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Early outcomes after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension in the era of epoprostenol sodium

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Abstract

Objectives: Pulmonary endarterectomy (PEA) for chronic thromboembolic pulmonary hypertension (CTEPH) is technically demanding. We reviewed the surgical outcomes of consecutive patients who underwent PEA with aggressive use of pulmonary vasodilators, including epoprostenol sodium.

Methods: We retrospectively assessed perioperative clinical data of 122 patients with CTEPH who underwent PEA with hypothermic circulatory arrest between 2005 and 2013. Peri-operatively, all of the patients received pulmonary vasodilator therapy, including epoprostenol sodium and beraprost sodium.

Results: Patients were classified as having CTEPH type 1 (n=57), type 2 (n=32), and type 3 (n=33) disease according to the Jamison classification system. In-hospital mortality was 7.4% (n=9), caused by right heart failure (n=5), pulmonary hemorrhage (n=3), and pneumonia (n=1). The 113 patients who survived PEA showed significantly decreased mPAP (46±11 to 23±10 mmHg, P<0.01) and PVR (826±357 to 237±153 dyne·s^{-1}·cm^{-5}, P<0.01).

Conclusions: Aggressive pulmonary vasodilator treatment during surgical PEA results in favorable early outcomes. This treatment also leads to immediate and substantial improvement in pulmonary hemodynamics in patients with CTEPH.

Keywords: Chronic thromboembolic pulmonary hypertension, Pulmonary endarterectomy, Pulmonary vasodilator

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH), defined as a mean pulmonary artery pressure (mPAP) ≥25 mmHg, is caused by organized thrombi obstructing the pulmonary arteries, and is associated with respiratory failure.[1] In the United States, the incidence of CTEPH after acute pulmonary thromboembolism varies between 0.1% and 9.1%, but it has increased in recent years.[2–4] Available data have suggested that the rate of CTEPH is higher if asymptomatic and unscreened patients are taken into account. Although the incidence of CTEPH in Japan is less than that in Western countries,[5] the official number of patients was >1800 in 2012, and this continues to increase.

Although the pathogenesis of CTEPH remains unclear, it appears to be a sequela of classic thromboembolism modified by misguided resolution of thrombus. This then leads to occlusive vascular remodeling of the pulmonary vessels. Additionally, some risk factors of recurrent thromboembolism are present in CTEPH, such as elevated factor VIII, lupus anticoagulant antiphospholipid antibodies, and protein C, protein S, and antithrombin III deficiency.[6]

The prognosis of patients with CTEPH undergoing medical treatment is poor, largely because of severe ventilation–perfusion mismatch, pulmonary hypertension, and decreased cardiac output. In patients with an mPAP >50 mmHg, the 5-year survival is as low as 10%.[7]

Pulmonary endarterectomy (PEA) is the only curative treatment for CTEPH.[8–16] The San Diego group procedure for PEA through median sternotomy with intermittent deep hypothermic circulatory arrest is the established surgical treatment for CTEPH.[12,15,16] Surgery can decrease PAP and pulmonary vascular resistance (PVR), thereby increasing the cardiac index. Because PEA is relatively invasive, it is mostly performed at centers with surgeons who have experience. However, the outcomes of PEA remain uncertain because of limited available data.

We have performed PEA according to the San Diego group procedure since 2001. In 2005, we added oral pulmonary vasodilators and intravenous epoprostenol sodium for perioperative management of all patients with CTEPH. We also used epoprostenol sodium for postoperative management. Although epoprostenol sodium was used for postoperative care of patients with CTEPH before 2005, the surgical outcome was poor. Our decision to use epoprostenol sodium preoperatively and

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postoperatively was based on the findings of Nagaya et al.[17] They reported that continuous intravenous epoprostenol prior to PEA resulted in a highly significant decrease in PVR, an increase in cardiac output, and excellent postoperative outcome in patients with severe CTEPH, as defined by a PVR >1200 dyne·s^{-1}·cm^{-5}.[17]

In this study, we reviewed the early outcomes of a consecutive series of patients with CTEPH who underwent PEA at our institution after 2005, which is the era of epoprostenol sodium.

Methods

Study cohort

We retrospectively reviewed the clinicopathological data of 122 patients who underwent PEA at Fujita Health University Hospital between 2005 and 2013. The institutional review board approved this retrospective, observational study. The approval included a waiver of informed consent. All of the 122 patients underwent preoperative pulmonary angiography, right heart catheterization, and computed tomographic scanning.

The baseline characteristics of the patients are shown in Table 1. The mean age was 55±11 years (±standard deviation [SD]) and 88 (72%) patients were women. Sixteen (13%) patients had a coexisting coagulation abnormality (protein C deficiency, n=7; protein S deficiency, n=3; antiphospholipid syndrome, n=6). None of the patients had antithrombin III deficiency. Thirty-seven (30%) patients had deep vein thrombosis, and four (3%) had deep vein thrombosis and a coagulation abnormality. The mean preoperative arterial oxygen and carbon dioxide tensions were 59±10 and 37±5 mmHg. Fifty-five (45%) patients had a preexisting inferior vena cava filter. Most of the patients (96%) were in New York Heart Association (NYHA) functional class III or IV, and all of the patients required home oxygen therapy. After admission to hospital, all of the patients received pulmonary vasodilator therapy, including epoprostenol sodium, beraprost sodium, bosentan hydrate, sildenafil citrate, and tadalafil. Intravenous infusion of epoprostenol sodium was started at 2 ng·kg^{-1}·min^{-1} and was increased by 1–2 ng·kg^{-1}·min^{-1} up to 6 ng·kg^{-1}·min^{-1} at intervals of at least 15 min. This was performed to allow assessment of the clinical response.

Table 1 Baseline characteristics of patients with CTEPH who underwent PEA

Variable	n=122
Women, n (%)	88 (72)
Age (y)	55±10.6
Hypertension, n (%)	27 (22)
Diabetes, n (%)	8 (7)
Dyslipidemia, n (%)	12 (10)
Smoking, n (%)	18 (15)
Coagulation abnormality, n (%)	16 (13)
Deep vein thrombosis, n (%)	37 (30)
Preoperative inferior vena cava filter, n (%)	55 (45)
Mean pulmonary artery pressure (mmHg)	47±11 (26–73)
Pulmonary vascular resistance (dyne·s^{-1}·cm^{-5})	847±373 (258–1869)
Cardiac index (L·min^{-1}·m^{-2})	2.3± 0.6 (1.3–4.4)
Blood gas analysis (mmHg)	
Arterial oxygen tension	59±10 (40–90)
Arterial carbon dioxide tension	37±5 (26–54)
New York Heart Association functional class, n (%)	
I	0 (0)
II	5 (4)
III	108 (89)
IV	9 (7)

Values are number (%) or mean±standard deviation (range) CTEPH, chronic thromboembolic pulmonary hypertension; PEA, pulmonary endarterectomy.

The preoperative mPAP was 47±10 mmHg and 43% of patients had an mPAP >50 mmHg. The preoperative PVR was 847±373 dyne·s^{-1}·cm^{-5}, and 21% of patients had a PVR >1000 dyne·s^{-1}·cm^{-5}. The preoperative cardiac index was 2.3±0.6 L·min^{-1}·m^{-2}.

Surgical techniques

The indications for PEA included: (1) mPAP >30 mmHg; (2) PVR >300 dyne·s^{-1}·cm^{-5}; (3) accessible proximal edge of pulmonary thrombi; and (4) NYHA functional class greater than II in the absence of significant comorbidities.

Surgery was performed through a median sternotomy with intermittent deep hypothermic circulatory arrest according to the San Diego group procedure.[12,15,16] PEA was performed using cycles of 15 min of circulatory arrest followed by 10 min of reperfusion at a core temperature of 18°C. We did not perform surgery on the tricuspid valve, even when regurgitation was severe, because regurgitation was expected to regress postoperatively owing to diminished pulmonary hypertension. Weaning from cardiopulmonary bypass (CPB) was performed with care because hemodynamics were unstable as a result of residual pulmonary hypertension due to hypothermia, CPB, and reperfusion injury of the lungs. Patients who could not be successfully weaned from CPB because of hypotension, hypoxia, and/or pulmonary bleeding were supported by percutaneous extracorporeal membrane oxygenation (ECMO) via the femoral artery and vein. With ECMO, mean blood flow was maintained at 2.5 to 3 L·min^{-1} to support respiratory and circulatory function. Weaning from ECMO was attempted when cardiac hemodynamics and oxygenation were stable.

Anticoagulation therapy with intravenous heparin was administered for the first week after surgery with a target of activated clotting time from 150 to 180 s, followed by oral warfarin therapy with a target international normalized ratio of approximately 2.0.

Data collection and statistical analysis

Perioperative data were collected from hospital records. For 112 of the 113 survivors of PEA, postoperative pulmonary hemodynamic data for calculating mPAP and PVR were obtained by right heart catheterization within 1 month after PEA. Data for the remaining one patient were obtained before removal of a Swan–Ganz thermodilution catheter. Operative death was defined as death within 30 days after surgery.

Continuous data are shown as the mean±SD (and range, as indicated), and categorical variables are presented as frequencies and percentages. All analyses were performed with SPSS 18 software (IBM Corporation, Armonk, NY). The Wilcoxon signed-rank test was used for comparison of preoperative and postoperative pulmonary hemodynamic data. Univariate analysis was performed with the *t*-test or the Mann–Whitney test for continuous variables and with the χ^2 test or Fisher's exact test for categorical variables. P values were corrected for multiple comparisons. P<0.05 was considered statistically significant.

Results

Operative data

Operative parameters during PEA are shown in Table 2. CTEPH was classified into four types according to Jamison,[1] based on the location and morphology of thromboemboli and the vascular wall found at the time of surgery. Type 1 (n=57) was characterized by fresh (acute) thrombus in the main and lobar pulmonary arteries. Type 2 (n=32) was characterized by intimal thickening and fibrosis with or without organized thrombus proximal to the segmental arteries. Type 3 (n=33) was characterized by fibrosis, intimal webbing, and thickening with or without an organized thrombus within distal segmental arteries alone. Type 4 (n=0) was characterized by microscopic distal arteriolar vasculopathy without visible thromboembolic disease.

Early outcomes

Postoperatively, 31 patients required ECMO and 11 patients required circulatory assist with an intra-aortic balloon pump (Table 3). Preoperative PVR of the patients who required ECMO after PEA was 993±386 dyne·s^{-1}·cm^{-5}. The mean duration of postoperative respiratory support was 7±9 (range: 1–58) days. There were nine (7.4%) in-hospital deaths caused by right heart failure (n=5), pulmonary hemorrhage (n=3), and pneumonia (n=1). The eight patients who died of heart failure and pulmonary hemorrhage also had persistent pulmonary hypertension and required ECMO, accounting for 26% (n=31) of patients who needed ECMO after PEA. The nine non-survivors of PEA showed a higher preoperative mPAP (51±13 mmHg) and PVR (1052±500 mmHg) than those who survived PEA (mPAP, 46±11 mmHg; P=0.28 and PVR, 826±357 dyne·s^{-1}·cm^{-5}, P=0.3), but the differences were not significant. The 113 survivors of PEA showed a significant decrease in mPAP (46±11 to 23±10 mmHg, P<0.01) and PVR (826±357 to 237±153 dyne·s^{-1}·cm^{-5}, P<0.01), and a significant increase in the cardiac index (2.4±0.6 to 2.9±0.6 L·min^{-1}·m^{-2}, P<0.01). Although 96% of the patients were classified as NYHA functional class III or IV before surgery, 18 (16%) showed class I and 89 (79%) showed class II after PEA. The mean duration of hospital stay for the survivors was 44±25 days (10–153 days).

Table 2 Operative parameters for patients with CTEPH who underwent PEA

Variable	n=122
Operation time, min	437±88 (295–865)
Cardiopulmonary bypass time, min	253±43 (185–456)
Cardiac arrest time, min	141±24 (87–207)
Lowest body temperature, °C	18±0.7 (15.3–19.6)
Jamison classification	
Type 1	57 (47%)
Type 2	32 (26%)
Type 3	33 (27%)
Type 4	0 (0%)

Values are mean±SD (range) or number (%) of patients. CTEPH, chronic thromboembolic pulmonary hypertension; PEA, pulmonary endarterectomy.

Table 3 Postoperative results of patients with CTEPH

Variable	n=122
Operative mortality (within 30 days)	7 (5.7%)
Time to operative death, days	13±8 (2–22)
In-hospital mortality	9 (7.4%)
Time to in-hospital death, days	36±48 (2–147)
ICU stay for survivors, days	13±14 (2–69)
Hospital stay for survivors, days	44±25 (10–153)
Postoperative use of ECMO	31 (25%)
Postoperative use of IABP	11 (9%)
Respiratory support, days	7±9 (1–58)

Values are number (%) or mean±SD (range). CTEPH, chronic thromboembolic pulmonary hypertension; ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump.

Discussion

This study showed that PEA was an effective surgical therapeutic option for patients with CTEPH to obtain immediate and significant improvement in pulmonary hemodynamics. However, this surgical procedure is reportedly associated with high mortality (2.2–14%) because it is technically demanding and requires intensive postoperative management.[8,10–12,16,18–22] Although the overall in-hospital mortality rate in our study was 7.4%, the mortality among the 103 patients who were treated after 2007 was 4.8%, which is lower than that reported in previous studies. In contrast, the in-hospital mortality was 21% for the 20 patients who underwent PEA from 2001 to 2004 in our institute, whose preoperative mPAP was 50±10 mmHg and PVR was 1058±295 dyne·s^{-1}·cm^{-5}. These patients had the same selection process and surgical procedure as those used currently.

Several factors are likely to contribute to a favorable early outcome of PEA. There is undoubtedly a learning curve for such a complex surgical intervention. Several centers have shown that the learning curve for PEA is an important factor in improving surgical outcomes.[5,15,16] This learning curve applies to the entire multidisciplinary team of surgeons, radiologists, and pulmonary hypertension physicians, who each provide their expertise to the decision-making process.

Additionally, aggressive pulmonary vasodilator treatment, including epoprostenol sodium, may be linked to improved clinical outcomes. As shown in the current study, all of our patients had been treated with epoprostenol sodium preoperatively and postoperatively since 2005.

Dartevelle and colleagues stressed the importance of preoperative PVR as a risk factor and reported a postoperative mortality rate of 20% among patients with a preoperative PVR >1200 dyne·s^{-1}·cm^{-5}.[22] Yildizeli and associates also recently reported 100% survival after PEA for patients with a preoperative PVR <300 dyne·s^{-1}·cm^{-5}.[23] In our study, eight of the nine patients who died after PEA required ECMO because of persistent pulmonary hypertension and bleeding. Indeed, the in-hospital mortality of patients who required ECMO after PEA was higher than that of those who did not require ECMO. Therefore, persistent pulmonary hypertension and bleeding requiring support with ECMO after PEA is considered to be the most important risk factor for in-hospital mortality.

In addition to the standard medical treatment of CTEPH, including diuretics, oxygen therapy, and life-long anticoagulant therapy, pulmonary vasodilator therapy should be aggressively incorporated into perioperative management. Similar to inoperable patients with severe CTEPH, patients undergoing PEA may also benefit from epoprostenol sodium, beraprost sodium, bosentan hydrate, sildenafil citrate, and tadalafil.[24] Primary and secondary forms of pulmonary hypertension are associated with increased release of vasoconstrictor thromboxane

A2 and decreased endogenous prostacyclin.[25] As the logical treatment choice, synthetic prostacyclin or prostaglandin analogs, such as epoprostenol and beraprost, are expected to provide symptomatic and hemodynamic improvement, as well as improved survival, in patients with severe primary pulmonary hypertension.[26,27] Other promising drugs with different pharmacological effects include endothelin receptor antagonists (bosentan) and phosphodiesterase type-5 inhibitors (sildenafil). Combination therapy with oral sildenafil and beraprost may attenuate development of pulmonary hypertension.[28–30]

Epoprostenol sodium was approved in 1995 by the United States Food and Drug Administration for treatment of PAH. Epoprostenol sodium is a potent pulmonary and systemic vasodilator, and an inhibitor of platelet aggregation, and may modulate pulmonary vascular remodeling.

Jensen and colleagues have suggested that pulmonary vasodilators have a minimal benefit in preoperative mPAP.[31] However, we believe that pulmonary vasodilators, especially epoprostenol sodium, should be used postoperatively and preoperatively to improve the prognosis. This advocacy is based on previous findings that 10–35% of patients who undergo PEA develop persistent pulmonary hypertension[10,32–35] and that persistent pulmonary hypertension (PVR >500 dyne·s^{-1}·cm^{-5}) is an independent risk factor for death after PEA.[10,12,21]

This study has some limitations. First, the data were collected retrospectively and some events were incompletely reported or missing. Second, our study included a relatively small number of patients from a single center. Third, our study did not include non-surgical patients. Therefore, we could not compare the surgical group with a medically managed group.

Although the present study only showed only outcomes of PEA, they are thought to have a large effect on late outcomes after PEA. We will investigate the late outcomes and prognostic factors of this challenging surgery in the future.

Conclusion

Aggressive treatment with pulmonary vasodilators, including epoprostenol sodium, results in immediate and substantial improvement in pulmonary hemodynamics. Additionally, this treatment has favorable effects on early survival of patients with CTEPH undergoing PEA.

Conflicts of Interest

The authors declare no conflicts of interest associated with this manuscript.

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