Survival after pulmonary thromboendarterectomy: Effect of residual pulmonary hypertension

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Objective: Pulmonary endarterectomy is the treatment of choice for chronic thromboembolic pulmonary hypertension. In many patients hemodynamics are normalized early after surgical intervention. However, the effect of residual pulmonary hypertension on postoperative clinical status and survival is unknown.

Methods: Data were collected prospectively on all patients who underwent pulmonary endarterectomy in a continuous national series between 1997 and December 2007. Postoperatively, patients underwent scheduled reinvestigation, including functional testing and right heart catheterization, at 3 months after the operation. They were divided into 2 groups based on mean pulmonary artery pressure: group 1, less than 30 mm Hg; group 2, 30 mm Hg or greater.

Results: Three hundred fourteen patients underwent pulmonary endarterectomy, survived to hospital discharge, and completed the 3-month follow-up period. At 3 months after pulmonary endarterectomy, there was a significant reduction in mean pulmonary artery pressure for the whole cohort (48 ± 12 to 26 ± 10 mm Hg, $P < .001$). However, 31% of the patients had residual pulmonary hypertension. Group 1 patients enjoyed significantly better exercise capacity and improved symptoms compared with group 2 patients. In addition, there were significantly fewer patients receiving targeted medical therapy in group 1 versus group 2 (0% vs 25%, $P < .001$). Conditional survival after discharge from the hospital for the whole cohort was 90.0% at 5 years and was not different between groups (90.3% for group 1 vs 89.9% for group 2, $P = .36$).

Conclusions: For patients undergoing pulmonary endarterectomy, survival after hospital discharge is excellent. Residual pulmonary hypertension significantly compromised symptom status and functional capacity but did not appear to adversely affect medium-term survival. The effect of targeted medical therapy in patients with residual pulmonary hypertension after pulmonary endarterectomy needs to be evaluated further. (J Thorac Cardiovasc Surg 2011;141:383-7)

Chronic thromboembolic pulmonary hypertension (CTEPH) is a serious condition. Historically before the development of surgical treatment, survival was very poor.[1] In a recent cohort of patients comprehensively followed in the modern era, outcomes had improved.[2] Pulmonary endarterectomy is the treatment of choice to relieve pulmonary artery obstruction in patients with CTEPH and has been remarkably successful.[3] The largest and most comprehensive series to date demonstrates that in the postoperative period patients enjoy a reduction in pulmonary pressure and an improvement in cardiac function with few complications and a low risk of mortality.[4]

However, not all patients are suitable for surgical intervention, and it is increasingly recognized that some patients have residual pulmonary hypertension (PH) after pulmonary endarterectomy.[5-7] Estimates of the number of patients with residual PH after pulmonary endarterectomy have varied from 5% to 35% depending on the definition, and few units have evaluated these patients comprehensively. One other center has reported post–pulmonary endarterectomy persistent PH, with an incidence of 35% (33/93 patients) at 1 year.[5] Another center recently reported a 24% incidence of increased pulmonary vascular resistance (PVR) after pulmonary endarterectomy and showed that advanced New York Heart Association (NYHA) class was associated with poorer survival.[8] When we reported all incident cases of CTEPH in the United Kingdom between 2001 and 2006, we found that in 198 patients investigated at 3 months after pulmonary endarterectomy, using the formal definition of PH (mean pulmonary artery pressure [mPAP] >25 mm Hg and PVR >240 dynes $\cdot$ sec^{-1} $\cdot$ cm^{-5} at rest), residual PH was present in 35%.[2] To our surprise, survival at 3 years remained excellent and was not different from that of the larger group with no residual PH. In the past, medical management of patients with CTEPH has proved disappointing,

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Abbreviations and Acronyms

CTEPH = chronic thromboembolic pulmonary hypertension
mPAP = mean pulmonary artery pressure
NYHA = New York Heart Association
PH = pulmonary hypertension
PVR = pulmonary vascular resistance

with little response to vasodilator therapy.[9,10] However, newer targeted medical therapies might provide some advantage, and therefore it is important to identify patients who could benefit from medical treatment even after pulmonary endarterectomy surgery.[11-16]

Many units have now reported in-hospital results after pulmonary endarterectomy surgery. Outcome after discharge from the hospital has been more difficult to quantify and less frequently reported. We have recently published the results of pulmonary endarterectomy surgery after hospital discharge for all United Kingdom patients.[2,17] Even though this series included patients from the beginning of our pulmonary endarterectomy program, we found remarkable improvement in functional and hemodynamic parameters at 3 months and 1 year, with excellent medium-term survival at 5 years.

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 have a distal small-vessel vasculopathy in the nonobstructed vascular beds with histologic changes similar to those seen in idiopathic PH.[18,19] Indeed, this 2-compartment model was proposed many years ago by Moser and Braunwald[20] after their early experience of treating this condition. This fact explains why some patients have a degree of persisting PH even after apparently successful surgical clearance of all visible disease. Persistently increased PVR in the immediate postoperative period is known to be a significant risk factor for in-hospital death, especially if greater than 500 dynes · s^{-1} · cm^{-5}.[2,4] The effect of residual PH in the longer term is not completely understood. The objective of this study was to determine the effect of residual PH on symptom status and survival after pulmonary endarterectomy in the largest cohort followed to date.

MATERIALS AND METHODS

All patients with CTEPH were discussed preoperatively at a weekly multidisciplinary team meeting with PH physicians, specialist radiologists, and pulmonary endarterectomy surgeons. All data were entered prospectively into a dedicated surgical and PH database, as previously reported.[17] An inferior vena caval filter was inserted in all patients preoperatively. Pulmonary endarterectomy was performed by using principles similar to those used by the University of California, San Diego group.[4,21] All patients underwent surgical intervention with deep hypothermia, but complete arrest of the circulation was not used in every case.[17,22] Anticoagulation was continued postoperatively in all cases.

At 3 months after pulmonary endarterectomy, all patients were invited to return to Papworth Hospital for full review by the pulmonary vascular disease physicians. NYHA class, 6-minute walk test, and right heart catheterization data were recorded. These variables were again examined at 12 months after pulmonary endarterectomy, although right heart catheterization was not repeated unless there was residual PH at 3 months or changes in symptom status, echocardiographic estimates of pulmonary artery pressure, or both. Patients continued follow-up at their local PH specialist center after 1 year.

Based on the mPAP at 3 months, patients were divided into 2 groups: those with mPAPs of less than 30 mm Hg (group 1) and those with potentially prognostically important post–pulmonary endarterectomy PH mPAPs of 30 mm Hg or greater (group 2). Thirty millimeters of mercury was chosen as the division because pressures of greater than and less than this level at baseline appeared to correlate with impaired or normal survival in Riedel and colleagues' original account of survival in patients with CTEPH.[1] It was also a more useful practical definition of residual PH in patients after pulmonary endarterectomy because it coincided with the pressure criteria accepted in our hospital above which to consider use of advanced medical therapies in suitable patients with class III symptoms.[2]

Survival after discharge from the hospital was calculated with a censor date of December 31, 2008. For patients from England and Wales, the National Health Service spine summary care record-tracking system was used based on the patient's individual National Health Service number. For patients from Scotland and Ireland, survival status was checked with the general practitioner during the first 2 weeks of January 2009 by 2 independent researchers from the Papworth research and development department.

Statistics

Analysis was performed with the SPSS version 13.0 statistical software package (SPSS, Inc, Chicago, Ill). Continuous variables are described as the mean ± standard deviation or median ± interquartile range and compared by using Student's t test or the Mann–Whitney U test, as appropriate. Categorical data are expressed as proportions and compared by using the χ^2 test. Follow-up over time was assessed by using repeated-measures analysis of variance or the Friedman test, as appropriate. Estimation of cumulative survival was performed by using the Kaplan–Meier method and compared with the log-rank test.

RESULTS

During the period from the start of the program in 1997 and December 2007, 314 patients underwent pulmonary endarterectomy at Papworth hospital, survived to hospital discharge, and completed follow-up. Full hemodynamic data were available for 306 patients at 3 months (97.4% complete). The mean age of the study population was 55 years (range, 17–81 years), and 54.3% were male. Thirty-one percent of patients had an mPAP of 30 mm Hg or greater at 3 months after pulmonary endarterectomy.

The NYHA class for the whole cohort at baseline and follow-up is shown in Figure 1, A, and the hemodynamic data are shown in Table 1. As expected, by 3 months after pulmonary endarterectomy, there was a significant reduction in mPAP (48 ± 12 to 26 ± 10 mm Hg, $P < .001$) and PVR (805 ± 365 to 301 ± 232 dynes · s^{-1} · cm^{-5}, $P < .001$). Cardiac index was increased significantly for the whole group (2.0 ± 0.7 to 2.5 ± 0.5 L · min^{-1} · m^{-2}, $P < .001$).

Patients in group 1 enjoyed significantly better exercise capacity and improved symptoms compared with those in group 2 (Table 2 and Figure 1, B). The postoperative 6-minute walk distance was significantly greater in group

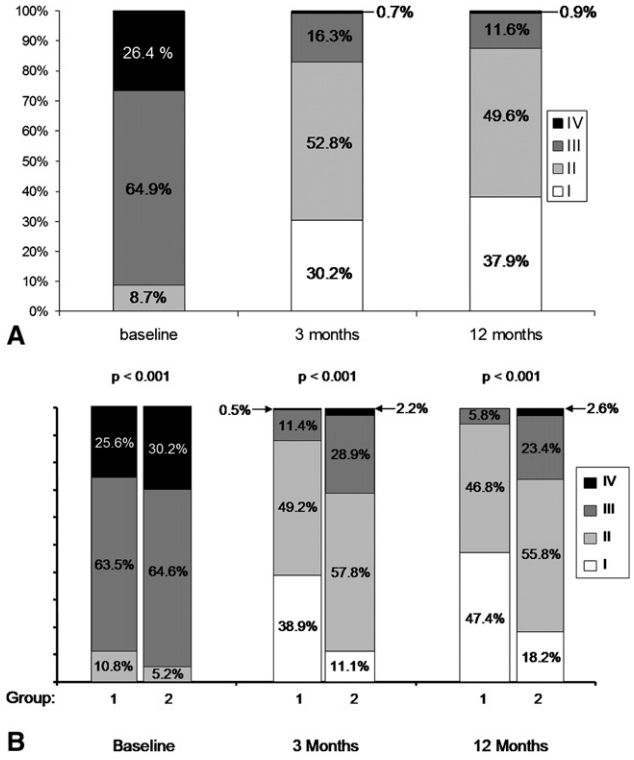

FIGURE 1. A, New York Heart Association class at baseline and 3 and 12 months after pulmonary endarterectomy for the whole cohort. B, New York Heart Association class at baseline and 3 and 12 months after pulmonary endarterectomy for each group. Group 1, Mean pulmonary artery pressure of less than 30 mm Hg; group 2, mean pulmonary artery pressure of 30 mm Hg or greater.

1 at 3 months, as well as at 12 months (Figure 2). Of interest, the only preoperative parameter found to be different between the groups was 6-minute walk distance, which was lower in group 2 even at baseline (Figure 2). After the 3-month hemodynamic assessment and clinical review, 24 patients were started on targeted medical therapy, 7.6% of the cohort. All these patients were in group 2, and therefore 25% of those with residual PH required treatment. The

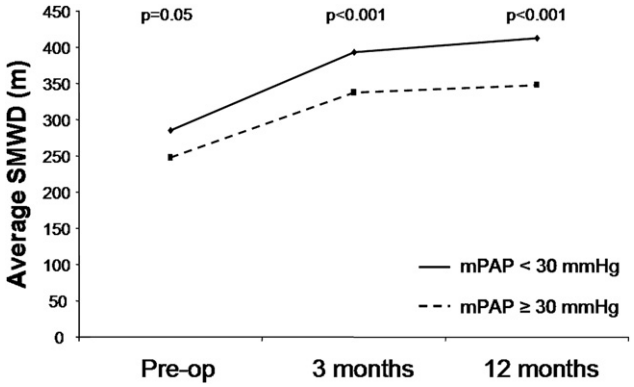

FIGURE 2. Six-minute walk test distance in meters. *mPAP*, Mean pulmonary artery pressure.

TABLE 1. Hemodynamic data for the cohort (median ± interquartile range)

	Preoperative (n = 314)	3 mo (n = 306)	*P* value
mPAP (mm Hg)	48 ± 12	26 ± 10	<.001
PVR (dynes · s^{-1} · cm^{-5})	805 ± 365	301 ± 232	<.001
CI (L · min^{-1} · m^{-2})	2.0 ± 0.7	2.5 ± 0.5	<.001
SMWD (m)	269 ± 119	367 ± 108	<.001

Patients underwent right heart catheterization at 3 months as part of routine follow-up. Eight patients did not have full right heart catheterization data at 3 months. *mPAP*, Mean pulmonary artery pressure; *PVR*, pulmonary vascular resistance; *CI*, cardiac index; *SMWD*, 6-minute walk distance.

disease type, classified intraoperatively, on a subset of 135 patients after 2004 is shown in Table 3.

mPAP, cardiac index, and PVR were not different between groups 1 and 2 preoperatively. However, the preoperative 6-minute walk distance was lower in group 2 (247 ± 121 vs 282 ± 121 m, $P = .03$); this was the only difference between the groups.

During the period of this study, 368 patients with CTEPH were treated by means of pulmonary endarterectomy. Fifty-four patients died before the 3-month assessment, and the surviving 314 patients make up the study cohort. Early (before 3 months) mortality was era dependent: 25% (29/114 patients) for the years 1997-2002 and 2.7% (3/110 patients) for 2006-2007. Conditional survival after discharge from the hospital at a mean follow-up of 4.2 years was 92.6% and was not different between groups (92.7% for group 1 vs 92.6% for group 2, $P = .36$, Figure 3). Survival for all patients, including deaths in the first 3-month period, was 76% at 5 years, with a conditional survival of 90%. Survival status at the censor date could not be confirmed in 2 patients, and therefore follow-up was 99% complete. No patients underwent lung transplantation after pulmonary endarterectomy, but 1 patient underwent a redo endarterectomy for recurrent disease 3 years after the original procedure.

DISCUSSION

We have reported that the excellent early results of pulmonary endarterectomy surgery are sustained by 1 year.[17] We have now extended this work by examining the effect of

TABLE 2. Comparison between patients without (group 1) or with (group 2) residual pulmonary hypertension (median ± interquartile range)

3 mo after operation	Group 1 (n = 210)	Group 2 (n = 96)	*P* value
mPAP (mm Hg)	20 ± 5	38 ± 8	<.001
PVR (dynes · s^{-1} · cm^{-5})	181 ± 88	541 ± 250	<.001
CI (L · min^{-1} · m^{-2})	2.5 ± 0.6	2.5 ± 0.62	NS
SMWD (m)	386 ± 106	337 ± 97	<.001
NYHA class I or II (n)	88.1% (170/193)	68.9% (62/90)	<.001

mPAP, Mean pulmonary artery pressure; *PVR*, pulmonary vascular resistance; *CI*, cardiac index; *NS*, not significant; *SMWD*, 6-minute walk distance; *NYHA*, New York Heart Association.

TABLE 3. Comparison of disease type at the time of the operation by means of Jamieson classification

Disease type	Group 1 (n = 86)	Group 2 (n = 49)	*P* value
1	41 (48%)	15 (31%)	NS
2	38 (44%)	22 (45%)	NS
3	7 (8%)	10 (20%)	NS
4	0 (0%)	2 (4%)	NS

Data were only available for 135 patients.[22] *NS*, Not significant.

potentially significant residual PH on symptom status, functional capacity, and intermediate survival for all of the United Kingdom patients surviving pulmonary endarterectomy from the start of our series in 1997 to the end of 2007. As expected, patients with normalized hemodynamics (group 1) had minimal symptoms and better exercise capacity. However, those with residual PH by our definition (group 2) still showed significant improvement compared with their preoperative status. Importantly, we have confirmed that both groups had equally good survival at 5 years. A significant implication of these results is that pulmonary endarterectomy should be considered in all patients with CTEPH, including those with severely increased PH, because as long as the PVR can be reduced enough to survive the perioperative period, the prognosis is very good, even in those in whom hemodynamics do not fully normalize.

Although the majority of patients are ''cured'' by pulmonary endarterectomy and regain normal pulmonary pressures, residual PH might be thought of as an inevitable consequence of the 2-compartment model of CTEPH.[18-20] The finding from the Vienna group that 92% of patients with ''associated medical conditions'' (splenectomy, indwelling venous catheters, and inflammatory diseases) had residual PH after pulmonary endarterectomy[5] substantiates this hypothesis because many of these medical conditions are associated with a more distal type of disease. However, it could also be argued that residual PH is a complication of inadequate surgical clearance, and every effort should be made to ensure a complete clearance at the time of the operation for patients to enjoy the best result of pulmonary endarterectomy. With increasing institutional and surgical experience, most centers report improved in-hospital survival as case volume increases. Little is known about residual PH after pulmonary endarterectomy surgery because only 2 other centers have reported detailed outcomes in this way.[5,8] Bonderman and associates[5] reported an incidence of 35% by 1 year, and Corsico and colleagues[8] reported an incidence of 24% at 4 years, albeit in smaller series with different definitions at later time points. Taken together with our data, the evidence suggests that up to one third of patients might be affected despite apparently successful pulmonary endarterectomy surgery. It is known that operative mortality is reduced with increasing institutional experience, and one might expect a similar reduction is residual PH in surviving patients. However, it could also be argued that more experienced centers are more likely to accept patients with worse hemodynamics and more distal disease with the inevitable consequence of some residual PH.[23,24]

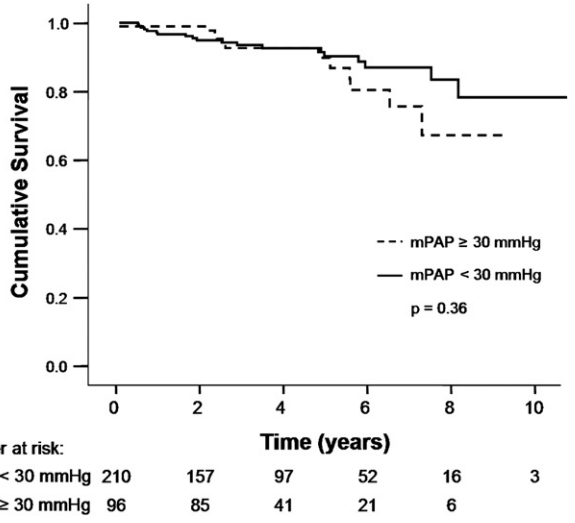

FIGURE 3. Effect of residual pulmonary hypertension on survival after hospital discharge. *mPAP*, Mean pulmonary artery pressure.

A classification scheme for thromboembolic disease was proposed based on operative findings.[23] This scheme has been adopted by many centers, including our own. Unfortunately, we did not start recording this information prospectively into the database until 2004, and therefore information was not available on the whole cohort. As might be expected, there was a trend suggesting that more patients in group 2 had distal (type 3) disease.

The results presented in this article suggest that residual PH (by our definition) after pulmonary endarterectomy surgery does not have a significant effect on survival. This initially appears counterintuitive because the degree of PH in patients with CTEPH at presentation correlates with survival.[1] A similar apparent anomaly is also sometimes observed in trials of drug treatment in patients with PH, when a significant improvement is observed in one outcome measure in response to treatment but does not translate into similar improvements in a second end point, despite both end points correlating at baseline.[16] It might be that the absolute pulmonary artery pressure, cardiac output, or walk distance greater or less than a threshold value is more important than the change in response to treatment. It is also important to recognize that the majority of patients with residual PH in this study, even by our enhanced definition, had only modestly increased pulmonary pressures (mean for group 2, 38 mm Hg), and in addition, some were receiving targeted pulmonary vasodilator therapy. It is likely that improved medical care might be contributing to the unexpectedly good results in those with residual PH. At present, despite the publication of the Bosentan Effects in Inoperable Forms of Chronic Thromboembolic Pulmonary Hypertension study,

this remains an unlicensed indication for drug therapy and must be viewed with caution until more data are available and larger trials have been completed. However, if the dual-compartment model of CTEPH is correct, one might expect an improvement with targeted therapy in patients after pulmonary endarterectomy. It also highlights the importance of structured follow-up and reassessment so that residual PH can be diagnosed and appropriate treatment instituted.[16,25]

In conclusion, we confirm that pulmonary endarterectomy is a remarkably good treatment for patients with CTEPH, and even if significant residual PH is present, patients leaving the hospital alive have a very good medium-term survival. The best functional outcome is obtained in patients with completely normalized hemodynamics after surgical intervention.

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