229 patients underwent PTE at Papworth hospital and survived to hospital discharge. Follow-up data was available for 223 (97.3% complete). The average age of the study population was 55.2 years and 125 (54.3%) males. No patients at baseline were in NYHA class I. A total of 12.4% were in NYHA class I. A total of 12.4% were in NYHA class II. A total of 20.6% were in NYHA class III. A total of 46.9% were in NYHA class IV. A total of 1.3% were in NYHA class V. A total of 8.9% were in NYHA class VI. A total of 9.8% were in NYHA class VII. A total of 96.3% were in NYHA class I. A total of 80.3% were in NYHA class II. A total of 74.4% were in NYHA class III. A total of 53.2% were in NYHA class IV. A total of 32.3% were in NYHA class V. A total of 14.9% were in NYHA class VI. A total of 9.8% were in NYHA class VII. A total of 96.3% were in NYHA class I. A total of 80.3% were in NYHA class II. A total of 74.4% were in NYHA class III. A total of 53.2% were in NYHA class IV. A total of 32.3% were in NYHA class V. A total of 14.9% were in NYHA class VI. A total of 9.8% were in NYHA class VII. A total of 96.3% were in NYHA class I. A total of 80.3% were in NYHA class II. A total of 74.4% were in NYHA class III. A total of 53.2% were in NYHA class IV. A total of 32.3% were in NYHA class V. A total of 14.9% were in NYHA class VI. A total of 9.8% were in NYHA class VII. A total of 96.3% were in NYHA class I. A total of 80.3% were in NYHA class II. A total of 74.4% were in NYHA class III. A total of 53.2% were in NYHA class IV. A total of 32.3% were in NYHA class V. A total of 14.9% were in NYHA class VI. A total of 9.8% were in NYHA class VII.

Table 1

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<th>Table 1</th>
<th>Haemodynamic data (median ± IQR)</th>
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<tr>
<td></td>
<td>Preoperative (n = 226)</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>47 ± 14</td>
</tr>
<tr>
<td>PVR (dynes cm⁻¹)</td>
<td>800 ± 494</td>
</tr>
<tr>
<td>CI (l/min m²)</td>
<td>1.9 ± 0.7</td>
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Patients underwent right heart catheterisation at 3 months as part of routine follow-up. Only in the early part of the series, or where elevated mPAP was found at 3 months was RHC performed at 12 months, hence the discrepancy in numbers. Because of this, the 12-month data must be interpreted with caution (mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; CI: cardiac index; a: p < 0.001, Friedman test; b: p < 0.001 vs preoperative, Wilcoxon signed ranks test).
NYHA class II, 62.7% were in NYHA class III and 24.9% were in NYHA class IV (Fig. 2). Prior to operation, the median mPAP was 47 ± 14 mmHg, the median pulmonary vascular resistance was 800 ± 494 dynes s cm⁻¹ and the median cardiac index was 1.9 ± 0.7 l/min m². Haemodynamic data are summarised in Table 1. At 3 months after PTE, there was a significant reduction in mean pulmonary artery pressure and pulmonary vascular resistance (47 ± 14 to 25 ± 14 mmHg, 800 ± 494 to 244 ± 253 dynes s cm⁻¹, p < 0.001), and significant increase in cardiac index (1.9 ± 0.7 to 2.5 ± 0.6 l/min m², p < 0.001). After the first few years, patients no longer underwent routine right heart catheterisation at 12 months, but instead underwent investigation only if there was concern at the 3-month study. Thus the 12-month data must be interpreted with caution.

There was a significant increase in 6-min walk distance at 3 months (mean 269 ± 123 to 375 ± 104 m, p < 0.001). At 12 months, there was a further increase in 6-min walk distance (375 ± 104 to 392 ± 98 m, p = 0.004). The results of the 6-min walk test are displayed in Fig. 1. At 3 months, 30.9% were in NYHA class I, 55.9% were in NYHA class II, 12.3% were in NYHA class III and 0.5% were in NYHA class IV (p < 0.001 vs preoperative). At 12 months there was further improvement in NYHA class: 40.7% were in NYHA class I, 50.3% were in NYHA class II, 8.5% were in NYHA class III and 0.5% were in NYHA class IV (p < 0.001 vs 3 months) (Fig. 2).

In this group of 229 hospital survivors after PTE, there were 14 late deaths. Causes of death included sepsis, stroke, intracerebral haemorrhage, ovarian cancer, metastatic carcinoma and one patient died in the post-partum period. The cause of death could not be identified in seven patients. Conditional survival was 94% at 3 years, 92.5% at 5 years and 88.3% at 10 years follow-up (Fig. 3).

This report has concentrated on the outcome of patients following hospital discharge after PTE surgery. To put these patients in proper context the overall experience is reported below. During the same period (1997 to June 2006) a total of 291 patients undertook PTE surgery at Papworth hospital. For all 291 patients undergoing PTE between 1997 and June 2006, actuarial survival was 74.6% at 3 years, 72.7% at 5 years and 69.3% at 10 years. These figures include all patients who died in the immediate postoperative period and those who died later but were never well enough to leave hospital. As of July 2007, 360 patients have now been treated by PTE and in the last 100 cases (November 2005 to July 2007) there have been four hospital deaths.

4. Discussion

This study demonstrates that the dramatic early results of PTE surgery previously reported from many centres are sustained by 1 year. This is the largest series to date to report post PTE outcome after discharge from hospital and the first to report extended follow-up of a complete national patient cohort. The patient demographics and degree of post-operative improvement in RHC indices, walk test distances and NYHA class are similar to previously reported smaller individual series. We have demonstrated that the known early benefit of PTE is certainly still present 1 year after surgery. Compared with the historical reports of survival for patients with severe CTEPH, the longer-term survival in this postoperative patient cohort is remarkably good.

The organisation of pulmonary hypertension care in the UK National Health Service has facilitated this report. We believe that our system of designated national pulmonary hypertension centres covering the whole country and a single surgical centre allows the best chance for comprehensive follow-up of patients and a unique opportunity to report their outcome post PTE surgery.
The haemodynamic results at 3 months after PTE are similar to those previously described in the immediate postoperative period with mPAP almost half that measured pre PTE. It was difficult to justify continuing to perform a further invasive test at 1 year for the majority of patients. In our patients, these assessments proved that exercise capacity was increased at 3 months, and even further increased at 12 months, although the haemodynamic improvements were not increased further at 12 months compared to 3 months. It is not surprising that there is continued functional improvement at 12 months, since the 3-month follow-up period represents an intermediate step in the postoperative recovery process.

Many earlier publications detailing PTE outcomes have concentrated on in-hospital survival. The most experienced centre (UCSD) has reported an in-hospital survival of approximately 95% after PTE in 1500 patients [19]. Our series has concentrated on the outcome after hospital discharge. However, we have included all patients from the first operation at the start of our PTE series and therefore it is possible that these results may actually be an underestimate of the true benefit of PTE in the longer-term. Our current in-hospital survival now approaches that of the most experienced centre at UCSD, but this series includes our initial experience of PTE with a higher in-hospital mortality in the earlier years. Despite this it is very clear that patients who survive to hospital discharge after PTE surgery have an excellent outlook with over 90% being still alive at 5 years. Of those who died, death was caused by diseases unrelated to pulmonary hypertension in half, although chronic anticoagulation may have been contributory. Others have shown, with smaller numbers, that long-term survival after PTE is good. Actuarial survival rates of 90% and 80% at 3 and 5 years after PTE have been reported [14,16,21]. Lung transplantation has also been implemented as a therapeutic strategy for CTEPH. However, actuarial survival rates after lung transplantation for all diagnoses are 61% and 49% at 3 and 5 years, and are worse for primary pulmonary hypertension [22]. In comparison, our patients had an actuarial survival of 74.6% at 3 years and 72.7% at 5 years with a conditional survival of 94% and 92.5% at 3 and 5 years after PTE. It is clear that PTE is to be preferred over lung transplantation for the treatment of CTEPH.

There are some limitations to this report. We have described outcome in a continuous national series of patients undergoing PTE in a single institution from 1997 to 2006. Prior to 2000 when we became the only commissioned UK centre, a small number of patients may have undergone PTE at other hospitals in the UK with unknown results. The management of patients, operating surgeons and techniques have necessarily evolved with time and experience over the period of this study. We were unable to collect haemodynamic and functional data on 6 of the 229 patients, so follow-up is not 100% complete. The result of haemodynamic assessment at 12 months must be interpreted with caution because the number of patients is smaller, and the numbers include a significant number who were reassessed because of residual pulmonary hypertension at the 3-month assessment. The late survival data should also be interpreted with some caution as the number of patients is quite small after 5 years follow-up since the series only commenced in 1997 and less procedures were performed in the early years.

In conclusion, the current comprehensive report contributes to a growing body of literature that demonstrates the success of PTE for the treatment of CTEPH. Patients enjoy continued improvement in symptoms, function and survival.

Acknowledgements

The authors acknowledge Robin Condliffe for help with data collection and validation of patient survival through the UK CTEPH national survey. We also acknowledge Denise Hodkins and Maureen Rootes for help with data collection. Mr John Dunning was the lead PTE surgeon from the start of the programme until end 2003. We are indebted to the contributions to patient care made by the referring pulmonary hypertension physicians, and radiologists. The PTE anaesthetists were Drs Alain Vuylysteke (intensive care), Ray Latimer, Roger Hall, John Knesshaw, Joe Arrowsmith and Andrew Klein. We thank Dr Ryan Zarychanski for his assistance with the statistical analysis.

References

results were sustained at 12 months; and regarding the 6-min walk, that's even walk test from 280 to 390 m. And they could also show that these 3-month…

Dr A. Haverich

I have two questions to the authors:

1. How many of the patients in that 30% actually went on to get transplantation.
2. How many of the patients in this group presented here and were there any differences if that…


Dr P. Dartevelle

There was no statistically significant difference between the 3-month and 12-month time point. I know it’s 2.5 versus 2.4, but that was not a statistically…

Dr W. Klepetko

We're looking at that at the moment. What we do is we assess them for their degree of residual pulmonary hypertension and then they are followed by the pulmonary physicians and they go on to medical therapy based on what the pulmonary hypertension physician feels is necessary. Of the ones who have residual pulmonary hypertension, greater than 90% of them will go back on to pulmonary vasodilators.

Dr A. Averich (Hannover, Germany): I think this is probably one of the best contributions at this year’s meeting of the EACTS.

This is for two reasons. Number one, the data collection on the national basis is something that is very unique in our specialty and gives opportunity to overview a large patient population with the results being elucidated accordingly. Also, the fact that it’s been done in a prospective fashion over a 9-year period puts a lot of weight to the results just being presented.

Dr W. Klepetko

How many of your patients were still on relevant medication 1 year after therapy?

Dr Freed

We’re looking at that at the moment. What we do is we assess them for their degree of residual pulmonary hypertension and then they are followed by the pulmonary physicians and they go on to medical therapy based on what the pulmonary hypertension physician feels is necessary. Of the ones who have residual pulmonary hypertension, greater than 90% of them will go back on to pulmonary vasodilators.

Dr A. D’Armini (Pavia, Italy): I have a question about the haemodynamic results. You showed that the cardiac index increased from 2.1 before the operation to 2.4 after 1 year. And this is not a very high increase. Do you have any explanation for this? Did you study the right ventricle remodelling in some way?

Dr Freed

I need to qualify the 12-month data by saying that not all patients underwent a right heart catheter at 12 months. If you look at the 3-month data, that’s complete for the entire cohort of patients, they all had a right heart catheter and that was 2.5.

Now, the 12-month time period, that represents patients primarily who had residual pulmonary hypertension, although early on in the series we were also routinely doing 12-month right heart catheter.

There was no statistically significant difference between the 3-month and 12-month time point. I know it’s 2.5 versus 2.4, but that was not a statistically significant difference. And I don’t feel personally that there is actually any clinical significance of that difference either.

Dr A. D’Armini: And did you see if maybe patients with a long disease history they have less recovering of the right ventricle function?

Dr Freed: We didn’t look at that specifically.

Dr P. Dartevelle (Le Plessis Robinson, France): What was the mortality rate of this series of 230 patients and what was the cause of mortality after surgery? Because you have some patients who died after 3 months, and what was the cause of the mortality?
Dr Freed: In this series of 230 patients there were 14 late deaths. And in 7 of them, we were unable to determine the cause of death. In other words, they died at home or they died and didn’t get a postmortem analysis or we weren’t able to determine the cause of death.

In the remaining seven, we had two who had cerebral complications, one a cerebral bleed, one a stroke. We have had several that have had metastatic carcinoma from ovarian or other sources. One patient died following a road traffic accident. And that sums up the group. There was another patient who died of sepsis.

So they appeared, other than seven we couldn’t determine, they appeared to be unrelated to the pulmonary hypertension.