Survival and Quality of Life for Patients With Peripheral Type Chronic Thromboembolic Pulmonary Hypertension

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Background The validity of pulmonary thromboendarterectomy for treatment of relatively peripheral type of chronic thromboembolic pulmonary hypertension (CTEPH) remains uncertain. The survival and quality of life (QOL) of patients with relatively peripheral type of CTEPH was investigated at follow up.

Methods and Results Between April 1999 and March 2006, 83 consecutive patients with CTEPH were evaluated for surgical indication and underwent computed tomography angiography. The extent of central disease was scored (ie, CD score), and a CD score of ≤1 was judged as relatively peripheral disease. Forty-three patients were excluded from surgery, and 40 patients, including 14 cases of relatively peripheral disease, underwent surgery. Long-term survival and QOL scores at follow up (1–3 years) were compared between the surgically and medically treated groups of relatively peripheral disease. Survival curves between the 2 treatment groups were not significantly different (p=0.78) because of high operative mortality (21.4%). However, improvement in physical functioning, role function (physically related), general health perception (as assessed by the Medical Outcome Study Short Form 36), and baseline dyspnea index were significantly higher in the group treated surgically compared with the medically treated group.

Conclusions Pulmonary thromboendarterectomy offers better QOL even in those patients with relatively peripheral type of CTEPH, although operative mortality must be reduced. (Circ J 2008; 72: 958–965)

Key Words: Chronic thromboembolic pulmonary hypertension; Prognosis; Quality of life

C}hronic thromboembolic pulmonary hypertension (CTEPH) is a relatively rare disease. Its natural history and etiology remain unclear.1–5 There have been a number of reports that pulmonary thromboendarterectomy (PTE) is an effective modality for treatment in selected patients with CTEPH.1–3,6–11 However, the hemodynamic benefit varies according to the location and extent of the thromboembolic occlusion, and Bergin and colleagues reported that the computed tomography (CT) angiographic extent of central disease (ie, CD score) is related to a low pulmonary vascular resistance (PVR) after surgery.12 Our preliminary data also showed high operative mortality with CD scores of 0 (25%) and 1 (20%), compared with those with a CD score of ≥2 (7.7%), so we classified those patients with a CD score of ≤1 as having relatively peripheral type CTEPH. The cause of operative death was related to residual pulmonary hypertension as a result of failure to remove a distal obstruction. New guidelines have recommended a post-surgical estimated reduction in PVR of >50%.10 The validity of PTE might be limited to central-type patients, especially in institutions in which the operation is performed infrequently.

The prognosis of CTEPH in the medically treated group had been thought to be poor13–15 but Ono et al reported that oral beraprost sodium improved their survival.16 Recently, there have been some reports about improved 6-min walk distance and pulmonary hemodynamics after epoprostenol17,18 sildenafil19 and bosentan20–22 in patients with CTEPH. These new drugs might improve vascular remodeling, and may offer improved survival in patients with relatively peripheral type CTEPH, in whom we predicted a poor reduction in PVR after surgery. We retrospectively tested the validity of PTE from the aspects of survival and quality of life (QOL) at long-term follow up in patients with relatively peripheral type CTEPH.

Methods

Patients Between April 1999 and March 2006, a total of 83 patients admitted consecutively to Chiba University Hospital were diagnosed as having CTEPH and evaluated for surgical indication. CTEPH was defined as having a mean pulmonary arterial pressure (PpA) of ≥25 mmHg with normal wedge pressure in patients who had dyspnea on exertion during a period of more than 6 months. In addition, lung
perfusion scans were required to demonstrate a segmental or larger defect concomitant with a normal ventilation scan. Finally, chronic thromboembolic findings were confirmed by pulmonary angiography.23

The population studied comprises more female patients (n=56) than male patients (n=27). Duration from the symptom onset to cardiac catheterization was 34±37 months. Age at catheterization varied from 18 to 78 years, with a mean ± SD of 54±13 years. Altogether, 33 patients (39.8%) had a history of deep vein thrombosis, 27 (32.5%) revealed abnormalities in the screening for coagulopathy, and 19 (24.1%) had antiphospholipid antibodies. Mean PPA, cardiac index and PVR were 44.1±11.7 mmHg, 2.59±0.54 L·min−1·m−2, and 876±303 dynes·s−1·cm−5, respectively. Arterial oxygen tension (PaO2) was 58.6±10.7 torr. Patients were classified according to criteria of the New York Heart Association as either functional class I (n=2), II (n=22), III (n=55), or IV (n=4). Forty patients underwent PTE (Fig 1). Forty-three patients were excluded from surgery because of: a mild disease (mean PPA ≤30 mmHg) (n=11); relatively peripheral type of thrombi (n=26); aged >70 years (n=3); having an associated disease (n=2); and too severe (n=1) (Fig 1).

Helical CT Angiography and CD Score
CT angiography was performed with a Somatom Plus 4 (Siemens, Forchheim, Germany) between 1999 and 2001, and the scanning parameter setting was 2-mm collimation. From 2002, the LightSpeed Ultra (GE Medical Systems, Milwaukee, WI, USA) was used, and the scanning parameter settings changed to 8×1.25 mm between January 2002 and December 2002, and to 16×1.25 mm between January 2003 and 2006, according to hardware and software modifications.24

By the method of Bergin et al, central arteries were defined as vessels proximal to the segmental branches and were divided into 4 portions.12 These portions included the right and left main pulmonary arteries proximal to the upper lobe branches, and the right and left descending portions of the central arteries between the upper lobes and the segmental branches. Disease within central vessels was identified by the presence of abnormal tissue lining the arterial wall or by irregularity of the intimal surface. The CD score was quantified by adding up the number of abnormal central portions in each patient up to a maximum score of 4. Two investigators retrospectively calculated the scores independently by workstation, and if the score differed, it was changed to either 1 score up or down by consensual agreement of the 2 investigators. The inter-observer agreement between the 2 investigators was also confirmed by Kendall's rank correlation coefficient for concordance for the first 22 patients (concordance=0.92, p<0.01, n=22).

Study Group
Relatively Peripheral Type In the surgically treated group, 14 cases were classified as relatively peripheral type (CD score ≤1), and 26 cases in the medically treated group (other than mild disease) were enrolled in the study as relatively peripheral type (Fig 1).

Central Type and Mild Disease Twenty-five surgically treated patients who were classified as central type (CD score ≥2), as well as 6 patients who had central type but were medically treated for other reasons, served as central type. Eleven patients excluded from surgery because of mild disease (mean PPA ≤30 mmHg) were also analyzed (ie, mild disease) (Fig 1).
treatments in 24 patients and after additional treatments in QOL at follow up was demonstrated before additional surgery. An inferior vena cava filter was inserted in 15 of such patients. Change in PVR of >300 dynes·s–1·cm–5, even after oral anticoagulant therapy. More recently, bosentan (n=4), sildenafil (n=2), and beraprost sodium therapy for >6 months; (2) WHO functional class of NYHA functional class I/II/III/IV for patients in whom PVR was insufficiently reduced by oral anticoagulant therapy, as well as 4 survivors with <1 month of follow-up. Ten patients did not return their questionnaires. Patients were asked to complete a self-administered questionnaire, which included health-related QOL scores, as set by the Medical Outcome Study Short Form 36 (SF-36)25–27 and the baseline dyspnea index3 within 2 weeks after the date of baseline right heart catheterization. We also sent out questionnaires to patients between 12 and 36 months of follow up after the date of diagnosis for medically treated cases or after surgery. Both questionnaires were collected from 58 (85.3%) of 68 patients after excluding 5 postoperative deaths and 6 deaths that occurred within 1 year of medical therapy, as well as 4 survivors with <1 month of follow up. Measurements At least 3 months after an acute episode, pulmonary hemodynamics, cardiac output by thermodilution technique, and blood gases were measured with the patient in a supine position while breathing air. The cardiac index was calculated as cardiac output divided by body surface area. PVR was calculated conventionally as the ratio of the difference between mean PrA and pulmonary wedge pressure to cardiac output. The data of initial diagnosis were evaluated in 79 of 83 patients, and 4 surgically treated patients were re-examined just before surgery and their data were evaluated for pre-operative data. Cardiorespiratory variables were also measured after surgery. Criteria for PTE The selection criteria for PTE were slightly modified from those defined by Moser and colleagues.2 Our criteria were: (1) Mean PPA of >30 mmHg, resulting in calculated PVR of >300 dynes·s–1·cm–5, even after oral anticoagulant therapy for >6 months; (2) WHO functional class of ≥3; (3) Thrombi defined as accessible to current surgical techniques (ie, presence at main, lobar or segmental arteries); and (4) Absence of severe associated disease.8,9 For patients with relatively peripheral type in whom we might be able to access a few thrombi, the patient’s willingness for surgery despite the high operative mortality at the time was the most important indication. Median sternotomy under cardiopulmonary bypass with deep hypothermia and circulatory arrest technique has been performed. Since 1999, 40 operated patients were enrolled in this study. An inferior vena cava filter was inserted in all patients pre-operatively. Home oxygen therapy and beraprost sodium were also used for patients in whom PVR was insufficiently reduced by surgery.

Treatment in Medically Treated Patients With Relatively Peripheral Type All patients received warfarin therapy and home oxygen therapy. We used beraprost sodium in patients with symptomatic CTEPH, including 23 of 26 patients with a CD score of ≤1. Three patients had severe flush and refused this treatment. More recently, bosentan (n=4), sildenafil (n=2), as well as epoprostenol (n=2), were also used in progressive patients even after beraprost sodium therapy. An inferior vena cava filter was inserted in 15 of such patients. Change in QOL at follow up was demonstrated before additional treatments in 24 patients and after additional treatments in 2 patients (ie, one for bosentan, the other for sildenafil).

Assessment of QOL Patients were asked to complete a self-administered questionnaire, which included health-related QOL scores, as set by the Medical Outcome Study Short Form 36 (SF-36)25–27 and the baseline dyspnea index3 within 2 weeks after the date of baseline right heart catheterization. We also sent out questionnaires to patients between 12 and 36 months of follow up after the date of diagnosis for medically treated cases or after surgery. Both questionnaires were collected from 58 (85.3%) of 68 patients after excluding 5 postoperative deaths and 6 deaths that occurred within 1 year of medical therapy, as well as 4 survivors with <1 month of follow-up. Ten patients did not return their questionnaires.

Investigation of Long-Term Outcome We contacted all of the 83 patients and/or their families by mail or telephone in October 2006. Sixty-nine patients survived and 14 patients had died. Survival time was calculated from the initial date of diagnosis by right heart catheterization in the medical group, and was calculated from the date of surgery in the surgical group. The Human Subject Committee at Chiba University approved the study, and written, informed consent was obtained from each patient at the time of diagnosis.

Statistical Analysis Cardiorespiratory variables and QOL before and after surgery or at follow up were compared using the 2-tailed paired t-test. Log rank test was used to compare the survival curves between groups. Comparisons of 2 groups were analyzed by unpaired t-test and chi-square test, where appropriate. Pearson’s correlation coefficient was also used to compare postoperative QOL with postoperative parameters. A p-value of <0.05 was considered significant.

Results Baseline Characteristics of Relatively Peripheral Type The mean age of the surgical and medical groups at diagnosis was similar. The duration of symptoms from the onset of symptoms to diagnosis for the surgically treated group was slightly longer than that for the medical group (55.6±43.7 vs 33.1±27.9 months, p=0.054). Pulmonary hemodynamics and blood gases were similar between the 2 groups (Table 1). Baseline Characteristics of Central Type For patients with central type, the PaO2 in the surgical

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<th>Table 1 Clinical Characteristics of Subgroups</th>
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<td>PaO2 (torr)</td>
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<td>NYHA functional class I/II/III/IV</td>
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Values are presented as the mean±SD. *p=0.054 by unpaired t-test, ***,***,†p<0.01 by unpaired t-test or chi-square test. Duration of symptoms, duration from symptom onset to cardiac catheterization; Pzu, pulmonary arterial pressure; PVR, pulmonary vascular resistance; NYHA, New York Heart Association.
Quality of Life With Chronic Pulmonary Embolism

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Surgical Outcome
In 14 patients with relatively peripheral type, 3 patients died in hospital because of residual pulmonary hypertension during the early postoperative period within 1 month after surgery (operative mortality 21.4%). In 26 patients with central type, 2 patients died (7.7%) in hospital: 1 from residual pulmonary hypertension and the other from pulmonary hemorrhage (Fig 1).

In both relatively peripheral and central types, pulmonary hemodynamics improved significantly, but postoperative mean Ppa and PVR were significantly higher in patients with relatively peripheral type. Although there were no significant differences between them in terms of improvement in mean Ppa, PVR and PaO₂, the percentage decrease in PVR was significantly smaller in patients with relatively peripheral type (Table 2).

Survival Analysis of Patients With Relatively Peripheral Type
In 26 medically treated patients with relatively peripheral type, 5 died during follow up (1–42 months), 4 patients died of right cardiac failure, and one of recurrence, and all patients continued to need oxygen therapy (Fig 1). No death was observed during follow up in the 11 survivors of the surgically treated group. Six of 11 patients did not need oxygen therapy at follow up. Fig 2 shows the Kaplan–Meier survival curves from the operation date in the surgical group and the diagnosis date in the medical group to the time of death or last follow up in the 40 patients with relatively peripheral type (Table 2).
peripheral type. In survivors, the time since the operation date or the diagnosis date to last follow up was an average of 3.9±2.0 (median 4.1, range 1–7) years. The initial decline in the surgical group represents in-hospital deaths. No statistically significant difference was found in the survival curves between the 2 groups (p=0.78). The 6-year survival rates in the surgically and medically treated groups were 78.6% and 77.6%, respectively.

**Survival Analysis in Others**

Fig 3 shows the Kaplan–Meier survival curves for the groups mild disease, medical (medically treated group with central type for other reasons), and surgically treated with central type. The 6-year survival rate in the surgically treated group was 92.3%. The medical group with central type showed a significantly poorer survival rate compared with the mild disease group (p=0.039) or surgical group with central type (p=0.014). In 11 patients with mild disease, none died of CTEPH, although 1 patient died of multiple myeloma (Fig 1). In the medical group with central type, 3 patients died (2 of right cardiac failure and 1 of hemoptysis).

In the surgical group with central type, all survived except 2 patients from peri-operative deaths. Only 3 patients needed oxygen therapy at follow up (Fig 1).

**QOL at Follow up in Patients With Relatively Peripheral Type**

QOL was reassessed at follow up (range 1.0–3.3, median 1.8 years) in 19 of 26 medically treated patients and in 10 of 11 post-surgery survivors (Fig 1). In the surgical group, 5 of 8 SF-36 and baseline dyspnea index scores improved significantly at follow up, but in the medical group only 2 SF-36 scores improved (Fig 4). Improvement in the scores of physical functioning (27.0±24.9 vs 2.7±18.0, p<0.01), role function (physically related) (60.0±44.4 vs 20.8±32.4, p<0.05), general health perception (20.2±26.0 vs –3.6±13.3, p<0.01), and baseline dyspnea index (6.3±2.3 vs –0.2±2.4, p<0.01) were significantly greater in the surgically treated group than in the medically treated group.

**QOL at Follow up in Others**

QOL was reassessed at follow up in 19 of 24 survivors in...
the surgical group with central type, and in 8 of 10 survivors in the mild disease group (Fig 1). However, QOL was reassessed in only 2 patients in the medical group with central type because 3 patients had died and another did not complete the questionnaire. In the surgically treated group with central type, 7 of 8 SF-36 scores and baseline dyspnea index improved at follow up. In the mild disease group, 5 of 8 SF-36 scores improved significantly at follow up.

**Prediction of QOL at Follow up in the Surgically Treated Group**

In patients with relatively peripheral type, physical functioning ($r=-0.88$, p<0.01) and general health perception ($r=-0.75$, p<0.01) of the SF-36 and baseline dyspnea index ($r=-0.93$, p<0.01) at follow up significantly correlated with postoperative PVR, and 6 of the SF-36 scores and baseline dyspnea index at follow up significantly correlated with a percentage decrease in PVR (Table 3). In all cases that included central type, physical functioning ($r=-0.69$, p<0.01), role function (physically related) ($r=-0.38$, p=0.049), general health perceptions ($r=-0.45$, p=0.018), role function (emotion-related) ($r=-0.39$, 0.045) of SF-36 and baseline dyspnea index ($r=-0.68$, p<0.01) at follow up significantly correlated with postoperative PVR. Similarly, 6 of the SF-36 scores and baseline dyspnea index at follow up correlated with a percentage decrease in PVR.

**Discussion**

PTE did not offer a survival benefit for patients with relatively peripheral type because of high operative mortality, but did result in significantly better QOL. The 6-year survival rate for the surgically treated group was 78.6% for relatively peripheral type and 92.3% for central type, values which are close to that obtained by Archibald et al’s study (ie, 75% 6-year survival rate)29 However, medical treatment offered better survival for patients with relatively peripheral type and with a mean PaO2 of >30 mmHg when compared with previous reports13–15

Several issues need to be considered when interpreting the results. We used CT angiography to classify the patients, which was then confirmed by selective pulmonary angiography. We agree that selective pulmonary angiography is a gold standard technique for diagnosing CTEPH.23 Yet, the mortality of patients with visible thrombi in a central pulmonary (ie, CD score =1) by CT was similar to that of patients with a score of 0. Hence, we then classified those patients with a CD score of ≤1 as having relatively peripheral type by CT findings only. Only 1 patient had thrombi limited to subsegmental arteries, and the other patients had at least surgically accessible thrombi in 1 of the segmental arteries, even in the medical group with relatively peripheral type. High operative mortality and the report of improved survival by beraprost sodium allowed us to legally choose medical treatment in these marginal cases.

![Table 3 Correlations of SF-36 Scores and Baseline Dyspnea Index With Post PVR, Percentage Decrease in PVR in Relatively Peripheral Type (n=10)](data:image/png;base64,iVBORw0KGgoAAAANSUhEUgAAAYAAAAAsCAYAAACe5u69AAAgAElEQVR42mO2d3d77EBAw/0P97IuE7k1zZQAAAAASUVORK5CYII=)

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<th>Physical functioning</th>
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<td>-0.88**</td>
<td>0.84**</td>
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<td>Role function (physically related)</td>
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<td>Bodily pain</td>
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<td>Baseline dyspnea index</td>
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**Abbreviations see in Table 2.**

*Expressed as Pearson's $r$-value, *p<0.05, **p<0.01.
tinue oxygen therapy. Surgery offered better QOL even in relatively peripheral type patients with CTEPH.

In the present study, QOL at follow up correlated with postoperative PVR and a percentage decrease in PVR. Hoeper recommended that an estimated reduction in PVR of >50% could be indicated for surgery. In the present study, when patients were divided into 2 groups (ie, sufficiently improved group and modestly improved group) according to percentage decrease in PVR >50%, the sufficiently improved group showed significantly better QOL scores in physical functioning (p=0.01), role function (physically related) (p=0.045), general health perceptions (p=0.019), social functioning (p=0.017), role function (emotion-related) (p<0.01), mental health (0.03), and baseline dyspnea index (p=0.03) than those in the modestly improved group at follow up. Furthermore, the number of patients with a percentage decrease in PVR was significantly smaller in patients with relatively peripheral type compared with those with central type. To achieve better QOL at follow up in patients with relatively peripheral type CTEPH, a reduction in PVR by sufficient PTE could be of major importance.

We recently reported that the D allele carrier in angiotensin-converting enzyme (ACE) gene polymorphism might be a poor prognostic factor for CTEPH. In the present series, ACE-ID genotypes were determined in 29 of 32 medically treated patients other than those in the mild disease group. Of 7 patients with II genotype type, no patient died, whereas of 16 with ID or DD genotypes, 6 died. All 7 patients with II genotype were classified as having relatively peripheral type. ACE gene polymorphism might also be associated with a better prognosis for patients with relatively peripheral type in the present series.

We have also reported the change in health-related QOL scores in medically treated patients. Although the data were limited in survivors with relatively peripheral type at follow up ≤3 years, SF-36 scores did not decrease, and role function (physically related) and vitality significantly improved. Medical treatment that includes beraprost sodium might offer better QOL even in relatively peripheral type patients with mean PRA of >30 mmHg.

The limitations of the study are that it was retrospective and that the number of patients in each subcategory was small. Unconfirmed and insufficient data regarding medical treatment for CTEPH ethically prevented us from randomizing the patients into medical and surgical groups, even those patients with relatively peripheral type. Large randomized studies using beraprost sodium, bosentan, or sildenafil in inoperable patients will be warranted. Recently, between 2003 and December 2006, the mortality in our series decreased to 9.1% compared with the rate of 19.0% between 1999 and 2002. Ogino et al also reported decreased mortality (8.0%) in CTEPH in Japan.

However, the mortality rate of 21.4% for patients with relatively peripheral type is high. In agreement with us, Hoeper et al have also reported that a pre-operative PVR value of >900 dyn·s·cm⁻⁵ is a risk factor for surgery. In patients with relatively peripheral type, all who had a pre-operative PVR value of ≤900 dyn·s·cm⁻⁵ survived, but all who had a pre-operative PVR value of >900 dyn·s·cm⁻⁵ did not (n=3).

Recent improvements in surgical skill and management in Japan can be expected to further decrease operative mortality, even in patients with relatively peripheral type. But until then caution should be exercised when evaluating relatively peripheral type patients with a PVR value of >900 dyn·s·cm⁻⁵.

In conclusion, this is the first study to investigate the change in QOL at follow up in patients with CTEPH, and PTE was found to result in significantly better QOL compared with medical treatment, even for patients with relatively peripheral type, although it must be emphasized that a reduction in operative mortality is essential.

Acknowledgment
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3. Fedullo PF, Auger WR, Kerr KM, Rubin LJ. Chronic thromboembolic pulmonary hypertension. N Engl J Med 2001; 345: 1465–1472. In conclusion, this is the first study to investigate the change in QOL at follow up in patients with CTEPH, and PTE was found to result in significantly better QOL compared with medical treatment, even for patients with relatively peripheral type, although it must be emphasized that a reduction in operative mortality is essential.

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