Long-Term Outcome of Chronic Thromboembolic Pulmonary Hypertension at a Single Japanese Pulmonary Endarterectomy Center

Hideki Miwa, MD; Nobuhiro Tanabe, PhD; Takayuki Jujo, PhD; Fumiaki Kato, PhD; Rie Anazawa, MD; Keiko Yamamoto, MD; Akira Naito, PhD; Hajime Kasai, PhD; Rintaro Nishimura, PhD; Rika Suda, PhD; Toshihiko Sugiura, PhD; Seichiro Sakao, PhD; Keiichi Ishida, PhD; Masahisa Masuda, PhD; Koichiro Tatsumi, PhD

Background: Several new treatments for chronic thromboembolic pulmonary hypertension (CTEPH) have appeared in recent years, which have led to changes in the treatment algorithm. Changes in survival rates and prognostic factors, however, have not been estimated so far.

Methods and Results: Two hundred and eighty patients were diagnosed with CTEPH at Chiba University Hospital between June 1986 and June 2016. Survival rate was investigated by date of treatment initiation (group 1, 1986–1998; group 2, 1999–2008; group 3, 2009–2016). Survival rates were also evaluated by treatment strategy: balloon pulmonary angioplasty (BPA), pulmonary endarterectomy (PEA), and medical treatment. Group 3 had significantly better disease-specific survival than groups 1 and 2 (5-year survival: 91.9% vs. 67.1%, 77.0%, respectively). For the non-PEA (BPA+medication) strategy, group 3 had better disease-specific survival than groups 1 and 2 (5-year survival: 94.9% vs. 54.6%, 74.2%, respectively). The PEA strategy had significantly better survival than the medication strategy in groups 1 and 2, whereas no difference was observed between the BPA, PEA, and medication strategies in group 3.

Conclusions: Survival in CTEPH in the recent era has significantly improved, especially in non-PEA patients. BPA and selective pulmonary vasodilators could improve survival in the non-PEA group. In the present study, no difference in survival was found between PEA and non-PEA.

Key Words: Balloon pulmonary angioplasty; Chronic thromboembolic pulmonary hypertension; Medical treatment; Pulmonary endarterectomy; Survival

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by unresolved thrombi and vascular remodeling, leading to increased pulmonary vascular resistance (PVR), high pulmonary arterial pressure, and right ventricular failure. Pulmonary endarterectomy (PEA) is considered a curative treatment for operable CTEPH patients.1 Although an advanced surgical technique is required, hospital mortality and complications at an experienced PEA center are usually very low.2 3 Meanwhile, persistent/recurrent pulmonary hypertension (PH) after PEA has been reported in 17–25% of patients.2 4 Balloon pulmonary angioplasty (BPA) uses a balloon catheter to dilate pulmonary stenosis. In 2001, Feinstein et al reported improvement in pulmonary hemodynamics using BPA in 18 patients. 5 This procedure, however, has not become widely available because of high morbidity associated with reperfusion pulmonary edema (RPE), which sometimes requires mechanical ventilation. Nevertheless, an improved technique using a small balloon and new imaging techniques enabled us to achieve improvement in pulmonary hemodynamics and exercise tolerance with acceptable complications and low hospital mortality rates in inoperable patients or patients with persistent PH after PEA.6 7 9 11 Riociguat is the first approved drug specific for inoperable...
CTEPH or persistent/recurrent PH after PEA based on the CHEST-1 study, which noted significant improvement in 6-min walk distance (6MWD) and World Health Organization (WHO) functional class at 16 weeks.\textsuperscript{12} Additionally, survival benefits of pulmonary arterial hypertension (PAH)-target therapies for CTEPH have also been demonstrated.\textsuperscript{13–15} Thus, several new treatments for CTEPH have appeared in recent years, which have led to changes in the treatment algorithm.\textsuperscript{1} Survival and prognostic factors, however, have not been estimated.

We conducted a retrospective analysis of data from long-term medical records of CTEPH patients at Chiba University Hospital to investigate the survival difference according to era, and according to PEA, BPA, and medication.

**Methods**

**Ethics**
By Japanese legislation, the need for informed consent was waived. In this study, patient identity was concealed, and data were compiled according to the requirements of the Japanese Ministry of Health, Labor and Welfare, which is dedicated to privacy, information technology, and civil rights. The protocol was approved by the Research Ethics Committee of Chiba University School of Medicine (approval number 2,584). Since 2009, all survivors have given written informed consent for a prospective cohort study (approval number 826).

**Inclusion Criteria**
This was a retrospective, single-center, cohort study of 280 patients with CTEPH diagnosed at Chiba University Hospital between June 1986 and June 2016. By the end of December 2016, follow-up data were obtained from 273 of the 280 patients by either contacting them or their primary physicians. One hundred and eighty-five patients were alive and 88 patients were deceased. The remaining 7 patients were censored at the final visit date by their primary physician. The mean follow-up period was 7.5±6.6 years.

CTEPH was defined as follows: (1) mean pulmonary arterial pressure (mPAP) ≥25 mmHg and normal wedge pressure on right heart catheterization (RHC); (2) persistent symptoms >3 months, and (3) chronic thrombi on lung perfusion, enhanced computed tomography, or pulmonary angiography.

Pulmonary hemodynamics were evaluated on RHC in all patients, before the initiation of BPA, and for those who received PEA. Cardiac output was measured using a thermodilution method, and PVR was calculated. Blood gas analysis was performed under room air at RHC. The central disease score was calculated by adding the number of abnormal central portions, defined as proximal to the segmental branches and divided into 4 portions.\textsuperscript{16} The Jamieson classification (types 1–4) according to the location and morphology of thromboembolic and vascular wall disease at the time of surgery was also used.\textsuperscript{17}

**Indications for Surgery**
The indications for PEA were as follows: (1) mPAP ≥30 mmHg or PVR ≥3.75 Wood units (WU); (2) WHO functional class ≥II; (3) thrombi accessible to current surgical techniques; and (4) absence of severe concomitant disease.
PEA was first performed in 1986 at Chiba University Hospital.

Indications for BPA
The indications for BPA were (1) surgically inaccessible lesions located peripheral to segmental artery; (2) proximal lesions in patients with inoperability due to comorbidity; or (3) residual PH after PEA; (4) WHO functional class ≥ II after medical therapy; and (5) understanding of the risks and benefits of BPA.

BPA and PEA were performed in some cases at several institutions other than the Chiba group (Chiba University Hospital and National Hospital Organization Chiba Medical Center) (PEA: Chiba group, n=153; others, n=6; BPA: Chiba University Hospital, n=5; others, n=24).

Definitions

Selective Pulmonary Vasodilators Patients received anticoagulant therapy. Some patients were treated with selective pulmonary vasodilators, defined as phosphodiesterase-5 inhibitors (PDE-5I), endothelin receptor antagonist (ERA), epoprostenol, or riociguat.14

Treatment Strategy Subgroups Patients were classified into 3 groups according to treatment strategy. Those who received PEA (those who underwent BPA after PEA were included) were classified into the PEA group. Those who underwent BPA (those who underwent BPA after PEA were excluded) were classified into the BPA group. Patients who were only medically treated were defined as the medication group. Furthermore, the BPA and medication groups were defined as the non-PEA group (Figure 1).

Era Subgroups In Japan, epoprostenol, bosentan, sildenafil, and riociguat have been available since 1999, 2005, 2008, and 2014, respectively. BPA in the present series was first performed in December 2009. Thus, we defined the patients in group 1 (1986–1998) as those who could receive PEA and anticoagulant and oxygen therapy, those in group 2 (1999–2008) as those who could be prescribed selective pulmonary vasodilators in addition to existing treatments, and those in group 3 (2009–2016) as those who could additionally undergo BPA (Figure 1).

Table 1. Subject Characteristics vs. Era

| Group | n | Group | n | Group | n | P-value |
|-------|---|-------|---|-------|---|---------|
| Sex (F/M) | 39/16 | 55 | 70/35 | 105 | 90/30 | 120 | 0.3882 |
| Age (years) | 52.4±12.7 | 55 | 55.8±12.3 | 105 | 60.2±11.8* | 120 | 0.0002 |
| Comorbidit | 21.8 | 55 | 28.6 | 105 | 22.5 | 120 | 0.4952 |
| mRAP (mmHg) | 3.8±4.0 | 54 | 5.8±4.4* | 104 | 5.5±3.5* | 120 | 0.0099 |
| mPAP (mmHg) | 43.8±10.9 | 54 | 44.8±11.9 | 104 | 44.1±11.1 | 120 | 0.8567 |
| PVR (WU) | 10.3±4.9* | 54 | 10.4±4.9* | 104 | 8.9±3.8 | 119 | 0.0232 |
| CI (L·min⁻¹·m⁻²) | 2.6±0.6 | 54 | 2.5±0.7 | 104 | 2.9±0.8* | 119 | 0.0004 |
| PaO₂ (torr) | 58.4±10.5 | 54 | 58.4±10.3 | 104 | 57.3±9.1 | 117 | 0.6546 |
| PVOS (torr) | 33.4±4.5 | 53 | 32.3±4.1 | 103 | 33.4±3.8 | 116 | 0.0922 |
| BNP (pg/mL) | 179.0±152.6 | 8 | 262.8±305.2 | 103 | 201.9±304.1 | 119 | 0.2928 |
| WHO functional class (3–4) | 8.0 | 55 | 70.6 | 102 | 64.7 | 119 | 0.1214 |
| 6MWD (m) | 343.3±84.3 | 3 | 339.7±97.0 | 95 | 379.7±92.2* | 113 | 0.0102 |

Data given as mean±SD or %. *P<0.05 compared with †group 1, ‡group 2, and §group 3. 6MWD, 6-min walk distance; BNP, brain natriuretic peptide; BPA, balloon pulmonary angioplasty; CI, cardiac index; ERA, endothelin receptor antagonist; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; PaO₂, partial pressure of oxygen in arterial blood; PDE-5I, phosphodiesterase-5 inhibitor; PEA, pulmonary endarterectomy; PVOS, partial pressure of oxygen in mixed venous blood; PVR, pulmonary vascular resistance; WHO, World Health Organization.
Comorbidities that may have affected prognosis and decision for PEA or BPA were as follows: psychiatric disease, n=22; stroke, n=17; cancer, n=16; coronary artery disease, n=6; chronic obstructive pulmonary disease, n=6; chronic kidney disease, n=5; epilepsy, n=3; severe diabetes mellitus, n=2; old lung tuberculosis, n=1; interstitial pneumonia, n=1; and amyotrophic lateral sclerosis, n=1.

Era Subgroup Characteristics
The baseline characteristics of groups 1–3 are listed in Table 1. Patients in group 3 were significantly older than those in groups 1 and 2 (P=0.0001, P=0.0067, respectively).

Table 2. Subject Characteristics vs. Treatment

| Treatment | n (BPA: n=16) | n (PEA: n=159) | n (Medication: n=105) | P-value |
|-----------|---------------|----------------|-----------------------|---------|
| Sex (F/M) | 13/3          | 104/55         | 82/23                 | 0.0549  |
| Age (years) | 55.2±14.9     | 56.2±11.6      | 58.5±13.4             | 0.2861  |
| Comorbidity | 12.5          | 17.6           | 37.1*                 | 0.0008  |
| mRAP (mmHg) | 6.9±4.5       | 5.4±3.9        | 4.9±4.0               | 0.1491  |
| mPAP (mmHg) | 50.5±12.1*     | 46.4±10.0*     | 40.2±11.8             | <0.0001 |
| PVR (WU) | 10.9±3.6      | 10.3±4.1*     | 8.7±5.0               | 0.0122  |
| Cl (L·min⁻¹·m⁻²) | 2.7±0.7   | 2.6±0.7        | 2.8±0.8               | 0.14    |
| PaO₂ (torr) | 54.3±7.9      | 57.5±8.0      | 59.1±11.1             | 0.1609  |
| PvO₂ (torr) | 31.2±3.7      | 32.5±3.4      | 33.9±4.9*             | 0.0073  |
| BNP (pg/mL) | 381.4±536.4   | 222.0±271.6   | 211.5±285.4           | 0.1221  |
| WHO functional class (3–4) | 86.7*     | 74.5*       | 60.6                 | 0.0193  |
| 6MWD (m) | 349.4±93.2    | 367.2±89.6    | 353.9±105.9           | 0.5731  |
| Central disease score (2–4) | 7.7     | 55.2*       | 24.5                 | <0.0001 |
| BPA after PEA | –           | –           | –                    | –      |
| Selective pulmonary vasodilators | 68.8*   | 20.1        | 43.8*                | <0.0001 |
| PDE5-I | 37.5          | 10.1         | 23.8                 | 0.001   |
| ERA | 50.0          | 9.4          | 17.1                 | <0.0001 |
| Riociguat | 0.0          | 3.8         | 18.1                 | 0.001   |
| Epoprostenol | 6.3         | 0.6         | 3.8                  | 0.1099  |

Data given as mean±SD or %. *P<0.05 compared with †BPA, ‡PEA, and §Medication. Abbreviations as in Table 1.

Figure 2. Cumulative disease-specific survival rate vs. era. Survival of the BPA and PEA groups was calculated from the initiation date of each treatment, and that of the medication group was calculated from the date of diagnosis. Group 3 survival was significantly better than that of groups 1 and 2 (P=0.0002, P=0.0045, respectively). Group 1, 1986–1998; group 2, 1999–2008; group 3, 2009–2016.

Results
Baseline Characteristics
Just before treatment initiation (diagnosis date for the medication group), mean age of the 280 patients was 57.0±12.5 years, with a female predominance (199:81). mPAP, cardiac index (CI), and PVR were 44.3±11.3 mmHg, 2.70±0.73 L·min⁻¹·m⁻², and 9.71±4.51 WU, respectively. The percentage of patients with WHO functional class 3–4 was 69.9%. The Jamieson classification in the PEA group was type 1 in 64.1%, type 2 in 22.0%, type 3 in 13.2%, and type 4 in 0.6% of patients.
PVR in group 3 was significantly lower than in groups 1 and 2 (P=0.0453, P=0.0124, respectively). A higher percentage of use of selective pulmonary vasodilators was observed in group 3 than in groups 1 and 2 (P<0.0001, P<0.0001, respectively) and in group 2 than in group 1 (P=0.0103). A higher percentage of BPA was observed in group 3 than in groups 1 and 2 (P=0.0007, P<0.0001, respectively). There was no significant difference in the percentage of PEA between the 3 groups. A higher percentage of Jamieson classification types 1 or 2 in group 2 was observed (P=0.0109).

Treatment Subgroup Characteristics

The baseline characteristics of the BPA, PEA, and medication groups are listed in Table 2. mPAP in the medication group was significantly lower than in the BPA and PEA groups (P=0.0005, P<0.0001, respectively). PVR in the medication group was also significantly lower than in the PEA group (P=0.0054). Selective pulmonary vasodilators were used not only in the medication but also in the BPA and PEA groups (cases were collected only when given before BPA or PEA). Additionally, there were no significant differences in baseline hemodynamics between patients with/without selective pulmonary vasodilator use in the medication group (Table S1).

Overall Survival

Eighty-eight patients died during follow-up. Seventy-two patients had CTEPH-related death (group 1, 29/55 patients; group 2, 34/105; group 3, 9/120), such as right ventricular failure, perioperative death, and sudden death. Sixteen patients died of other causes such as stroke (n=3), interstitial pneumonia (n=2), senile deterioration (n=2), amyotrophic lateral sclerosis (n=1), acute myocardial infarction (n=1), renal failure syndrome (n=1), multiple myeloma (n=1), skin cancer (n=1), asphyxia (n=1), burn trauma (n=1), and unknown (n=2).

The 1-, 3-, 5-, and 10-year overall survival from initiation of treatment in 280 patients was 88.9%, 83.3%, 78.8%, and 69.9%, respectively. Group 3 had significantly better survival than the medication group (P=0.0375, P=0.0389, respectively). In group 3, however, there were no significant survival differences between the treatment groups. BPA, balloon pulmonary angioplasty. Group 1, 1986–1998; group 2, 1999–2008; group 3, 2009–2016.

Figure 3. Cumulative disease-specific survival rate vs. treatment group in (A) all patients, (B) group 1, (C) group 2 and (D) group 3. In (A) all patients, the pulmonary endarterectomy (PEA) group had significantly better survival than the medication group (P=0.0121). In (B) group 1 and (C) group 2, the PEA group had significantly better survival than the medication group (P=0.0375, P=0.0389, respectively). In (D) group 3, however, there were no significant survival differences between the treatment groups. BPA, balloon pulmonary angioplasty. Group 1, 1986–1998; group 2, 1999–2008; group 3, 2009–2016.
Disease-Specific Survival

The 1-, 3-, 5-, and 10-year disease-specific survival from initiation of treatment in 280 patients was 89.2%, 84.8%, 81.2%, and 73.1%, respectively. Group 3 had significantly better disease-specific survival than groups 1 and 2 (P=0.0002, P=0.0045, respectively; Figure 2).

The 1-, 3-, 5-, and 10-year disease-specific survival was 88.1%, 86.6%, 84.1%, and 80.6% for PEA; and 90.4%, 91.7%, 76.1%, and 62.4% for the medication group. The 1-, 3-, and 5-year survival in the BPA group was 93.8%, 87.1%, and 87.1%. The PEA group had significantly better survival than the medication group (P=0.0012; Figure 3A). Similarly, the PEA group had significantly better survival than the medication group in groups 1 (P=0.0375) and 2 (P=0.0389; Figure 3B, C). There was no significant survival difference between the BPA, PEA, and medication groups in group 3 (Figure 3D). In group 3, 5-year survival in the BPA, PEA, and medication groups was 87.1%, 89.9%, and 100%, respectively.

In the PEA group, there were no significant survival differences between groups 1, 2, and 3 (Figure 4A). Conversely, in the non-PEA group, group 3 had significantly better disease-specific survival than groups 1 and 2 (P=0.0001, P=0.0061, respectively; Figure 4B).

In group 3, all who had received BPA after PEA survived, although there was no significant survival difference, compared with those who had received only PEA (P=0.2642; Figure S3).

Prognostic Factors for Disease-Specific Survival

In the 280 patients, group 3, WHO functional class 1–2, low mean right atrial pressure (mRAP), low mPAP, low PVR, low brain natriuretic peptide, high CI, PEA, and selective pulmonary vasodilators were associated with better outcomes on univariate Cox proportional hazard analysis (Table S2).

In the PEA group, low PVR, group 3, and Jamieson classification types 1–2 were associated with better survival on univariate analysis, and low PVR and Jamieson classification types 1–2 were independently associated with better survival on multivariable analysis (Table 3). In the non-PEA group, we included only PVR out of mPAP, PVR, and mRAP on multivariate analysis. PVR is a widely used prognostic factor for CTEPH and the association of mPAP, PVR, and mRAP with survival cancelled each other out because of the strong correlation between them. Group 3, low PVR, WHO functional class 1–2, and selective pulmonary vasodilators were independently associated with better survival on multivariable analysis (Table 4).

Discussion

In a single, PEA-expert center, using follow-up data obtained from 273 of 280 patients (97.5%), we evaluated the change in survival according to era, as well as survival differences between 3 treatments (PEA, BPA, medication). This is the first study showing time-dependent improved survival in all CTEPH patients, including patients who underwent BPA. The present study has shown (1) significantly improved survival for patients with CTEPH in the recent era; (2) improved survival especially in the non-PEA group; and (3) no survival difference between 3 treatments in the recent era.

Several matters need to be considered when interpreting these results. First, the BPA group existed only in group 3. BPA was not a significant predictor for better disease-specific survival in this study. The number of patients treated with BPA, however, was small, and the BPA group had fair survival regardless of impaired baseline pulmonary hemodynamics, compared with the medication group. Additionally, all patients who underwent BPA due to residual PH after PEA were alive. In previous studies, BPA improved pulmonary hemodynamics and exercise tolerance for patients with inoperable CTEPH and those with residual PH after PEA.6–11 Recently, major morbidities such as RPE have decreased.8,10,19 Therefore, BPA, a new treatment option, could have resulted in improved survival in group 3.

Second, group 3 was a significant independent predictor of better outcome in the non-PEA group, in addition to low PVR and use of PAH-specific drug. Although BPA and-era were not included at the same time in the multivariable analysis due to a significant correlation of these factors, group 3 included most patients treated with BPA.
In addition, appropriate indication for BPA in the non-PEA patients and early diagnosis of CTEPH, resulting in low PVR, may be associated with better outcomes.

Conversely, group 3 was not a significant predictor for better survival in PEA patients, although hospital mortality decreased from 18.2% to 8.3%. In addition, type 3 or 4 Jamieson classification was associated with poor survival. The main cause of death was hospital death in the PEA group, and group 3 tended to include more distal type (central disease score, 0 or 1; Jamieson type, 3 or 4; Table 1). A more extended indication for PEA in group 3 may have resulted in reduced difference in mortality between groups 2 and 3; although hospital mortality decreased to 6.4% after 2012 (data not shown). Although the Jamieson classification could not be estimated preoperatively, BPA may be used instead of PEA in marginal patients with comorbidity and a relatively distal type on pulmonary angiogram, even with surgically accessible thrombi.

Third, high PVR was associated with poor outcome in both the PEA and non-PEA groups. Dartevelle et al showed that the perioperative mortality was 4% in patients with PVR <900 dynes·s·cm⁻⁵ and increased to 20% in those with PVR >1,200 dynes·s·cm⁻⁵. An international registry also showed that the mortality associated with PEA was 0%, 2.8%, 5.8%, and 10.6% in patients with PVR <400, 400–800, 800–1,200, and >1,200 dynes·s·cm⁻⁵, respectively. Nakanishi et al reported that PVR was associated with mortality in CTEPH patients treated by classical therapy. In addition, we previously reported that PVR >1,100 dynes·s·cm⁻⁵ was associated with high mortality in medically treated patients. Early awareness of CTEPH and early indication for PEA or BPA with improved skill for medically treated patients under discussion by a multiple disciplinary team may reduce the number of patients with severe condition and improve survival in

---

### Table 3. Prognostic Factors in the PEA group

|                | Univariate       | Multivariate     |
|----------------|------------------|------------------|
|                | HR (95% CI) P-value | HR (95% CI) P-value |
| Age            | 0.99 (0.960–1.018) 0.4022 | 0.98 (0.952–1.012) 0.2244 |
| WHO functional class 3–4 (vs. 1–2) | 2.08 (0.808–7.063) 0.138 | 1.09 (0.378–3.942) 0.8833 |
| mRAP (mmHg)    | 1.08 (0.993–1.157) 0.0719 |                  |
| mPAP (mmHg)    | 1.05 (1.011–1.083) 0.0094 |                  |
| PVR (WU)       | 1.16 (1.073–1.258) 0.0002 | 1.19 (1.085–1.311) 0.0003 |
| Cl (L·min⁻¹·m⁻²) | 0.46 (0.238–0.833) 0.0095 |                  |
| PaO₂ (torr)    | 1.03 (0.990–1.070) 0.1465 |                  |

**Treatment start date**

- Group 3 (vs. group 1): 0.38 (0.137–0.982) 0.0458 0.81 (0.254–2.356) 0.7121
- Group 3 (vs. group 2): 0.62 (0.225–1.581) 0.3177 1.54 (0.483–4.636) 0.4515
- Group 2 (vs. group 1): 0.61 (0.272–1.382) 0.2345 0.53 (0.216–1.290) 0.1586
- Comorbidity: 1.79 (0.750–3.868) 0.1776 1.85 (0.684–4.544) 0.2133

**Abbreviations as in Table 1.**

### Table 4. Prognostic Factors in the Non-PEA Group

|                | Univariate       | Multivariate     |
|----------------|------------------|------------------|
|                | HR (95% CI) P-value | HR (95% CI) P-value |
| Age            | 0.99 (0.968–1.015) 0.4386 | 0.996 (0.967–1.025) 0.7741 |
| WHO functional class 3–4 (vs. 1–2) | 3.39 (1.567–8.448) 0.0013 | 4.05 (1.555–11.57) 0.0038 |
| mRAP (mmHg)    | 1.14 (1.058–1.230) 0.0008 |                  |
| mPAP (mmHg)    | 1.03 (1.005–1.056) 0.0213 |                  |
| PVR (WU)       | 1.15 (1.082–1.217) <0.0001 | 1.07 (1.006–1.147) 0.0354 |
| Cl (L·min⁻¹·m⁻²) | 0.34 (0.174–0.615) 0.0002 |                  |
| PaO₂ (torr)    | 0.97 (0.937–0.999) 0.042 |                  |
| Central disease score 2–4 (vs. 0–1) | 2.16 (1.046–4.236) 0.0382 | 1.88 (0.783–4.221) 0.1515 |
| Selective pulmonary vasodilators | 0.40 (0.183–0.795) 0.0083 | 0.27 (0.107–0.611) 0.0015 |

**Treatment start date**

- Group 3 (vs. group 1): 0.10 (0.015–0.366) 0.0002 0.10 (0.005–0.519) 0.0036
- Group 3 (vs. group 2): 0.15 (0.024–0.533) 0.0015 0.10 (0.005–0.498) 0.0021
- Group 2 (vs. group 1): 0.65 (0.333–1.305) 0.218 0.97 (0.463–2.077) 0.9279
- Comorbidity: 1.04 (0.516–1.999) 0.9096 1.00 (0.437–2.192) 0.9979

**Abbreviations as in Table 1.**
these patients.

Fourth, selective pulmonary vasodilators contributed to improved survival for the non-PEA group. We previously reported that modern oral therapy contributed to better survival in CTEPH,\textsuperscript{14} PAH-target therapy has also been shown to improve survival in inoperable patients with CTEPH,\textsuperscript{13,15} supporting the present results. In contrast, Delcroix et al. reported that survival in patients who received PAH-target therapy was similar to that in untreated patients in the non-operated group.\textsuperscript{22} In the present study, there was no significant difference in PVR between patients with/without selective pulmonary vasodilator use in the medication group. The discrepancy might be explained by a remarkable hemodynamic difference in patients with/without pulmonary vasodilator use in the Delcroix et al. study. In addition, the start date for survival analysis was the diagnosis date in the medication group, but the start of selective pulmonary vasodilators in group 1 (approximately 5%) was delayed, resulting in an advantage of selective pulmonary vasodilators for survival. Use of pulmonary vasodilators, however, was a predictor of better survival on multivariate analysis, when the start date was judged as the start of medication.

Fifth, we identified significantly better baseline hemodynamics (lower PVR) in group 3 than in groups 1 and 2. The patients treated with BPA or PEA in group 3 were frequently pretreated with selective pulmonary vasodilators (BPA, 69%; PEA, 42%), which might lead to decreased PVR. In the current study, low PVR was independently associated with survival in both the PEA and non-PEA groups. The necessity of pretreatment before BPA or PEA should be further investigated.

Sixth, survival differences according to treatment have decreased in the recent era. Selective pulmonary vasodilators may contribute to improved survival in the medication group, otherwise BPA could improve survival for patients with deteriorating health status even after PEA or medical treatment.

Finally, for overall survival, 3-year survival in the PEA group was 88.3%, similar to the 89% reported in an international registry. Three-year survival in the medication group was 95.2% (70% in the international registry).\textsuperscript{24} The indications for PEA, BPA, or medical treatment at Chiba group, therefore, could be justified.

Study Limitations
First, this study was a retrospective, cohort study conducted at a single institution. Second, changes in hemodynamics and quality of life among treatments could not be compared. Third, the sample size of the BPA group was small. Fourth, the indication for BPA, PEA, and selective pulmonary vasodilators was non-randomized.

Conclusions
Survival for patients with CTEPH in the recent era was significantly improved, especially in the non-PEA group. BPA and selective pulmonary vasodilators could improve survival in the non-PEA group. In the recent era, no survival difference was seen between the PEA and non-PEA groups.

Acknowledgments
We are grateful to Dr. Hiromi Matsubara (Okayama Medical Center), Professor Tohru Sato (Kyorin University), Dr. Takeshi Ogo (National Cerebral and Cardiovascular Center), and Dr. Takashi Kawakami (Keio University) for performing successful BPA, and Professor Motomi Ando (Fujita Health University) and Professor Hitoshi Ogino (National Cerebral and Cardiovascular Center, Tokyo Medical University) for performing excellent PEA. We would also like to thank Editage (www.editage.jp) for English-language editing.

Disclosures
N.T. was supported by a research grant from the Ministry of Education, Culture, Sports, Science and Technology of Japan (2561148), and a grant to The Intractable Respiratory Diseases and Pulmonary Hypertension Research Group, from the Ministry of Health, Labor and Welfare (H29-027), a grant to the Pulmonary Hypertension Research Group from the Japan Agency for Medical Research and Development, AMED (15-17 ek0109127j0003). T.J. was supported by a Grant-in-Aid for Young Scientists (JSPS KAKENHI Grant Number 16K19444) from the Japanese Ministry of Education and Science. S.S. was supported by a grant to The Intractable Respiratory Diseases and Pulmonary Hypertension Research Group, from the Ministry of Health, Labor and Welfare (H29-027), a grant to the Pulmonary Hypertension Research Group from the AMED (15-17 ek0109127j0003), and a Grant-in-Aid for Scientific Research (JSPS KAKENHI Grant Number 15K09210) from the Japanese Ministry of Education and Science; K.T. was supported by a grant to The Intractable Respiratory Diseases and Pulmonary Hypertension Research Group, from the Ministry of Health, Labor and Welfare (H29-027), a grant to the Pulmonary Hypertension Research Group from the AMED (15-17 ek0109127j0003). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

N.T. is a member of an endowed department sponsored by Actelion Pharmaceuticals and received lecture honoraria from Bayer, Daiichi-Sankyo, Actelion Pharmaceuticals, and Bristol Myers Squibb. T.J. is a member of an endowed department sponsored by Teijin Pharma. F.K. and R.S. received a research grant from FinoxoSmithKline; and K.T. received lecture honoraria from Actelion Pharmaceuticals and Daiichi-Sankyo. The other authors declare no conflicts of interest.

References
1. Kim NH, Delcroix M, Jenkins DP, Channick R, Dartevelle P, Jansa P, et al. Chronic thromboembolic pulmonary hypertension. J Am Coll Cardiol 2013; 62: D92 – D99.
2. Mayer E, Jenkins D, Lindner J, D’Armini A, Kloek J, Meyns B, et al. Surgical management and outcome of patients with chronic thromboembolic pulmonary hypertension: Results from an international prospective registry. J Thorac Cardiovasc Surg 2011; 141: 702 – 710.
3. Madani MM, Auger WR, Pretorius V, Sakakibara N, Kerr KM, Kim NH, et al. Pulmonary endarterectomy: Recent changes in a single institution’s experience of more than 2,700 patients. Ann Thorac Surg 2012; 94: 97 – 103.
4. Cannon JE, Su L, Kiely DG, Page K, Toshner M, Swietlik E, et al. Dynamic risk stratification of patient long-term outcome after pulmonary endarterectomy: Results from the United Kingdom National Cohort. Circulation 2016; 133: 1761 – 1771.
5. Feinstein JA, Goldhaber SZ, Lock JE, Fernandes SM, Landzberg MJ. Balloon pulmonary angioplasty for treatment of chronic thromboembolic pulmonary hypertension. Circulation 2001; 103: 13 – 13.
6. Kataoka M, Inami T, Hayashida K, Shimura N, Ishiguro H, Abe T, et al. Percutaneous transluminal pulmonary angioplasty for the treatment of chronic thromboembolic pulmonary hypertension. Circ Cardiovasc Interv 2012; 5: 756 – 762.
7. Sugimura K, Fukumoto Y, Satoh K, Nohchio K, Miura Y, Aoki T, et al. Percutaneous transluminal pulmonary angioplasty markedly improves pulmonary hemodynamics and long-term prognosis in patients with chronic thromboembolic pulmonary hypertension. Circ J 2012; 76: 485 – 488.
8. Mizoguchi H, Ogawa A, Minemasa M, Mikouchi H, Ito H, Matsubara H. Refined balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension. Circ Cardiovasc Interv 2012; 5: 748 – 755.
9. Inami T, Kataoka M, Ando M, Fukuda K, Yoshino H, Satoh T. A new era of therapeutic strategies for chronic thromboembolic pulmonary hypertension by two different interventional approaches: pulmonary endarterectomy and percutaneous transluminal
Kawakami T, et al. Additional percutaneous transluminal pulmonary angioplasty for residual or recurrent pulmonary hypertension after pulmonary endarterectomy. *Int J Cardiol* 2015; **183**: 138–142.

Dartevelle P, Fadel E, Mussot S, Chapelier A, Herve P, de Perrot M, et al. Chronic thromboembolic pulmonary hypertension. *Eur Respir J* 2004; **23**: 637–648.

Nakanishi N, Kyotani S, Satoh T, Kunieda T. Pulmonary hemodynamics and long-term outcome in patients with chronic pulmonary thromboembolism and pulmonary hypertension. *Nihon Kyobu Shikkan Gakkai Zasshi* 1997; **35**: 589–595 (in Japanese).

Delcroix M, Lang I, Pepke-Zaba J, Jansa P, D’Armini AM, Snijder R, et al. Long-term outcome of patients with chronic thromboembolic pulmonary hypertension: Results from an international prospective registry. *Circulation* 2016; **133**: 859–871.

**Supplementary Files**

**Supplementary File 1**

Figure S1. Cumulative overall survival rate vs. era.

Figure S2. Cumulative overall survival rate vs. treatment for (A) all patients; (B) group 1; (C) group 2; and (D) group 3.

Figure S3. Cumulative disease-specific survival between patients who had only pulmonary endarterectomy (PEA) and those who received balloon pulmonary angioplasty (BPA) after PEA in group 3.

Table S1. Baseline medication group characteristics vs. selective pulmonary vasodilator status

Table S2. Univariate prognostic factors in the 280 patients

Please find supplementary file(s); http://dx.doi.org/10.1253/circj.CJ-17-1242