Pulmonary endarterectomy: outcomes in patients aged >70†

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Abstract

OBJECTIVES: Advanced age is not a barrier to cardiac surgery, with reports demonstrating excellent outcomes, but the effect of age on more complex surgery has not been studied. We assessed the outcomes of pulmonary endarterectomy (PEA) surgery in patients aged >70.

METHODS: A retrospective review of consecutive patients who underwent PEA between January 2006 and March 2011 at a national referral centre. The total cohort was dichotomized according to age on the day of surgery, either below or above 70 years. Outcomes were in-hospital mortality, overall survival and the length of ICU and hospital stays.

RESULTS: Four hundred and eleven patients underwent PEA during the 5-year period. The mean age was 56.9 years (range, 17–84 years). The in-hospital mortality was 14 of 308 (4.6%) for patients <70 years compared with 8 of 103 (7.8%) for patients ≥70 years (P = 0.21). The overall survival at 1, 2 and 3 years was 91.4, 89.9 and 87.7% in the <70-year old group and 85.9, 84.1 and 84.1% in the >70-year old group (log-rank test, P = 0.07), respectively. The length of ICU and in-hospital stays was longer in the >70-year old group, by 1 and 2 days, respectively (P = 0.005 and 0.001).

CONCLUSIONS: PEA surgery in patients ≥70 years is safe and carries a comparable risk of early mortality in younger patients, but there is an increase in resource use due to longer ICU and hospital stays. Advanced age should be taken into consideration when assessing suitability for PEA, but age per se should not be a contraindication to surgery.

Keywords: Pulmonary endarterectomy • Age • Outcomes • Cardiac surgery • Chronic thromboembolic pulmonary hypertension

INTRODUCTION

Following the establishment of pulmonary endarterectomy (PEA) as the most appropriate treatment of choice for chronic thromboembolic pulmonary hypertension (CTEPH) [1], experience has grown with improving results being reported [2]. The surgical aim is a true endarterectomy to produce an immediate and sustained fall in pulmonary vascular resistance (PVR), improvement in cardiac output and gas exchange. PEA surgery requires a prolonged cardiopulmonary bypass using hypothermia for organ protection. Despite the latter, a recent trial has demonstrated that remarkably low mortality can be achieved without any deterioration in the cognitive function [3].

Cardiac surgery in elderly patients is becoming increasingly common. As the elderly represent the fastest growing population in industrialized nations, this trend will certainly continue [4]. Numerous clinical studies have demonstrated satisfactory operative morbidity and mortality in elderly patients [5–9] and improved the quality of life [10]. Acceptable results were also reported for non-elective cardiac surgery procedures in the elderly [11, 12] and in those who also require the use of hypothermia and circulatory arrest [13]. To date, there has been no report on the outcomes for older patients undergoing PEA surgery.

The objective of this study was to review the outcomes of PEA surgery in the patients over 70-years old and to compare the results with the younger patients undergoing this surgery.

METHODS

Patient selection

All patients undergoing PEA between January 2006 and March 2011 at Papworth Hospital were reviewed. Data were prospectively collected in a dedicated database. All patients were followed up until 28 March 2011 for survival and other outcomes, at that time the database was locked and the data were analysed. The local ethics committee approved this report, and as

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individual patients were not identified and the analysis was based on the existing observational data, individual patient consent was not necessary. Patients were selected for PEA surgery at multidisciplinary team meetings which comprised of surgeons, pulmonary hypertension physicians and radiologists.

**Surgical technique**

Surgery was performed through a median sternotomy incision with a hypothermic cardiopulmonary bypass at 20°C using the established techniques described previously [1].

**Outcome measures**

Survival to discharge was defined as discharge from the hospital (alive) to the patient’s usual home or a place of care or transfer to another hospital for care that was not related to their PEA procedure. The length of in-hospital (length of stay, LOS) and ICU stays were calculated from the date of surgery to discharge or the date of death if the patient died in hospital. Patients who were still in hospital at the time of the database closure were excluded from this analysis. The incidence of the following complications was also recorded: requirement for extra corporeal membrane oxygenation (ECMO), return to theatre for any reason, re-intubation, requirement for tracheotomy and chest infection. The overall survival time was calculated from the date of surgery to the date of death or to 28 March 2011, if the patient was still alive. Survival status at the time of analysis was ascertained from the Office for National Statistics database and was available for all patients in the study. At 3 months following surgery, all patients returned to Papworth Hospital and their New York Heart Association (NYHA) classes were recorded, and the patients were invited to undergo a 6-min walk test (6MWT) and a right heart catheter study.

**Statistical analysis**

The patient group was dichotomized according to age on the day of surgery as above or below 70-year-old, and outcomes for these two groups were compared. For descriptive purposes, continuous variables were summarized as the mean (standard deviation) or the median (interquartile range), and categorical variables were reported as the frequency (percentage of the group total). In exploratory analyses, univariate unadjusted comparisons between the two age groups were performed using Pearson’s χ² test or Fisher’s exact test for categorical variables and the independent-group Student’s t-test or Mann-Whitney U-test for continuous variables. For binary outcomes, the effect of age group was assessed using logistic regression models; for NYHA class, a proportional odds regression was used; and for continuous outcomes, linear models were used to assess the effect of age group. For all regression analyses, sex and the type of disease were included in the Cox regression models. No departures from the proportional hazard assumption could be identified using the Schoenfeld residuals and associated tests. Significance levels were taken from likelihood ratio tests comparing the models with and without the effects of age. Statistical tests were two-sided and a 5% type I error was described as ‘significant’. The above analyses were completed using STATA version 11.1 (StataCorp LP, Texas, USA).

Since life expectancy should be lower in the older age groups over the long term, we estimated the relative risk of death in patients after PEA surgery compared with age-sex-matched controls from the general population. The age-sex-matched expected survival was taken from the Government Actuarial Department website for England and Wales (http://www.ons.gov.uk/ons/rel/lifetables/decennial-life-tables/english-life-tables-no-15/index.html). A proportional hazard model was used to assess the relationship between post-PEA survival and age-sex-matched population survival separately for the two age groups. This model was fitted in the WinBUGS version 1.4 (WinBUGS 1996–2003, Imperial College, UK).

**RESULTS**

**Baseline demographics**

A total of 411 patients underwent PEA during the review period. One hundred and three patients were older than 70 years on the date of surgery, and 308 were younger. The mean age of the whole cohort was 56.9 years (SD, 15.5; range, 17–84). The baseline characteristics are summarized in Table 1.

The patients aged ≥70 were more likely to have distal disease, preoperative NYHA class IV and had a shorter baseline mean 6-min walk distance compared with the younger PEA patients. Preoperative spirometry demonstrated that the patients ≥70 years have significantly lower forced vital capacity (FVC) and forced expiratory volume in first second (FEV₁), but when expressed as a percentage of the predicted for their age, sex and size, this group actually had higher values (Table 1). There was no evidence that the lung function was related to survival as the power to detect any relationship was low. The hazard ratio for FVC (%) was 0.99 (95% CI, 0.97–1.01; P = 0.339) and for FEV₁ (%) was 0.98 (0.96–1.00; P = 0.103).

Concomitant surgery was performed in 20 (19.4%) patients in the elderly group vs. 1 (10.1%) in the younger group (P = 0.013). Despite this, the mean bypass time was shorter for those aged ≥70 (P = 0.054), with similar circulatory arrest times (34.3 vs. 33.5 min, P = 0.64).

**Main outcomes in hospital**

The unadjusted comparisons of the main outcomes are given in Table 2. The in-hospital mortality was eight of 103 patients (7.8%) in the older group vs. 14 of 308 (4.6%) in the younger (Fisher’s exact test, P = 0.212). The mean (SD) age in the patients who died in hospital was 63.1 (14.0) and in survivors was 56.6 (15.5), P = 0.054. Eleven patients were older than 80 at the time of surgery. One died while in hospital due to an unrelated complication, and all others survived more than 1-year postsurgery.

Using logistic regression, the odds ratio for in-hospital mortality following PEA for the patients aged ≥70 was 1.77 (95% CI,
relative to the younger patients ($P = 0.214$). When adjusted for female sex and the type of disease, this increased slightly to 1.89 (95% CI, 0.70–5.08), but remained non-significant ($P = 0.206$).

There were no differences between the age groups in complications requiring ECMO, requirement for any re-surgery, re-intubation or tracheotomy. There was also no difference in the incidence of postoperative chest infection. Overall, 25.7% of the patients aged <70 had at least one complication compared with 27.6% in the older patients ($P = 0.780$).

The older patient group stayed in ICU a median of 1 day longer ($P = 0.001$) and the total length of stay a median of 2 days longer ($P = 0.004$; Table 2).

### Follow-up at 3 months

At 3 months after surgery, the patients aged ≥70 were more likely than the younger patients to remain in NYHA class III or IV (34.6 vs. 18.2%, $P = 0.009$; Table 2). The odds ratio of patients aged ≥70 (compared with the younger group) who have improved only one NYHA class at 3 months was 2.21 (95% CI, 1.35–3.63; $P = 0.002$). This was reduced slightly to 1.93 (95% CI, 1.11–3.31) when adjusted for baseline NYHA, female sex and the type of disease ($P = 0.018$).

The unadjusted mean difference in the 6-min walk distance between the older and younger groups was 79.1 m (95% CI, 49.7–108.5) with the younger patients walking further, $P < 0.001$. When we adjusted for the baseline walk distance, female sex and the type of disease, the difference between the age groups was reduced to 39.5 m (95% CI, 18.6–60.4; $P < 0.001$) in favour of younger patients.

There was no difference in the mean pulmonary artery pressure (mPAP) between the groups. When we adjusted for the baseline mPAP, female sex and the type of disease, the difference between the age groups was only 2.9 mmHg, lower in the younger patients (95% CI, 0.4–5.4; $P = 0.022$), however, clinically not significant.

PVR was lower in the younger patients by 80.7 dynes/s/cm⁻⁵ (95% CI, 9.6–151.7; $P = 0.026$); however, when adjusted for the baseline PVR, female sex and the type of disease, the difference did not reach statistical significance (60.5 dynes/s/cm⁻⁵; 95% CI, −3.7, 124.7; $P = 0.065$).

### Overall survival

Older patients showed a trend of poorer survival overall (log-rank test, $P = 0.070$), but this might be expected given the long follow-up (Fig. 1).

The unadjusted hazard ratio of death for the patients aged ≥70 was 1.71 (95% CI, 0.95–3.09) compared with the younger patients ($P = 0.073$; Table 3). The results changed only slightly.
when we adjusted for female sex and the type of disease (hazard ratio, 1.85; 95% CI, 0.96–3.56; P = 0.064).

The expected survival for an age-sex-matched population, taken from the census data from the UK, is also shown in Fig. 1. The overall survival of both groups is lower than the expected for the general population. In those who survive surgery, the younger patients (<70) have a survival rate that is closer to that expected in the early years after PEA, but the older patients (≥70) have a survival rate that is closer to the population average in the longer term (Fig. 2).

The average hazard ratio for the observed survival compared with the expected survival over a 5-year time horizon for the younger PEA patients was 6.27 (95% CI, 1.66–21.07) and for the older PEA patients was 1.92 (95% CI, 0.84–3.70). Thus, over the 5-year period, the younger PEA patients were six times as likely to die as a member of the general population with the same age-sex distribution, whereas the older PEA patients were only 1.9 times as likely to die as someone from an age-sex-matched normal population. The ratio of these relative risks has been estimated to be 0.47 (95% CI, 0.07–1.40), so that there is no ‘significant’ difference between the two relative risks (i.e. the interval for the ratio is 1). However, the signs are that the older patients are returned to a survival pattern that is closer to the general population than do younger patients undergoing PEA.

| Table 2: Summary of results of simple unadjusted comparison of outcomes up to 3 months postsurgery |
|---|---|---|---|
| Outcomes | Age <70 | Age ≥70 | P-value |
| Hospital mortality (%) | 14/308 (4.6%) | 8/103 (7.8%) | NS |
| Complications | | | |
| ECMO | 7 (2.2%) | 3 (2.9%) | NS |
| Bleeding or tamponade | 35 (11.3%) | 15 (14.5%) | NS |
| Tracheotomy | 6 (1.9%) | 4 (3.8%) | NS |
| Chest infection | 29 (9.4%) | 10 (9.2%) | NS |
| Other (X) | 70 (22.7%) | 24 (22.2%) | NS |
| ICU stay [days; median (IQR)] | 3 (3) | 4 (4) | 0.001 |
| Length of stay [days; median (IQR)] | 16 (11) | 18 (11) | 0.004 |
| NYHA class at 3 months [n (%)] | | | |
| 1 | 85 (35.1) | 16 (21.3) | 0.009 |
| 2 | 113 (46.7) | 33 (44.0) | |
| 3 | 43 (17.8) | 25 (33.3) | |
| 4 | 1 (0.4) | 1 (1.3) | |
| 6 min walk distance at 3 months [m; mean (SD)] (see text) | 373.4 (115.0) | 294.3 (111.7) | <0.001 |
| mPAP at 3 months [mmHg; mean (SD)] | 27.0 (9.6) | 29.1 (10.1) | NS |
| PVR at 3 months [dynes/s/cm⁻⁵; mean (SD)] | 307.8 (253.9) | 388.5 (284.3) | 0.02 |
| Overall survival (years, %) | | | |
| 1 | 91.4 | 85.9 | 0.07 |
| 2 | 89.9 | 84.1 | |
| 3 | 87.5 | 84.1 | |

Complication (X): neurological complication, sternal wound infection, transient renal dysfunction, prolonged oxygen requirement and need for pulmonary vasodilator drug therapy. Six-min walk distance at 3 months was available for 77 of 103 and 246 of 308 patients, respectively. Mean PAP at 3 months was available for 74 of 103 and 235 of 308 patients. PVR at 3 months was available for 71 of 103 and 204 of 308 patients.

| Table 3: Observed and population expected numbers of deaths |
|---|---|---|---|
| Year | Observed deaths | Population expected deaths |
| | Age <70 | Age ≥70 | Age <70 | Age ≥70 |
| 1 | 25 | 14 | 1.68 | 2.93 |
| 2 | 3 | 1 | 1.83 | 2.95 |
| 3 | 3 | 0 | 1.99 | 3.20 |
| 4 | 1 | 1 | 2.17 | 3.45 |
| 5 | 0 | 1 | 2.37 | 3.71 |

Population expected deaths are derived from census data for an age-sex-matched population.

Figure 1: Observed and age-sex-matched population survival for PEA patients.
Hospital mortality was only slightly higher for the patients aged ≥70, and both groups suffered an equal number of complications. The patients in the older group were likely to spend a median of one additional day in ICU and two additional days in hospital compared with those in the younger group. There was some evidence that longer-term survival was poorer for the older patients compared with the younger group. However, both groups had reduced survival compared with the general population with the same age–sex distribution, and the older group’s survival was closer to the age–sex-matched population survival (the hazard ratio of ~2 compared with 6 for the younger group). The likely explanation is that the older patients have a range of comorbidities so that they are less likely to be referred for PEA surgery due to these comorbidities, making the older group more selected. Thus, post-PEA survival patterns are closer to those for a general population in the older age group. The likely explanation is that the older patients have a range of comorbidities so that they are less likely to be referred for PEA surgery due to these comorbidities, making the older group more selected. Thus, post-PEA survival patterns are closer to those for a general population in the older age group.

Improvements in anaesthesia, cardiopulmonary bypass, surgery and intensive care have made cardiac surgical surgery possible in elderly patients with reduced functional reserve. Hence, cardiac surgery in the elderly is now part of daily practice [14]. Because of the ageing population in the Western world, the patient group with heart disease amenable to surgical treatment is expected to grow and will pose an expanding clinical problem to cardiac surgeons. CTEPH may develop in up to 3.8% of patients within the first 2 years after an acute pulmonary embolism [15]. Left untreated, the disease has a poor prognosis, proportional to the severity of pulmonary hypertension. PEA is recognized as the standard treatment for CTEPH in most patients [1, 16]. The procedure involves the removal of fibrous obstructive tissue from the pulmonary arteries during circulatory arrest under deep hypothermia. The subsequent degree of relief of pulmonary hypertension is variable, but in many cases may be total with the restoration of pulmonary haemodynamics to normal or near normal [16].

The decision to operate is made on the basis of the severity of clinical symptoms, the amount and surgical accessibility of the thromboembolic lesions, the degree of impairment of pulmonary haemodynamics and the presence of comorbidities.

We have previously shown that conditional survival (from 3 months) after discharge from the hospital was 90% at 5 years in a cohort of 314 patients who underwent PEA [17]. To date, there is no risk assessment model for PEA, with various groups exploring pre- and intraoperative parameters as the predictors of outcomes. Schafer and colleagues [18] recently demonstrated that patients with underlying parenchymal lung disease have an increased risk of early mortality and prolonged mechanical ventilation.

Stoica et al. [6] showed that the in-hospital mortality of octogenarians following cardiac surgery in specialized units was significantly better than predicted by EuroSCORE. They found that octogenarians undergoing cardiac surgery have dramatically better long-term survival than an age- and sex-matched UK population, with a more than 50% reduction in standardized mortality. They did acknowledge a selection bias in the older patients. These results were supported by other groups [19]. However, EuroSCORE is not validated for PEA [20].

We found no significant correlation between the groups regarding the duration of bypass and circulatory arrest and outcome. Other groups reported encouraging results regarding emergency aortic surgery involving hypothermic bypass in septuagenarians [13]. In our cohort, the median stay in ICU and hospital was prolonged in septuagenarians compared with the younger group. Peterson et al. [21] pointed out 20% higher costs for octogenarians secondary to the prolonged hospital stay. Engoren et al. [22] reported 35% higher costs in the elderly group undergoing cardiac surgery, despite having identical median ICU and postoperative length of stay compared with the younger group having had cardiac surgery. In our group, the prolonged ICU and hospital stays would have had an economic impact, but we have not yet assessed this in detail in this study. Other groups have explored ways to reduce PEA morbidity and mortality by measuring procalcitonin and interleukin-6 levels post-PEA for the early detection of infection [23] or non-invasive ventilation [24].

The differences in the 6MWT were not clinically significant in our study. The 6MWT is used to assess the functional status [25]; however, it is a self-paced test, likely to be affected in the elderly population due to reduced muscle mass and arthritis. Therefore, this may not be a valid functional assessment in older patients and has not been validated for this use.

STUDY LIMITATIONS

We acknowledge several limitations to the current study.

(i) From the patient’s perspective, functional status following surgery may be more important than survival. The quality-of-life improvements in the elderly having had cardiac surgery were confirmed by several groups [8, 9], but to date there has been no similar study in the PEA group of patients. The 6-min walk distance may not be a good assessment of performance in the elderly.

(ii) The observational nature of this review, combined with some missing data, may affect the full interpretation of the results. However, the survival and LOS were almost 100% complete, providing an accurate estimate of these outcomes.

(iii) Missing outcomes at 3 months were assumed ‘missing completely at random’ in the analysis, an assumption that is
difficult to assess with the current data. However, most of the missing cases arose since the patients had not reached the 3-month time point by the time of analysis or were in the early period of the PEA service or had died within 3 months, so that we do not expect a substantial bias in the estimates of the effects of age. (iv) We do not have an estimate of the relative survival probabilities for being in the PEA risk group, but we can say by how much the post-PEA patients are at increased risk compared with age-sex-matched controls. (v) Because the mortality rate is quite low (~1% per year) for population controls for the younger PEA group, the relative risks are measured imprecisely.

CONCLUSION

In the present study, septuagenarians showed a very good medium-term survival following PEA. PEA surgery has an acceptable safety profile, and the risk in the patients aged ≥70 is only slightly greater than that of the younger patients, but there is a greater resource use for older patients due to longer ICU and hospital stays. Advanced age should be taken into consideration when assessing suitability for PEA, but is not a contraindication to surgery.

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REFERENCES


APPENDIX: CONFERENCE DISCUSSION

Dr J. Linder (Czech Republic): My first question concerns the functional class after operation. In your presentation at 3 months after operation in the elderly group, 34% of patients were in groups 3 and 4, and can you explain how it was at 6 months after operation and one year?
The second question concerns the tricuspid insufficiency. Can you tell us what is the strategy of your centre regarding tricuspid insufficiency, and can you expect better outcome of tricuspid insufficiency with tricuspid plasty?

**Dr Berman:** Regarding the first question, we do follow up to 1 year at Papworth and for 5 years at regional centre, and NYHA class does improve further between 3 months and 1 year. This change may be more marked in the older who take longer to recover. We are now starting a follow-up study, mainly related to quality of life in this particular group.

Regarding the tricuspid surgery, it varies because we have various degrees of right ventricular dysfunction at the time of the referral, some of them hypertrophic, and some of them are beyond hypertrophic, dilated. In the vast majority of the cases, usually we do not attempt to correct the tricuspid regurgitation, because if we get good clearance of the surgical disease, based on our experience, the tricuspid regurgitation will improve.

**Dr H. Schäfers (Homburg/Saar, Germany):** Two short questions. I know your unit started operating on this disease earlier than 2006. I wondered why you started your analysis in 2006. Maybe I’m misinformed, maybe you can briefly comment.

The symptoms have been alluded to. In the older patients you find what we also sometimes see, a higher PVR, which may be related to a longer duration of the disease, longer duration of symptoms. And I wonder whether you have any data on that? With results being so good, do you have any upper age limit?

**Dr Berman:** First of all, you were not misinformed, you are right, the unit started doing pulmonary endarterectomy in 1998, and in 2000 the service was formally commissioned. However, the number of cases and the protocol was refined and there was a learning curve. So from 2006 onwards, there is a standardized protocol for all cases. There is an MDT, which involved a radiologist, pulmonary hypertension physician, and surgeon. And all the cases are being discussed and acted on. So only from 2006 onwards was there a protocolized approach to all cases, so that’s why we started then.

Regarding the results in the elderly, I briefly mentioned, this surgery is not for everyone. For the sake of time, we didn’t go into details; it involves deep hypothermia, 20 degrees. Most of the cases will have a period of circulatory arrest; we saw a median of 33 minutes or so. So all cases, and particularly the elderly ones, are carefully assessed according to the protocols for surgery, and discussed, and the informed consent process followed.

**Dr Schäfers:** And what is your upper age limit now? Is there an age where you think this type of operation is simply too much for the elderly person?

**Dr Berman:** We have a small subgroup of octogenarians. The oldest one was 84 years old. And from this cohort, there were 11 patients, octogenarians, with one mortality during the whole period, and this was addressed in the paper.