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RAPID COMMUNICATION

Percutaneous Transluminal Pulmonary Angioplasty Markedly Improves Pulmonary Hemodynamics and Long-Term Prognosis in Patients With Chronic Thromboembolic Pulmonary Hypertension

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Background: Distal-type chronic thromboembolic pulmonary hypertension (CTEPH) is a fatal disease for which a new therapeutic strategy needs to be developed. We examined the effects of percutaneous transluminal pulmonary angioplasty (PTPA).

Methods and Results: We prospectively enrolled 12 patients with distal-type CTEPH. After stabilizing their condition with pulmonary vasodilators, we then performed PTPA, which markedly improved pulmonary hemodynamics and pulmonary artery structure, as confirmed by angiography and optical coherence tomography, and also significantly improved their long-term prognosis compared with 39 historical controls.

Conclusions: PTPA is a promising therapeutic option for distal-type CTEPH. (*Circ J* 2012; **76:** 485–488)

Key Words: Chronic thromboembolic pulmonary hypertension; Optical coherence tomography; Percutaneous transluminal pulmonary angioplasty

Chronic thromboembolic pulmonary hypertension (CTEPH) is a distinct disease entity of pulmonary hypertension (PH) with a mean pulmonary arterial pressure (PAP) greater than 25 mmHg and is classified into central- and distal-types.[1–6] Central-type CTEPH is diagnosed when PH persists for more than 6 months after acute pulmonary embolism associated with thrombotic obstruction of the large pulmonary artery (PA).[1–5] Although pulmonary thromboendarterectomy is an established treatment for central-type CTEPH, it is limited to only central-type CTEPH and is not feasible for distal-type CTEPH.[2,4] Thus, distal-type CTEPH remains a fatal condition because of the lack of effective treatment.[2,3,5]

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Although it has been reported that balloon pulmonary angioplasty may be useful for distal-type CTEPH, the interventional procedure is complicated by pulmonary hemorrhage and edema, right ventricular failure, and even death.[4,7] Thus, a safer and more effective therapeutic strategy with an appropriate imaging method needs to be developed.

Optical coherence tomography (OCT) is an interferometer-based imaging modality that produces a 2-D image of optical scattering from the internal tissue microstructure with a high resolution of approximately 10–20 μm, 10-fold higher than that of intravascular ultrasound. We recently demonstrated that OCT is useful for observing PA lesions in distal-type CTEPH.[5,8] In the present study, in order to develop an effective and safe treatment for distal-type CTEPH, we examined our modified method of percutaneous transluminal pulmonary angioplasty (PTPA) combined with OCT evaluation.

Methods

The study protocol was approved by the Ethical Committees of Tohoku University and all patients provided written informed consent.

Patients

From July 2009 to September 2011, we prospectively enrolled 12 patients with distal-type CTEPH, including 2 patients with post-thromboendoarterectomy and residual PH (58±13 [SD] years, 11 females, 1 male, WHO-functional class (WHO-FC) II in 4, III in 5 and IV in 3). In order to stabilize their condition, we first treated them medically for 1–3 months, comprising

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Table. Clinical Course of the Patients With Distal-Type CTEPH

	Historical control group (n=39)	PTPA group (n=12)		
		Baseline	Medical therapy	After PTPA
M/F	7/32	1/11	–	–
Age (years)	64±10	58±13		
WHO-FC				
II	23 (59%)	4 (33%)	6 (50%)	12 (100%)
III	12 (31%)	5 (42%)	5 (42%)	0
IV	4 (10%)	3 (25%)	1 (8%)	0
Hemodynamic variables				
mPAP (mmHg)	43.4±11.5	47.8±11.6	43.2±9.5	24.8±4.9**,††
RAP (mmHg)	4.8±3.6	7.3±2.3	6±2.7	3.3±1.5**,††
CI ($L \cdot ml^{-1} \cdot m^{-2}$)	2.47±0.64	2.17±0.35	2.66±0.47**	2.79±0.37**
PVR ($dyne \cdot s^{-1} \cdot cm^{-5}$)	848±393	971±500	672±236*	310±73**,††
6-min walk distance (m)	288±157	350±105	340±112	441±76*,†
BNP	206±282	335±386	78±113*	16±11*
Duration of treatment (years)	3.9±2.7	–	3.5±3.6	1.3±0.6
Medications (N, mean dose)				
Epoprostenol ($ng \cdot kg^{-1} \cdot min^{-1}$)	3 (11±8)	–	7 (12.4±6.8)	0
Beraprost (μg)	39 (143±69)	–	5 (240±73)	11 (310±76)
Sildenafil (mg)	6 (60±0)	–	11 (60±0)	11 (60±0)
Bosentan (mg)	6 (208.3±64.5)	–	5 (162.5±55.9)	5 (162.5±55.9)

Data are expressed as mean±SEM.
*P<0.05 and **P<0.01 vs. baseline; †P<0.05 and ††P<0.01 vs. medical therapy.
CTEPH, chronic thromboembolic pulmonary hypertension; PTPA, percutaneous transluminal pulmonary angioplasty; FC, functional class; mPAP, mean pulmonary arterial pressure; RAP, right atrial pressure; CI, cardiac index; PVR, pulmonary vascular resistance; BNP, brain natriuretic peptide.

epoprostenol in 7, beraprost in 5, sildenafil in 11 and bosentan in 5 (Table). After confirming stabilization, including systemic hemodynamics, right heart function, and nutrition, we then performed PTPA of typical flaps, webs or stenoses in the PA only after adequate antithrombotic treatment for more than 6 months.

PTPA for Distal-Type CTEPH

After right heart catheterization, we performed PTPA with a continuous infusion of heparin (400–600 U/h), using a highly maneuverable, soft-tipped 0.035-inch wire to enter the distally stenosed or occluded PA, and 2–7-mm balloons to dilate the target lesions to 50–75% of the vessel diameter after oral administration of hydrocortisone (500 mg). We selected those PA segments for balloon dilation with signs of intravascular webs, filling defects, or complete occlusion.[8] Before and after inflation, we performed 3 imaging evaluations (PA angiography and intravascular ultrasound in all patients and OCT in half of them) in order to assess the effectiveness and safety of PTPA. The PTPA procedure was limited maximally to up to 2 lobes in 1 procedure. After catheterization, the patients were observed for 1 day for possible development of reperfusion pulmonary edema. Catheterization was repeated at an interval of 4–8 weeks after PTPA in all patients, and additional PTPA was repeated until the mean PAP became less than 30 mmHg.

Long-Term Prognosis

The long-term prognosis of the 12 patients who underwent PTPA treatment was compared with that of 39 historical controls with distal-type CTEPH in our department (Table). There were no significant differences in the clinical characteristics or hemodynamics between the PTPA and control groups, except for less use of sildenafil and bosentan in the control group (Table).

Statistical Analysis

All statistical analyses were performed using GraphPad Prism 5.0E (GraphPad Software, La Jolla, CA, USA). Differences among groups were assessed using 1-way ANOVA followed by Fisher's protected least significant difference test. P<0.05 was considered to be statistically significant.

Results

Conventional pulmonary vasodilator therapy significantly improved plasma levels of brain natriuretic peptide and the cardiac index, but did not decrease PAP, pulmonary vascular resistance (PVR) or right atrial pressure (RAP) (Table). We performed PTPA in a step-wise manner (5±2 procedures for 14±7 lesions), which resulted in significant additional improvement of mean PAP and PVR (Table). OCT examination revealed that PTPA destroyed the typical flaps and webs in the PA and shifted them to the PA's walls (Figure A–F). Pulmonary angiography also showed that PTPA enlarged the lumen diameter (55±77% increase), although some severe occlusions by thrombus were resistant to PTPA. Furthermore, PTPA significantly improved the WHO-FC, RAP and 6-min walk distance (Table). Importantly, all 7 patients treated with intravenous epoprostenol were successfully tapered off to oral beraprost without any hemodynamic worsening (Table). A complication of PTPA was mild to moderate hemoptysis in 6 of the 12 patients, who were successfully managed with oxygen and non-invasive positive pressure ventilation without intubation. Importantly, no patient died during the mean follow-up period of 12 months, resulting in significant improvement in prognosis compared with the historical controls (Figure G).

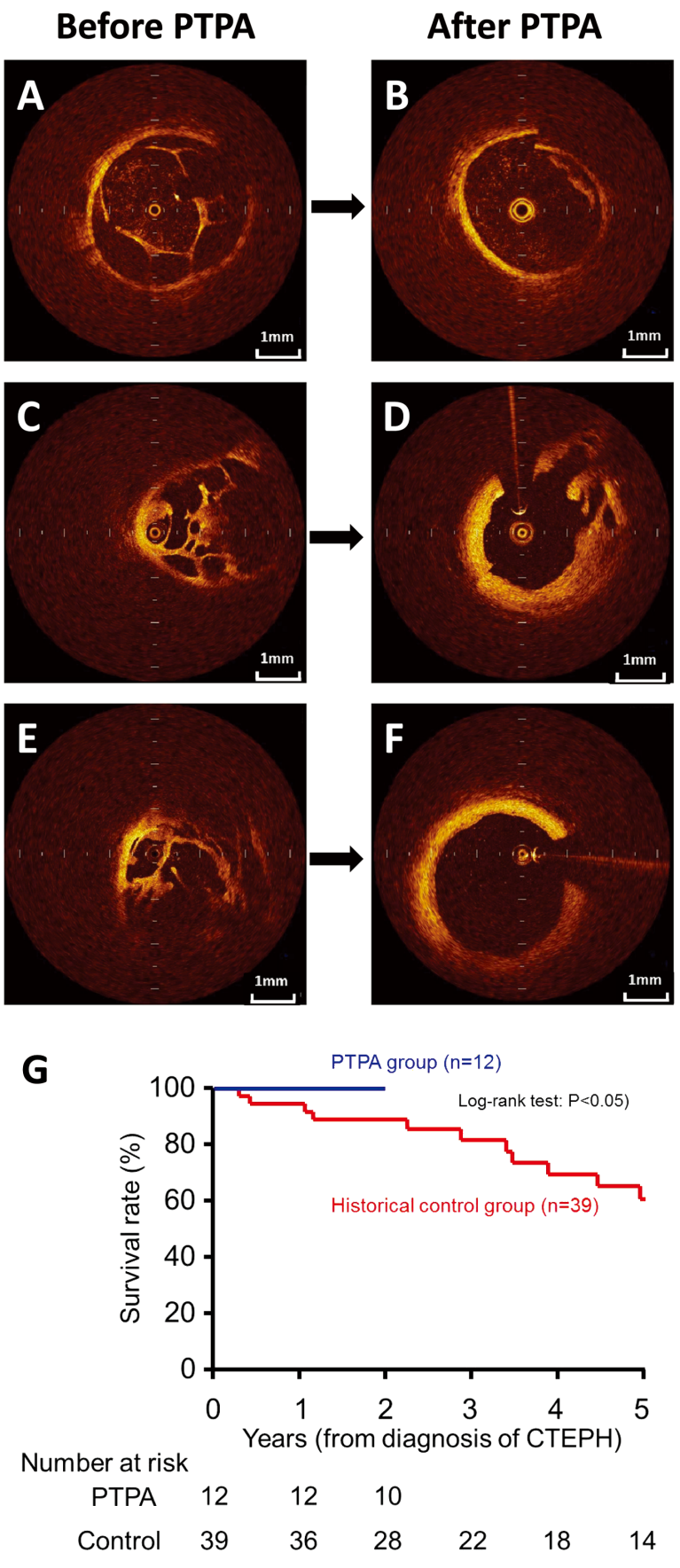

Figure. Effects of percutaneous transluminal pulmonary angioplasty (PTPA) in patients with distal-type chronic thromboembolic pulmonary hypertension (CTEPH). (**A**–**F**) OCT findings of typical flaps and webs in 3 patients with distal-type CTEPH before (**A**,**C**,**E**) and after PTPA (**B**,**D**,**F**). (**G**) Kaplan-Meier curves of the PTPA group and historical control group. OCT, optical coherence tomography.

Discussion

The novel findings of the present study are that PTPA, when performed in a step-wise manner, markedly improves pulmonary hemodynamics and long-term prognosis in patients with distal-type CTEPH with no major complications, and that OCT is useful for evaluating the effectiveness of PTPA.

PTPA has been considered as an alternative therapy only in selected patients who are inoperable because of distal lesions or recurrent PH after surgery, although the experience with this procedure is extremely limited.[4] It has already been reported that PTPA improves symptoms, exercise tolerance and PAP;[7] however, a safer procedure needs to be developed. The fundamental difference between the previous report[7] and the present study was that we used smaller sized balloons for fewer lobes per procedure, resulting in less severe complications as compared with the previous report.[7]

The present results indicate that PTPA combined with conventional vasodilator treatment is quite effective in improving pulmonary hemodynamics in patients with distal-type CTEPH, suggesting that PTPA is a promising new therapy for the disorder. Importantly, we were able to taper off intravenous epoprostenol without any hemodynamic worsening in all patients having intravenous therapy, which is important to improve their quality of life as well as the healthcare cost. Furthermore, the present study demonstrates that the PTPA therapy markedly improves the long-term prognosis of patients with distal-type CTEPH. Although the prognosis of patients with non-surgical CTEPH has been improved with recent progress in medical treatment,[9] we consider that additional PTPA can further improve their quality of life and long-term prognosis.

In conclusion, the present study demonstrates that PTPA combined with conventional vasodilator treatment is quite effective in improving the pulmonary hemodynamics and long-term prognosis in patients with distal-type CTEPH, although the procedure should be performed in a step-wise manner by specialists in PH centers to prevent major complications.

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Disclosures

None.

References

1. Lang IM, Klepetko W. Chronic thromboembolic pulmonary hypertension: An updated review. *Curr Opin Cardiol* 2008; **23:** 555–559.
2. Yoshimi S, Tanabe N, Masuda M, Sakao S, Uruma T, Shimizu H, et al. Survival and quality of life for patients with peripheral type chronic thromboembolic pulmonary hypertension. *Circ J* 2008; **72:** 958–965.
3. Miura Y, Fukumoto Y, Sugimura K, Oikawa M, Nakano M, Tatebe S, et al. Identification of new prognostic factors of pulmonary hypertension. *Circ J* 2010; **74:** 1965–1971.
4. Piazza G, Goldhaber SZ. Chronic thromboembolic pulmonary hypertension. *N Engl J Med* 2011; **364:** 351–360.
5. Fukumoto Y, Shimokawa H. Recent progress in the management of pulmonary hypertension. *Circ J* 2011; **75:** 1801–1810.
6. Do.e Z, Fukumoto Y, Takaki A, Tawara S, Ohashi J, Nakano M, et al. Evidence for Rho-kinase activation in patients with pulmonary arterial hypertension. *Circ J* 2009; **73:** 1731–1739.
7. Feinstein JA, Goldhaber SZ, Lock JE, Ferndandes SM, Landzberg MJ. Balloon pulmonary angioplasty for treatment of chronic thromboembolic pulmonary hypertension. *Circulation* 2001; **103:** 10–13.
8. Tatebe S, Fukumoto Y, Sugimura K, Nakano M, Miyamichi S, Satoh K, et al. Optical coherence tomography as a novel diagnostic tool for distal type chronic thromboembolic pulmonary hypertension. *Circ J* 2010; **74:** 1742–1744.
9. Condliffe R, Kiely DG, Gibbs JS, Corris PA, Peacock AJ, Jenkins DP, et al. Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. *Am J Respir Crit Care Med* 2008; **177:** 1122–1127.