Table 5 Changes in WHO FC from baseline to week 12

	WHO FC					
	Baseline		Week 12			
			I	II	III	IV
N		*N*	[*N*]	[*N*]	[*N*]	[*N*]
8	I	1	1	–	–	–
	II	5	–	5	–	–
	III	2	–	–	2	–
	IV	0	–	–	–	0

FC functional class, *WHO* World Health Organization

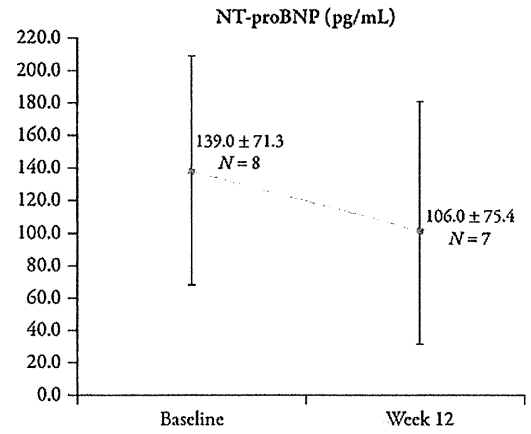

Fig. 1 NT-proBNP concentration measured at baseline and at week 12. $P = 0.5781$ at the 5% level (Wilcoxon signed rank sum test) *NT-proBNP* N-terminal prohormone of brain natriuretic peptide

condition. In addition, the earthquake and tsunami that hit eastern Japan on March 11, 2011, exposed flaws in the systems used to ensure patient safety and maintain a stable supply of medical resources during an emergency [21]. If essential utilities such as electricity and water networks are shut down following a disaster, it is likely that frozen gel packs would not be available, which may be a life-threatening issue for patients with PAH. The authors speculate that epoprostenol AS, which is stable for a longer time at room temperature than the GM formulation, could be valuable for continuing medical treatment during emergencies, and may have a positive impact on the quality of medical care, although additional examination of epoprostenol AS use is required in situations where the temperature exceeds 30 °C. Further studies are needed to evaluate the impact of higher environmental temperatures on the safety/tolerability and efficacy of this formulation, and to accumulate evidence supporting its clinical use.

Some limitations of this study warrant mention. Firstly, the sample size was small, which may prevent detection of small differences in hemodynamic factors or infrequent adverse events. Secondly, as the study was conducted in an open-label manner without a control group (e.g., of patients continuing epoprostenol GM during the 12-week treatment phase), it is possible that a study effect or patient bias contributed to the observed improvements in treatment satisfaction.

CONCLUSION

In conclusion, the present study showed that switching to a new formulation of epoprostenol was associated with an improvement in convenience in relation to treatment satisfaction, without unexpected adverse

Table 6 Changes in treatment satisfaction from baseline to 12 weeks after switching epoprostenol formulations

TSQM-9 domain	Baseline ($n = 8$)			12 weeks of administration ($n = 8$)					
	Actual scale			Actual scale			Changes from baseline		
	Mean ± SD	Median	[Min, Max]	Mean ± SD	Median	[Min, Max]	Mean ± SD	Median	[Min, Max]	*P* value[a]
Effectiveness	56.25 ± 7.55	58.4	[44.4, 66.7]	58.31 ± 14.55	61.1	[33.3, 72.2]	2.06 ± 10.68	0.0	[−11.1, 22.2]	0.9063
Convenience	51.40 ± 10.19	55.6	[33.3, 61.1]	58.33 ± 12.96	61.1	[33.3, 72.2]	6.93 ± 5.73	5.6	[0.0, 16.6]	0.0313
Global satisfaction	54.01 ± 31.30	60.5	[−8.3, 91.7]	54.19 ± 25.94	52.8	[22.2, 93.1]	0.18 ± 23.09	1.4	[−40.2, 30.5]	0.7188

SD standard deviation, *TSQM-9* Treatment Satisfaction Questionnaire for Medication

[a] *P* value based upon Wilcoxon signed rank sum test

events or deteriorations in pulmonary hemodynamic factors. Prospective studies in a larger group of patients are needed to confirm the safety of this formulation in long-term clinical use. Epoprostenol AS was approved in February 2013 in Japan as a generic drug with the same potency and effectiveness as the originally approved drug, epoprostenol GM. As intravenous epoprostenol sodium therapy may result in high medical costs, the introduction of cheaper generic drugs may help to reduce medical expenditure for treating PAH.

ACKNOWLEDGMENTS

The study and article processing charges were funded and supported by Actelion Pharmaceuticals Japan Ltd. The authors would like to thank Nicholas D. Smith, PhD, an employee of Edanz, for editorial support in the preparation of this manuscript, which was funded by Actelion Pharmaceuticals Japan Ltd. Dr Yuichi Tamura is the guarantor for this article, and takes responsibility for the integrity of the work as a whole.

Conflict of interest. Yuichi Tamura declares no conflict of interest. Tomohiko Ono declares no conflict of interest. Keiichi Fukuda declares no conflict of interest. Toru Satoh declares no conflict of interest. Shigetake Sasayama declares no conflict of interest.

Compliance with Ethics Guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients included in the study.

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Inducible Intrapulmonary Arteriovenous Shunt in a Patient with Beriberi Heart

To the Editor:

Transient intrapulmonary arteriovenous shunt (IPAVS) can be induced by exercise (1–3), a physiological condition producing high cardiac output. However, the involvement of IPAVS in pathological high-output condition, such as beriberi heart, is unclear.

The patient was a 37-year-old male with schizophrenia who was referred with a 2-week history of acute heart failure. His symptoms included dyspnea, hypotension, and prominent edema in the lower extremities. He was mildly hypoxemic with pulse oximeter-oxygen saturation (Sp_{O_2}) of 93% in room air and required subnasal oxygen. His echocardiographic findings were remarkable, showing the exaggerated left ventricular ejection fraction of 84% calculated by the Teichholz method. He received intravenous furosemide and inotropic agents for 2 weeks after the admission, until the diagnosis of beriberi heart was made with a low serum erythrocyte thiamine pyrophosphate level (11.0 ng/ml; normal range, 24–66 ng/ml). After the intravenous thiamine repletion, his hypotension, oligouria, and congestion quickly improved. He was weaned off of the inotropic agents, diuretics, and oxygen over the next few days. The catheter-based hemodynamic data in acute phase revealed excessively high cardiac output (14.0 L/min), decreased systemic vascular resistance (1.9 Wood units), and slightly elevated mean pulmonary artery pressure (26 mm Hg). The cardiac output normalized to 6.6 L/min 5 weeks after thiamine repletion.

The contrast-enhanced echocardiography in the supine position was performed to evaluate IPAVS as a possible contributor to his hypoxemia. In the acute phase, microbubbles opacified the left atrium seven cardiac cycles after the initiation of right-atrial opacification (Figure 1A, *upper panel*; Sp_{O_2} 99% with subnasal oxygen). In contrast, microbubble opacification became negative after the thiamine repletion (Figure 1A, *lower panel*; Sp_{O_2} 99% in room air). The transient, inducible IPAVS was identified in beriberi heart. The patient showed no recurring signs or symptoms of heart failure thereafter without further cardiovascular medications. The chest X-rays demonstrated improvement during this period (Figure 1B).

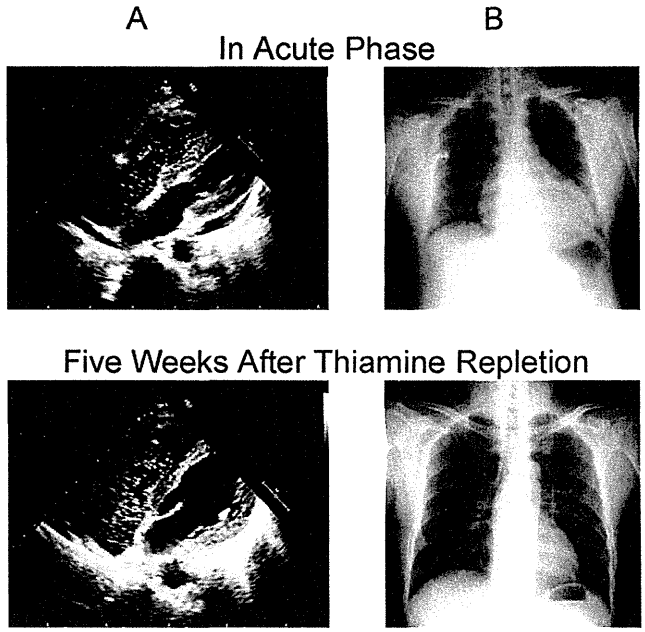

Figure 1. (*A*) Contrast-enhanced echocardiography and (*B*) chest X-rays in the acute phase and 5 weeks after the thiamine repletion. In the acute phase, microbubbles opacified the left atrium seven cardiac cycles after the initiation of right-atrial opacification (*A, upper panel*), whereas 5 weeks after the thiamine repletion, microbubble opacification became negative (*A, lower panel*). (*B*) The chest X-rays display improvement of cardiomegaly and congestion during this period.

The IPAVS not only exists in pathological characteristics such as hepatopulmonary syndrome, but also is induced by the certain physical properties in healthy individuals. The exercise-induced IPAVS using saline contrast microbubbles was demonstrated in subjects breathing room air (2). It is dependent on external environment; breathing hyperoxia prevented the exercise-induced IPAVS, whereas breathing hypoxia and normoxia resulted in a significant exercise-induced IPAVS (4).

The exact role of exercise-induced IPAVS is unclear. It was speculated that shunts might act as "pop-off valves" in response to increases in flow and pulmonary vascular resistance (1, 3) and function to reduce pulmonary vascular resistance and improve right ventricular function during exercise (5). Our patient with beriberi heart revealed high pulmonary flow resulting in slightly elevated pulmonary arterial pressure. This condition resembles exercise, where the inducible IPAVS may emerge in adaptive response to protect the pulmonary vasculature and right ventricle against pressure or volume overloading.

The pathological implications of the exercise-induced IPAVS are directed at two critical conditions: cerebral embolism and hypoxemia. The exercise-induced IPAVS may facilitate a pathway for emboli to circumvent the pulmonary microcirculation (6). It may also contribute to the reduction in pulmonary gas exchange efficiency that occurs during exercise (7). The immobile patients with beriberi heart are presumably more likely to clot than healthy individuals, and thus, predispose themselves to

Author Contributions: S. Nakano dealt with the patients and designed and drafted the manuscript. Y.T. interpreted the data, mostly regarding catheter-based hemodynamics, as he specialized in pulmonary hypertension. He also revised and approved the manuscript, and strongly recommended the clinical importance of intrapulmonary shunt in high-flow pulmonary hypertension. M.A., an echocardiography specialist, performed the contrast-enhanced echocardiography and interpreted the data. She revised and approved the manuscript. Y.S., J.T., T.M., T.S., and S. Nishimura are all members of the cardiology department. They collaborated in designing acquisition, analysis, and interpretation of data over the conference on multiple occasions. They all revised and approved the contents of the manuscript. K.F., who advised the other authors to construct the scientific way of thinking, greatly contributed to the report.

suffer cerebral emboli via inducible IPAVS. The hypoxemia that may develop in some patients with high-output cardiac failure may be a result or, conceivably, an enhancer of inducible IPAVS. Furthermore, although not proven, inducible IPAVS can be theoretically observed in other forms of high-output cardiac conditions in clinical setting, that is, anemia, thyrotoxicosis, sepsis, or administration of high dose of inotropic agents.

In conclusion, our patient with beriberi heart showed transient, inducible IPAVS. The potential impact of inducible IPAVS on unexplainable cerebral embolism or hypoxemia in pathological high-output conditions may become a novel investigational target.

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Erratum: Evolving Epidemiology of Pulmonary Arterial Hypertension

The authors would like to correct an error in the table that appears in their editorial published in the October 15, 2012 issue of the *Journal* (1). The tenth column of the table is labeled "Treatment Status on Enrollment"; in this column, the authors list the medicines that patients with pulmonary arterial hypertension (PAH) were on at the time of enrollment in the various registries. In the entry for the PAH registry in the United Kingdom and Ireland (2), the authors erroneously included the medicines that the patients were prescribed during the time of the registry (thus, the medicines that patients were started on). However, as is correctly mentioned in the text of the editorial, at the time of enrollment these patients were on no medicines. Therefore, that cell in the table should be changed to read "No PAH-specific therapies on enrollment."

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Erratum: Dieulafoy's Disease of the Bronchus

The authors would like to make a correction to their article published in the December 1, 2012 issue of the *Journal* (1). The middle initial was omitted for Dr. Fishman; his name should have appeared as Elliot K. Fishman.

Reference

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Official Journal of the Asian Pacific Society of Respirology
Respirology

ORIGINAL ARTICLE

Bone morphogenetic protein receptor type 2 mutations, clinical phenotypes and outcomes of Japanese patients with sporadic or familial pulmonary hypertension

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ABSTRACT

Background and objective: **Mutation of *bone morphogenetic protein receptor type 2* (*BMPR2*) is a cause of pulmonary arterial hypertension (PAH). We measured the prevalence of this mutation and its impact on the phenotypes and long-term clinical outcomes in Japanese patients.**

Methods: **Between 1999 and 2007, we consecutively enrolled and, until March 2012, followed 49 Japanese patients with PAH, including nine familial cases from seven families. We genotyped *BMPR2*, using direct sequencing and multiplex ligation-dependent probe amplification, to examine (i) the prevalence of *BMPR2* mutations and gene rearrangement, (ii) the relationship between *BMPR2* genotype and clinical phenotypes, and (iii) the long-term clinical outcomes of mutation carriers versus non-carriers under state-of-the-art medical therapy.**

Results: ***BMPR2* mutations were present in four of the seven families (57%) and in 14 of the 40 patients (35%) with sporadic PAH. The mean age at onset of PAH was 37.4 years in *BMPR2* carriers, versus 25.9 years in non-carriers ($P = 0.0025$). The gender distribution and hemodynamic status at time of diagnosis were similar regardless of the mutation status. The 5-year survival rate after diagnosis of PAH was 88.5% in *BMPR2* mutation carriers versus 80.9% in non-carriers (ns).**

Conclusions: **The prevalence of *BMPR2* mutations in Japanese with PAH was similar to that reported in other populations. At onset of PAH, *BMPR2* mutation non-carriers were, on average, younger than carriers, possibly due to the heterogeneity of this subpopulation. With state-of-the-art therapy, the long-term survival of patients with PAH was high, regardless of the mutation status.**

SUMMARY AT A GLANCE

The 57 and 35% prevalence of *BMPR2* mutations measured in Japanese patients with familial and sporadic pulmonary arterial hypertension, was similar to that measured in other populations. In this study of patients on state-of-the art medical therapy, the mean long-term survival of patients with versus without *BMPR2* mutations was similar.

Key words: *bone morphogenetic protein receptor type 2,* Japanese population, mutation, pulmonary arterial hypertension.

Abbreviations: *BMPR2, bone morphogenetic protein receptor type 2;* LTOT, long-term oxygen therapy; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a lethal disease due to abnormal cell proliferation, progressive narrowing and increase in the resistance of the pulmonary arterial vessels and, eventually, right heart failure. The recent development of effective pharmaceuticals, such as prostaglandin (PG) I_2, endothelin receptor antagonists, phosphodiesterase (PDE) 5 inhibitors, and supportive treatment with long-term oxygen therapy (LTOT), have markedly improved the prognosis of patients suffering from PAH. However, a therapy based on treatment of the underlying cause of disease has not been developed, the patients' quality

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Received 22 September 2012; invited to revise 19 October 2012; revised 21 January 2013; accepted 19 February 2013 (Associate Editor: O Jung Kwon).

Respirology (2013) **18**, 1076–1082
doi: 10.1111/resp.12117

of life remains impaired and the life-long treatment has considerable, negative socio-economic consequences.[1] Therefore, besides the search for new treatments, improved management being individualized and based on the expected long-term outcome and predicted response to drug therapy is needed.

In year 2000, *bone morphogenetic protein receptor type 2* (*BMPR2*) was identified as one of the genes responsible for the development of PAH.[2,3] This mutation is mechanistically associated with the abnormal proliferation of pulmonary vascular smooth muscle cells and dysfunction of vascular endothelial cells.[4,5] Missense, nonsense or frame-shift mutations due to the deletion or insertion of 1–4 nucleotides are present in 33–50% of patients suffering from familial PAH and in 12–26% of patients presenting with sporadic PAH.[6–12] In addition, exonal deletion/duplication of *BMPR2* gene is found in substantial frequency, suggesting that direct sequencing alone had underestimated the prevalence of heritable PAH,[13–15] which, in 2008, was classified as an independent disease entity in the Dana Point classification.[16]

Several studies have examined the different ages at time of onset, the disease severity, or both, in patients suffering from PAH with versus without *BMPR2* mutations,[7,17–22] although the clinical genetics of *BMPR2* mutations in Japanese are poorly known. In one study, *BMPR2* mutations were present in four of four (100%) patients presenting with familial PAH, and in 12 of 30 (40%) sporadic cases.[9] No study, however, has determined the frequency of *BMPR2* exonal deletion/duplication or the genotype-phenotype association in Japanese adult patients suffering from PAH.

The aims of this study were to examine (i) the prevalence of *BMPR2* mutations in Japanese patients presenting with PAH, using direct sequencing and multiplex ligation-dependent probe amplification (MLPA) methods, (ii) the relationship between *BMPR2* genotype and clinical phenotypes, (iii) the >5-year clinical outcomes of patients with versus without *BMPR2* mutations under state-of-the-art medical therapy.

METHODS

Patient population

Between October 1999 and March 2007, we enrolled 49 consecutive patients suffering from sporadic or familial PAH diagnosed in the adult or paediatric cardiology divisions of Keio University Hospital or referred from other institutions during the study period. The diagnosis of PAH was based on the measurements of a mean pulmonary artery pressure >25 mm Hg at rest and a pulmonary capillary wedge pressure <15 mm Hg by right heart catheterization.[23] Secondary pulmonary hypertension was excluded by history, blood tests, chest computed tomography scan, nuclear ventilation-perfusion scan and echocardiography. We classified nine patients from seven families as familial cases of PAH. We collected information from the medical records, including age, disease manifestations, New York Heart Association (NYHA) functional class at diagnosis, medications and other treatments and clinical outcomes. The study was reviewed and approved by the Institutional Review Board of Keio University School of Medicine (approval number 13-3-2), and all patients, or their parents if they were < 20 years of age, granted their written consent to participate.

Genotyping of the *BMPR2* gene

Genomic DNA was extracted from peripheral blood, and all exons in the *BMPR2* gene were amplified by polymerase chain reaction (PCR), using the primers described in Supporting Information Table S1. The PCR condition was one cycle at 95° for 9 min, 40 cycles at 95° for 30 s and 60° for 1 min and one cycle at 72° for 5 min. The nucleotide sequences of the amplified fragments were identified by direct sequencing, using an ABI 3700 sequencer (Applied Biosystems Inc, Foster City, CA, USA).

Exonal deletions or duplications were examined by the MLPA method, using the Salsa MLPA kit (MRC-Holland, Amsterdam, the Netherlands) as recommended by the manufacturer.

Statistical analysis

The data are presented as means ± standard deviation (SD) or counts. The phenotypes of patients with versus without *BMPR2* mutations were compared, using Student's *t*- or Fisher's exact tests, as appropriate. Survival and time to onset of LTOT were analysed by the Kaplan–Meier method, and the differences between groups compared by log-rank test. The statistical analyses were performed, using GraphPad Prism, version 4 (GraphPad Software Inc., La Jolla, CA, USA).

RESULTS

Patient characteristics

Important characteristics of the 49 patients, of whom 40 suffered from sporadic and nine from familial PAH from seven families, are shown in Table 1. The male to female ratio was approximately 1:2. The average age at the time of diagnosis was 30.4 years (range 6–59), the most prevalent disease manifestation was dyspnoea on exertion and nearly two-thirds of patients were in NYHA functional class III or IV.

Prevalence and types of *BMPR2* mutations

BMPR2 mutations were identified in 14 of 40 (35%) sporadic cases and in four of seven (57%) familial cases (Table 2). Of these 18 mutations, 10 (56%) were nonsense or frameshift, all resulting in premature stop codons. We identified five missense mutations in the ligand-binding or in the kinase activity domains, in exons 3, 8, and 9. The three nonsense mutations were identical to previously reported mutations,[3,9,21,22] and one (C2617C>T) was found in two unrelated patients. In contrast, all the frameshift or missense mutations identified in this study had not been pre-

Table 1 Characteristics of patients with familial and sporadic pulmonary arterial hypertension

	Pulmonary arterial hypertension		
	All patients ($n = 49$)	Familial ($n = 9$)	Sporadic ($n = 40$)
Men	17 (34.7)	3 (33.3)	14 (35.0)
Age at time of diagnosis, year	30.4 ± 13.1	36.1 ± 15.5	29.2 ± 12.4
Disease manifestations at time of diagnosis			
Symptoms			
Dyspnoea on exertion alone	25 (51.0)	5 (55.6)	20 (50.0)
Dyspnoea at rest	3 (6.1)	0	3 (7.5)
Syncope	6 (12.2)	0	6 (15.0)
Cough	1 (2.0)	1 (11.1)	0
Haemoptysis	1 (2.0)	0 (0.0)	1 (2.5)
Abnormal ECG at annual health check	13 (26.5)	3 (33.3)	10 (25.0)
NYHA functional class at diagnosis			
I	1 (2.0)	1 (11.1)	0 (0.0)
II	16 (32.7)	2 (22.2)	14 (35.0)
III	28 (57.1)	4 (44.4)	24 (60.0)
IV	1 (2.0)	1 (11.1)	0 (0.0)
Undetermined	4 (8.2)	1 (11.1)	3 (7.5)

Values are means ± standard deviation, or numbers (%) of observations.
ECG, electrocardiogram; NYHA, New York Heart Association.

Table 2 Individual *bone morphogenetic protein receptor type 2* mutations

	Type				
Patient no	Disease	Mutation	Exon	Nucleotide change	References
1	sporadic	Frameshift	3	c.339insA	
2	familial	Missense	3	c.276A>C	
3	sporadic	Nonsense	3	c.274C>T	[26]
4	sporadic	Frameshift	4	c.497delT	
5	sporadic	Missense	8	c.992A>G	
6	sporadic	Missense	8	c.1016T>A	
7	sporadic	Missense	9	c.1151C>T	
8	sporadic	Missense	9	c.1157A>C	
9	familial	Nonsense	9	c.1207C>T	[9]
10	sporadic	Frameshift	12	c.2504insA	
11	sporadic	Nonsense	12	c.2617C>T	[3,21,22,26]
12	sporadic	Nonsense	12	c.2617C>T	[3,21,22,26]
13	sporadic	Frameshift	12	c.2500delCAAA	
14	sporadic	Frameshift	12	c.2128delC	
15	familial	Frameshift	12	c.2009delC	
16	sporadic	exonal deletion	10		
17	familial	exonal deletion	1–3		
18	sporadic	exonal deletion	3		

viously described. Exonal deletions, identified in two sporadic and in one familial cases, represented 17% (3 of 18) of the mutations.

Phenotypes and patients management

Table 3 shows the clinical phenotypes, drug therapy and outcomes of the patients with versus without *BMPR2* mutations. The mean age of the former at the time of diagnosis of PAH was 37.4 years, significantly older ($P = 0.0025$) than the latter (25.9 years; Supporting Information Figure S1). The gender distributions, NYHA functional classes, and hemodynamic status at the time of diagnosis were similar in both groups.

All patients were treated with intravenous PGI_2, endothelin receptor antagonists, PDE5 inhibitors, alone or in combination. In addition, four patients received tyrosine kinase inhibitors in clinical trials. LTOT was introduced during the study period in 57.9% of patients with, and 60.0% of patients without

Table 3 Characteristics, treatments and outcomes of patients stratified by *bone morphogenetic protein receptor type 2 (BMPR2)* mutation status

	BMPR2 mutation		
	Present ($n = 19$)†	Absent ($n = 30$)	*P*
Demography			
Men	6 (31.6)	11 (36.7)	ns
Age at time of diagnosis, year	37.4 ± 12.7	25.9 ± 11.3	0.0025
Functional and hemodynamic status			
NYHA functional class ≥2	17 (89.5)	28 (93.3)	ns
Mean pulmonary artery pressure, mm Hg	60.8 ± 15.4	58.8 ± 12.0	ns
Pulmonary vascular resistance, mm Hg/l/min/m^2	21.5 ± 9.4	18.6 ± 8.6	ns
Cardiac output, l/min	3.0 ± 1.4	3.2 ± 0.9	ns
Pharmaceutical treatment			
Intravenous prostaglandin I_2	12 (63.2)	21 (70.0)	ns
Phosphodiesterase 5 inhibitors	13 (68.4)	14 (46.7)	ns
Endothelin receptor antagonists	12 (63.2)	17 (56.7)	ns
Tyrosine kinase inhibitors	2 (10.6)	2 (6.6)	ns
Clinical outcomes			
Long-term oxygen therapy (LTOT)	11 (57.9)	18 (60.0)	ns
Age at initiation of LTOT	44.6 ± 11.1	27.2 ± 12.4	0.0008
5-year survival rate	17 (88.5)	24 (80.9)	ns
Age at time of death	47.5 ± 9.8	27.0 ± 7.2	0.0020
Lung transplantation	0	3 (10.0)	ns
Age at time of death or transplantation	47.5 ± 9.8	23.2 ± 8.9	0.001

Values are means ± standard deviation, or numbers (%) of observations.
†Two members from the same family with mutation 17 were included in the analysis.
NYHA, New York Heart Association.

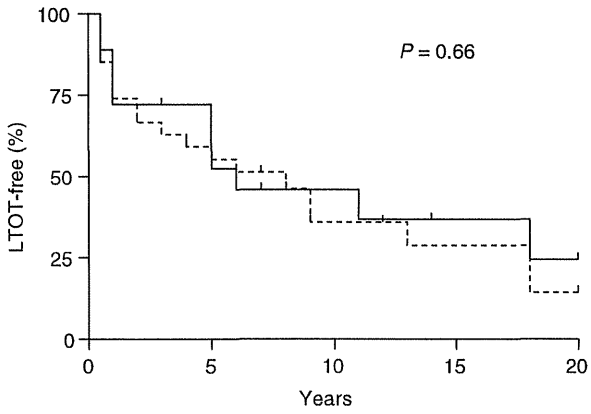

Figure 1 Years between onset of symptoms and introduction of long-term oxygen therapy (LTOT).
Solid lines, *BMPR2* carriers; dotted lines, mutation-free patients.

BMPR2 mutations. When LTOT was initiated, the patients without *BMPR2* mutations were 27.2 ± 12.4 years of age, significantly younger ($P = 0.0008$) than the carriers of mutations (44.6 ± 11.1 years), probably reflecting the age difference at the time of diagnosis. The time between onset of symptoms and introduction of LTOT was similar in both groups (Fig. 1).

Patient survivals

The median and mean ± SD overall follow-up was 79 and 80.3 ± 41.9 months, respectively. The 5-year survival rate after diagnosis of PAH was >80% (Table 3) and the overall patient survival similar (Fig. 2 and Supporting Information Fig. S2) regardless of the presence or absence of *BMPR2* mutations. On average, the patients without *BMPR2* mutations were significantly younger ($P = 0.002$) at the time of death (27.0 ± 7.2 years) than the carriers of mutations (47.5 ± 9.8 years), also reflecting the age difference at the time of diagnosis.

DISCUSSION

Our study showed that the prevalence of *BMPR2* point mutations and exonal deletions in Japanese patients suffering from PAH is similar to those observed in other ethnic populations. Furthermore, during this >5-year prospective observation of patients on optimal medical therapy, the evolution of disease towards lung transplantation or death was not influenced by the presence of *BMPR2* mutations.

Our observations suggest that *BMPR2* mutations are not detected by genotyping with direct sequencing alone in a considerable proportion of patients. In a French PAH registry, 115 *BMPR2* mutations were identified among 382 cases of PAH, of which 20 (17%) were exonal deletions.[20] In a study from Germany,[22] exonal deletions were present in six cases (12%) among 49 mutations,[22] and seven cases were detected among 50 mutations (14%) in 305 Han Chinese patients.[21] The prevalence was similar in our own observations with three cases among 18 mutations

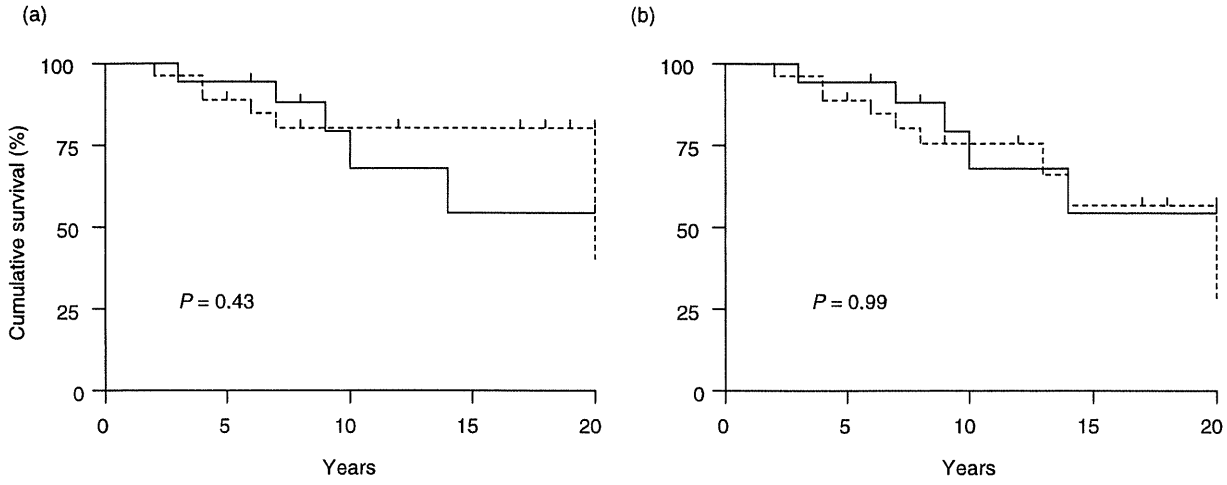

Figure 2 Years between onset of symptoms and death (a) or death/lung transplantation (b). Solid lines, *BMPR2* carriers; dotted lines, mutation-free patients.

(17%) and, combining all results, exonal deletions account for approximately 15% of *BMPR2* mutations among all ethnic groups.

On the other hand, the rates of *BMPR2* mutations have been inconsistent among studies of patients suffering from PAH. In several studies in Caucasians from Europe and the United States, 11–40% of sporadic and 55–70% of familial cases of PAH were *BMPR2* mutation-positive, including point mutations and exonal deletion/duplications.[15,17,18,20,22,24] In contrast, data in Asians are limited. Morisaki *et al.* studied 30 Japanese cases of sporadic PAH by direct sequencing and identified point mutations in 40%,[9] a slightly higher prevalence than the 12 cases among 40 subjects of sporadic PAH in our cohort (30%). In contrast, two studies performed in Han Chinese found a 14–17% prevalence of *BMPR2* mutations in patients presenting with sporadic PAH.[21,25] This discrepancy between Japanese and Han Chinese may be due to genetic backgrounds, different diagnostic means of excluding secondary PAH, or different genotyping techniques.

All missense mutations we identified were new and located in the kinase or ligand-binding domain, as previously reported. The frameshift mutations were also new. On the other hand, the three nonsense mutations (C274T, C1207T, C2617T) and one exonal deletion (exon 10) had been previously described.[3,9,21,22,26]

Except for the significantly older age of *BMPR2* mutation carriers at the time of diagnosis, the demographic and clinical characteristics of the two study groups were similar. In contrast to our observations, some of the previous studies found that patients who carried *BMPR2* mutations developed the disease at a younger age than non-carriers. The mean age of the mutation carriers at the time of diagnosis in our study (37.4 years) was similar with that reported by others (35.8 to 38.5 years).[17,19,20,22,24] However, the average age of our non-mutation carriers at the time of diagnosis was younger compared to other reports, because our *BMPR2* mutation-negative group included six patients who were <15 years old at the time of diagnosis. *BMPR2* mutations are less prevalent in children compared to adults, suggesting that the genetic factors behind the development of PAH are different in children.[27–30] A putative explanation is the high proportion of *ACVRL-1* mutation among children presenting with PAH,[28–30] a genetic defect that affects younger patients and is associated with a worse prognosis than the *BMPR2* mutation.[24] The heterogeneous genetic profile of groups without *BMPR2* mutations might explain the variable age at disease onset between different studies.

The 5-year survival of our patients suffering from PAH was >80%, which was better than the rates previously reported.[31] All study subjects were receiving intravenous PGI2, oral endothelin receptor antagonists, PDE5 inhibitors, either alone or in combination, which probably contributed to improved survival as suggested in meta-analyses and registry data.[32] Recent studies from France,[17] China[33] and Japan[34] also reported 5-year survival rates comparable to our data, although the relatively young age in the subjects in our study might also have affected the outcome. In addition, we were able to demonstrate that the prognosis of carriers and non-carriers of *BMPR2* mutations are similar under standard pharmacotherapy.

Although the prognosis of PAH patients has improved, there is no effective approach to prevent the development of the disease in subjects with *BMPR2* mutation. The transmission rate of *BMPR2* mutations to offspring is 50% with a penetration rate of approximately 20%,[35] suggesting that any offspring from a *BMPR2* mutation-carrier has a 10% risk to develop clinical PAH in the lifetime. Therefore, prenatal or pre-implantation genetic screening for PAH may be considered.[36] Benefits and risks of genetic testing and *in vitro* fertilization have to be thoroughly discussed between physicians and affected families.[37]

One of the limitations of our study is the modest number of patients enrolled at a single-centre. This could have imposed a referral bias, reflected by the

younger age at the time of diagnosis compared to previous reports, although it is partly due to the inclusion of paediatric patients in our study as discussed above. Another limitation of our study is that our search was limited to *BMPR2* mutations. Although we could not identify *BMPR2* mutation in approximately half of the familial cases, their clinical phenotypes and prognosis were similar to those in sporadic PAH with *BMPR2* mutations, suggesting that '*BMPR2*-negative' familial PAH may be associated with unidentified *BMPR2* mutations in untranslated regions.[38] Future studies should also include an analysis of mutations in other genes, such as *ACVRL-1* and *endoglin*, in hope of developing a personalized management of PAH.

In conclusion, *BMPR2* mutations were present in >1/3 of Japanese patients suffering from PAH. With the currently available treatment options, the long-term clinical outcomes of patients with versus without *BMPR2* mutations were similar.

Acknowledgement

This study was supported in part by a grant from the Ministry of Health, Labor, and Welfare awarded to the Respiratory Failure Research Group.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1 Age at time of diagnosis of PAH in 19 *BMPR2* mutation carriers versus 30 non-carriers.

Figure S2 Overall survival (a) and survival free from death or lung transplantation (b) after diagnosis of PAH. Solid lines, patients with *BMPR2* mutations; dotted lines, mutation-free patients.

Table S1 Polymerase chain reaction primers.

JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 6, NO. 7, 2013

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcin.2013.03.009

Pulmonary Edema Predictive Scoring Index (PEPSI), a New Index to Predict Risk of Reperfusion Pulmonary Edema and Improvement of Hemodynamics in Percutaneous Transluminal Pulmonary Angioplasty

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Objectives This study sought to identify useful predictors for hemodynamic improvement and risk of reperfusion pulmonary edema (RPE), a major complication of this procedure.

Background Percutaneous transluminal pulmonary angioplasty (PTPA) has been reported to be effective for the treatment of chronic thromboembolic pulmonary hypertension (CTEPH). PTPA has not been widespread because RPE has not been well predicted.

Methods We included 140 consecutive procedures in 54 patients with CTEPH. The flow appearance of the target vessels was graded into 4 groups (Pulmonary Flow Grade), and we proposed PEPSI (Pulmonary Edema Predictive Scoring Index) = (sum total change of Pulmonary Flow Grade scores) × (baseline pulmonary vascular resistance). Correlations between occurrence of RPE and 11 variables, including hemodynamic parameters, number of target vessels, and PEPSI, were analyzed.

Results Hemodynamic parameters significantly improved after median observation period of 6.4 months, and the sum total changes in Pulmonary Flow Grade scores were significantly correlated with the improvement in hemodynamics. Multivariate analysis revealed that PEPSI was the strongest factor correlated with the occurrence of RPE ($p < 0.0001$). Receiver-operating characteristic curve analysis demonstrated PEPSI to be a useful marker of the risk of RPE (cutoff value 35.4, negative predictive value 92.3%).

Conclusions Pulmonary Flow Grade score is useful in determining therapeutic efficacy, and PEPSI is highly supportive to reduce the risk of RPE after PTPA. Using these 2 indexes, PTPA could become a safe and common therapeutic strategy for CTEPH. (J Am Coll Cardiol Intv 2013;6:725–36) © 2013 by the American College of Cardiology Foundation

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Manuscript received January 7, 2013; revised manuscript received March 6, 2013, accepted March 14, 2013.

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 6, NO. 7, 2013
JULY 2013:725–36

Chronic thromboembolic pulmonary hypertension (CTEPH) is a progressive disease in which chronic thromboembolism in the pulmonary arteries leads to pulmonary hypertension (1–9). Medical therapies using anticoagulation and pulmonary vasodilators are somewhat effective for the treatment of CTEPH (1,10,11), and the most powerful conventional therapeutic strategy is invasive surgical pulmonary endarterectomy (12–16). However, our group and others recently reported that percutaneous transluminal pulmonary angioplasty (PTPA) markedly improved subjective symptoms and pulmonary hemodynamics in patients with CTEPH and may be a promising new therapeutic strategy (17–19).

Reperfusion pulmonary edema (RPE) is a major complication of PTPA. In addition, pulmonary endarterectomy, but not PTPA, can remove the majority of lesions in 1 procedure. Each lesion dilated by PTPA is still exposed to high pulmonary arterial pressure (PAP), and this could explain why the incidence of reperfusion lung injury following PTPA is higher than that after pulmonary endarterectomy. In 2001, Feinstein et al. (20) showed that pulmonary hemodynamics were markedly improved by pulmonary angioplasty in 18 patients, and that 11 (61%) of the 18 patients developed RPE. In our previous report, 27 (53%) of 51 cases of overall procedures and 19 (68%) of 28 cases of the first procedures developed RPE, and patients with more severe clinical signs and/or hemodynamic dysfunction at baseline had a higher risk of RPE after PTPA (17).

This study, therefore, sought to identify useful predictors for the risk of RPE as well as hemodynamic improvement after PTPA.

Abbreviations and Acronyms

BNP = B-type natriuretic peptide
CI = confidence interval
CO = cardiac output
CTEPH = chronic thromboembolic pulmonary hypertension
PAP = pulmonary arterial pressure
PAWP = pulmonary artery wedge pressure
PEPSI = Pulmonary Edema Predictive Scoring Index
PTPA = percutaneous transluminal pulmonary angioplasty
PVR = pulmonary vascular resistance
RAP = right atrial pressure
ROC = receiver-operating characteristic
RPE = reperfusion pulmonary edema

Methods

Study subjects. One hundred and forty consecutive PTPA procedures (54 first, 46 second, 20 third, 17 fourth, and 3 fifth procedures) in 54 patients with CTEPH who attended Keio University Hospital or Kyorin University Hospital, Japan, from January 2009 to May 2012 were enrolled. These 54 patients were diagnosed with CTEPH by demonstration of organized pulmonary thromboembolism using contrast-enhanced lung computed tomography, perfusion lung scintigraphy, and pulmonary angiography, and ruling out collagen vascular disease, pulmonary disease, left heart abnormality, and other systemic diseases by blood tests, pulmonary function tests, and echocardiography. Among the 54 enrolled patients, 8 patients had 1 procedure, 26 had 2, 3 had 3, 14 had 4, and 3 had 5 procedures. All the patients provided informed consent, and the PTPA treatment and study protocol was approved by the institutional review boards of the hospitals.

Examinations. Patients underwent right-sided heart catheterization just before PTPA, just after PTPA, and at the follow-up examinations. The timing of the follow-up right-sided heart catheterization after the last procedure was essentially 1 to 3 months, 6 months, 12 months, and every 1 year thereafter. The right atrial pressure (RAP), PAP, and pulmonary artery wedge pressure (PAWP) were measured at right-sided heart catheterization. The cardiac output (CO) was determined by the Fick technique using assumed oxygen consumption. Cardiac index was calculated by dividing CO by body surface area. The pulmonary vascular resistance (PVR) was calculated by subtracting PAWP from mean PAP and dividing by CO.

Six-min-walk distance and plasma B-type natriuretic peptide (BNP) level were measured both before PTPA and at follow-up with right-sided heart catheterization.

Indications for PTPA. The patients were selected as potential candidates for PTPA based on the following criteria: 1) more than 30 mm Hg of mean PAP or more than 3.75 Wood units (300 dynes/s/cm^{-5}) of PVR; 2) greater than New York Heart Association functional class II; 3) patient's own wish to undergo PTPA; and 4) did not fulfill aftermentioned exclusion criteria.

Adult patients with CTEPH who could understand the procedure of PTPA and possible complications and could give informed consent of their own free will were selected. Both the pulmonary endarterectomy and PTPA procedures were explained to them, including the possible complications of PTPA (based on the previous report by Feinstein et al. [20]) and the benefits and risks of pulmonary endarterectomy, the latter given by an experienced surgeon in some cases. Pulmonary endarterectomy was then recommended based on the evidence in patients whose main lesions were centrally located and whose operative risks were typical of the procedure. Our study basically selected patients with almost all the pulmonary thromboembolic lesions existing in the lobar, segmental, and subsegmental pulmonary arteries. PTPA targets basically the same lesions (lobar, segmental, and subsegmental lesions) as pulmonary endarterectomy, except for cases whose lesions exist in the main trunks of the pulmonary arteries. Thus, our study selected patients who rejected pulmonary endarterectomy or for whom we suggested PTPA was more appropriate than pulmonary endarterectomy because of their advanced age or poor physical condition. Additionally, our study included patients who had already undergone pulmonary

endarterectomy but had residual pulmonary hypertension due to lesions that could not be removed with pulmonary endarterectomy.

Meanwhile, our exclusion criteria were patients who were unable to lie on the treatment table during the procedure because of mental disorders, those with active infectious disease, and those who had serious complications such as hepatic disease, kidney disease, hemorrhagic tendency, or poorly controlled diabetes mellitus or hypertension.

During our study (from January 2009 to May 2012), 1 patient had pulmonary endarterectomy because the main lesions were centrally located, and another potential candidate of PTPA, other than the 54 enrolled patients in this study, selected pulmonary endarterectomy after explanation of both pulmonary endarterectomy and PTPA, including their possible complications and benefits.

Procedure of PTPA. Warfarin was stopped for 3 days before the procedure and replaced by heparin. The goal of activated clotting time during the procedure was 250 to 300 s. Warfarin was restarted after the procedure, and heparin infusion was continued until the efficacy of warfarin reached the optimal range. All patients were treated with warfarin long term. A catheter was inserted via the femoral vein or right jugular vein, with the latter selected if the patient had a filter in the inferior vena cava. A balloon wedge pressure catheter was inserted into the main pulmonary artery tract and replaced by a long spring guidewire before a 7- to 9-F long sheath was inserted into the main pulmonary artery tract. A 6- to 8-F guide catheter was then inserted through the long sheath, and a 0.014-inch guidewire was inserted through the target lesion. The target lesions were dilated by a 1.5- to 9.0-mm monorail or over-the-wire balloon catheter. The balloons were inflated by hand through inflation device for 15 to 30 s until they were fully expanded.

Angiography of the targeted side of the lung was performed before each procedure to select and determine the target lesions, but was not performed after the procedure. To determine the flow appearance and flow grade after angioplasty, selective angiography of the treated vessels was performed through catheters engaged in the treated vessels. The balloon size was determined by measurement of vessel diameter by intravascular ultrasound or the ruler to measure the vessel diameter on cine freeze-frame. The procedural success for each target lesion was defined by dilation of the lesion diameter to the same size as the reference vessel's diameter or by the perfusion flow level of Pulmonary Flow Grade 3 (shown in Table 1) after balloon dilation.

The enrolled patients had been treated with an appropriate combination of oral vasodilators such as bosentan, ambrisentan, sildenafil, tadalafil, or beraprost before the procedure. Epoprostenol, treprostinil, and iloprost were not used in any of the patients.

Table 1. Definitions of Perfusion in Pulmonary Flow Grade

Grade 0 (no perfusion or penetration with minimal perfusion of pulmonary arteries): There is no antegrade flow beyond the point of stenosis or occlusion in pulmonary arteries, or the contrast material passes beyond the area of lesions, but "hangs up" and fails to opacify the entire pulmonary artery bed distal to the lesions for duration of the cine run. The no-reflow phenomenon, which means persistent microcirculatory impairment after angioplasty, is included in this grade.
Grade 1 (partial perfusion of pulmonary arteries): The contrast material passes across the lesions and opacifies the pulmonary artery bed distal to the lesions. However, the rate of entry of contrast material into the vessels distal to the lesions or its rate of clearance from the distal bed of pulmonary artery (or both) are perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously stenosed or occluded vessel.
Grade 2 (complete perfusion of pulmonary arteries and partial perfusion of pulmonary veins): Antegrade flow into the bed of pulmonary artery distal to the lesions occurs as promptly as antegrade flow into the bed proximal to the lesions. However, the rate of appearance of contrast material from the bed of pulmonary veins perfused by the previously stenosed or occluded pulmonary artery or the rate of contrast clearance from the bed of perfused pulmonary veins (or both) is perceptibly slower than that from comparable areas not perfused by the previously stenosed or occluded vessel.
Grade 3 (complete perfusion of both pulmonary arteries and veins): Antegrade flow into the bed of the pulmonary artery distal to the lesions occurs as promptly as antegrade flow into the bed proximal to the lesions. Plus, the rate of appearance of contrast material from the bed of pulmonary veins perfused by the previously stenosed or occluded pulmonary artery and the rate of contrast clearance from the bed of perfused pulmonary veins are as promptly as those from comparable areas not perfused by the previously stenosed or occluded vessel.

Selection of target vessels. The selection criteria of target vessels are as follows: 1) the lobe with the poorest perfusion is identified by lung perfusion scintigraphy; 2) if any of the lobes in both lungs have the same degree of poor pulmonary blood flow in lung perfusion scintigraphy, the lobes in the right lung are selected because the manipulation technique in the right lung is relatively easier than that in the left lung, and the total blood flow distribution of the right lung is physiologically larger than that of the left lung; 3) if any of the lobes, including the inferior lobe in either the right or the left lung, have the same degree of poor distribution of pulmonary blood flow in lung perfusion scintigraphy, the inferior lobe is selected because it has physiologically more distribution of blood flow compared with the superior lobe and middle lobe; and 4) the targeted segmental branches are selected based on pulmonary angiography, which means, essentially, the lesions with less anatomical information about peripheral branches, such as chronic total occlusion and pouch defects, should be put off, and the lesions with more information about peripheral branches, such as webs and bands and abrupt narrowing, are selected, because information about peripheral branches distal to the target lesions are important in order to safely perform the procedure.

These criteria are particularly important in the first-time procedure. The purposes of these criteria are: 1) to perform a safe procedure without exacerbation of hemodynamics, in particular, in cases with poorer pulmonary hemodynamics; 2) to improve pulmonary hemodynamics as effectively as possible; and 3) to achieve successful revascularization

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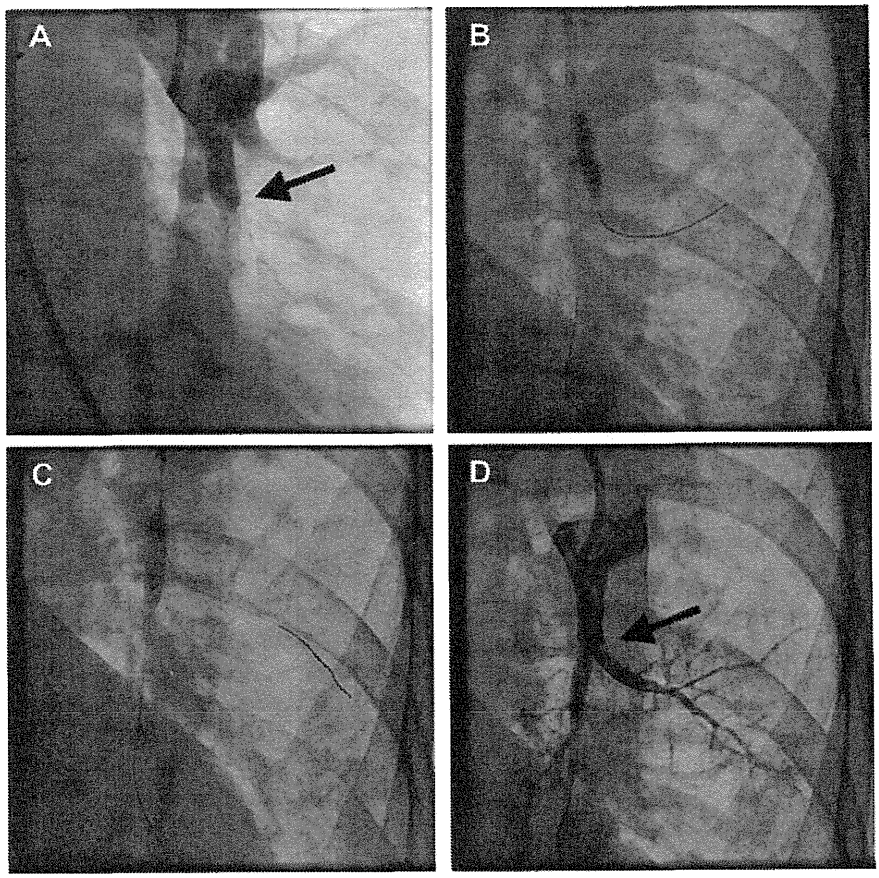


Figure 1. Representative Angiogram of PTPA

(A) Angiogram before percutaneous transluminal pulmonary angioplasty (PTPA). The target bifurcation lesion is indicated by an **arrow.** **(B)** Dilation of 1 of the branch lesions by balloon catheter. **(C)** Dilation of another branch lesion by balloon catheter. **(D)** Angiogram after PTPA.

without complications. But, to achieve final obliteration of pulmonary hypertension, almost all of the remaining lesions need to be treated. Thus, the remaining lesions are selected in series in accordance with the aforementioned criteria at the second session of PTPA.

Analysis of hemodynamic improvement at follow-up. The hemodynamic parameters at baseline, just before the first procedure, and at the time of follow-up after the last procedure were compared. Although the number of enrolled patients was 54, follow-up analysis was performed in 44 patients, in whom the follow-up examinations had been performed for a total observation period of more than 50 days.

Classification of pulmonary flow appearance. Table 1 shows the classification of pulmonary flow appearances seen with selective segmental pulmonary angiography. We named the classification "Pulmonary Flow Grade." The definitions of perfusion in Pulmonary Flow Grade were described by reference to the previous report regarding Thrombolysis in Myocardial Infarction classification in myocardial infarction (21). The flow appearance of the target vessels just before and after angioplasty was graded. The correlations between the change in flow grade and hemodynamic changes were investigated.

The change of Pulmonary Flow Grade score at the time of the procedure was calculated based on the levels of segmental branches of target pulmonary arteries. To cite a case in which a segmental branch (for example, A8) had 2 subsegmental branches (for example, A8a and A8b) and only 1 subsegmental branch (A8a or A8b) with baseline Pulmonary Flow Grade 1 was treated to grade 2, the change in score of Pulmonary Flow Grade was calculated as 0.5 (because the difference of grade 1 to grade 2 is divided by 2, the number of subsegmental branches). To cite another case in which a segmental branch (for example, A10) with baseline Pulmonary Flow Grade 1 was treated to grade 3, the change in score of Pulmonary Flow Grade was calculated as 2.

Measurement of the ratio of pressures across the lesions. The pressure difference across the stenosis in the target vessel was measured by a pressure wire (PrimeWire PRESTIGE, Volcano, San Diego, California), as the ratio of distal to proximal pressures across the target lesion. The correlation between Pulmonary Flow Grade score and the ratio of proximal to distal pressures of the target lesions was analyzed.

Definition of Pulmonary Edema Predictive Scoring Index. We proposed a new index, the Pulmonary Edema Predictive Scoring Index (PEPSI), to reflect both the change in angiographic flow and the baseline severity of pulmonary hypertension due to CTEPH. Thus, PEPSI is defined as follows:

$$\text{PEPSI} = (\text{sum total change of Pulmonary Flow Grade scores in PTPA}) \times \text{baseline PVR(Wood units)}.$$

Predictive variables for RPE. Eleven variables were chosen to analyze the relation to RPE. The predictive variables comprised hemoglobin, estimated glomerular filtration rate, BNP, whether the procedure was the first session or not, mean RAP, mean PAP, cardiac index, PVR, number of target vessels, and PEPSI.

Statistical analysis. All data are presented as median (25th to 75th percentiles). Significant differences were determined using the Mann-Whitney test or Wilcoxon matched pairs signed rank test, as appropriate. Correlation between the sum total change of Pulmonary Flow Grade scores and changes in the hemodynamic parameters from baseline to follow-up were analyzed using the Spearman rank correlation coefficient. Correlation between pulmonary flow grade and the ratio of pressure difference was analyzed using the Spearman rank correlation coefficient. Univariate analysis based on the logistic regression analysis was used to examine the relationship between the occurrence of RPE and the predictive variables. The results were expressed as odds ratios with 95% confidence intervals (CI). Multivariate analysis based on logistic regression analysis was used to examine the independent effect of each variable on the occurrence of RPE. The best predictive threshold for RPE was sought by means of receiver-operating characteristic (ROC) curves. The Youden index was utilized to define the best cutoff value on the ROC curve. Adjustments for the nonindependence of multiple procedures within patients were not made. A value of $p < 0.05$ was considered statistically significant.

Results

Clinical improvement by PTPA. A representative pulmonary angiogram during the PTPA is shown in Figure 1. The baseline characteristics of the 54 enrolled patients are detailed in Table 2. Among the 44 patients enrolled for follow-up analysis, the median observation period from the first procedure to the last follow-up conducted on each patient was 6.4 (4.5 to 8.6) months. A comparison of the examinations at baseline with those at follow-up is presented in Figure 2. Right-sided heart catheterization demonstrated a significant improvement in hemodynamic parameters (mean RAP, 5.5 [3 to 7] vs. 3.0 [2 to 5.8] mm Hg; mean PAP, 43 [38 to 53] vs. 25 [21 to 29] mm Hg; PVR, 9.4 [7.2 to 14.8] vs. 3.8 [2.9 to 5.5] Wood units; and cardiac index, 2.5 [1.9 to 2.9] vs. 2.8 [2.3 to 3.7] l/min/m^2; baseline vs. follow-up, respectively; $p < 0.01$). The right ventricular systolic pressure was also significantly improved from 84 (74 to 99) mm Hg to 48 (42 to 56) mm Hg ($p < 0.01$). Plasma BNP was significantly decreased after PTPA (126 [61 to 390] vs. 33 [20 to 54] pg/ml; $p < 0.01$). Although some of the data for the 6-min-walk distance were missing due to refusal of examination by some patients because of gait disorders or dyspnea, the 6-min-walk distance was significantly lengthened at follow-up from 342 (243 to 396) m to 405 (348 to 495) m ($p < 0.01$, $n = 33$).

Table 2. Baseline Characteristics of Patients

	Enrolled Patients (N = 54)
Age, yrs	63.5 (54.8 to 70.2)
Sex, female/male	41/13
NYHA functional class, I/II/III/IV	0/4/40/10
Number of patients previously treated with pulmonary endarterectomy	6
Mean RAP, mm Hg	5 (3 to 7)
Mean PAP, mm Hg	42.5 (37.0 to 52.3)
PVR, Wood units	9.2 (6.9 to 15.0)
Cardiac index, l/min/m^2	2.5 (1.8 to 2.9)
PAWP, mm Hg	7 (5 to 10)
SvO_2, %	66.0 (59.7 to 72.4)
6-min-walk distance, m	360 (278 to 407)*
BNP, pg/ml	126 (54 to 390)

Values are n or median (25th to 75th percentile). *n = 50, because 4 patients did not undergo the 6-min-walk examination due to a gait disorder or dyspnea.

BNP = B-type natriuretic peptide; NYHA = New York Heart Association; PAP = pulmonary arterial pressure; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SvO_2 = mixed venous oxygen saturation.

Correlations between total change in Pulmonary Flow Grade scores and hemodynamic changes. Among the 140 procedures in the 54 enrolled patients, the total number of target vessels was 525, the average number of target vessels per procedure was 4.0 (2.3 to 5.0), the average number of procedures per patient was 2 (2 to 4), and the average number of target vessels per patient was 9.5 (6.3 to 13.0). The duration of each procedure was determined by the extent of x-ray exposure, fluoroscopy times, and amount of contrast material in regard to the patients' renal function and cardiac function. Thus, the reason why most patients underwent multiple procedures is because if all target lesions were treated at 1 procedure, those parameters would be over

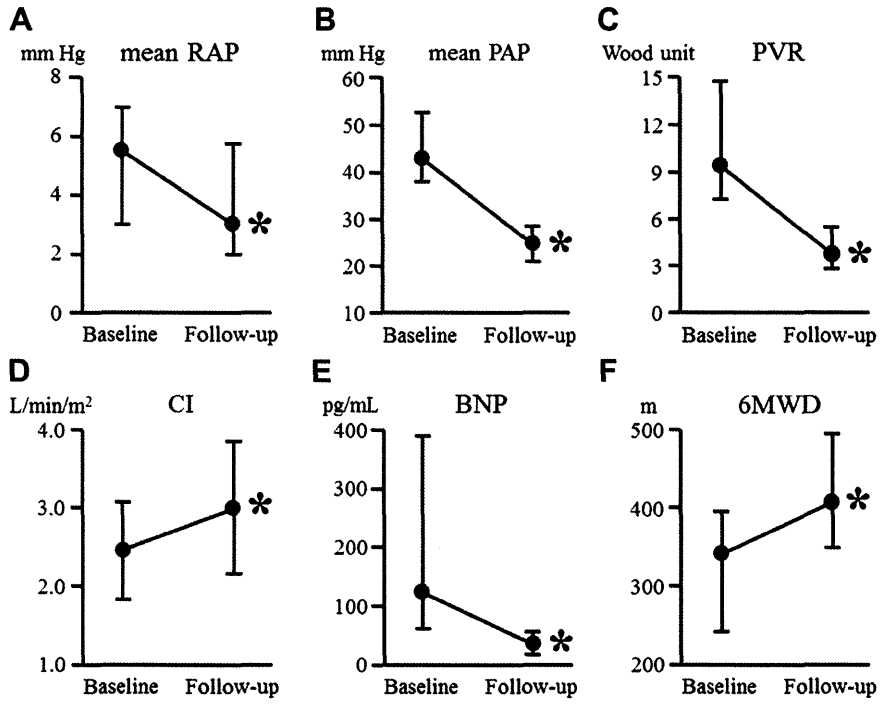


Figure 2. Therapeutic Efficacy of PTPA

Hemodynamic changes in mean right atrial pressure (RAP) **(A)**, mean pulmonary arterial pressure (PAP) **(B)**, pulmonary vascular resistance (PVR) **(C)**, cardiac index (CI) **(D)**, plasma B-type natriuretic peptide (BNP) **(E)**, and 6-min-walk distance (6MWD) **(F)** at follow-up after percutaneous transluminal pulmonary angioplasty (PTPA). All hemodynamic parameters, BNP, and 6-min walk distance were significantly improved at follow-up. *$p < 0.01$ versus baseline.

the limit. The average x-ray exposure, fluoroscopy times, and amount of contrast material per procedure were 1,531 (765 to 2,621) mGy, 74.1 (57.9 to 89.9) min, and 325 (250 to 370) ml, respectively.

The changes in Pulmonary Flow Grade scores from baseline to just after the procedure are shown in Table 3; approximately 88% of target vessels belonged to Pulmonary Flow Grade score 0 or 1 before the procedures, but approximately 89% of the target vessels changed to Pulmonary Flow Grade score 2 or 3 after angioplasty.

Correlations between the sum total changes in Pulmonary Flow Grade scores and the change in hemodynamic parameters such as PVR and mean PAP at follow-up were analyzed (Fig. 3). The sum total change of Pulmonary Flow Grade scores at the time of the procedure was significantly correlated with the change in PVR and mean PAP at follow-up ($p < 0.05$). However, the total number of target vessels at the time of the procedure was not correlated with the change of PVR nor mean PAP (data not shown).

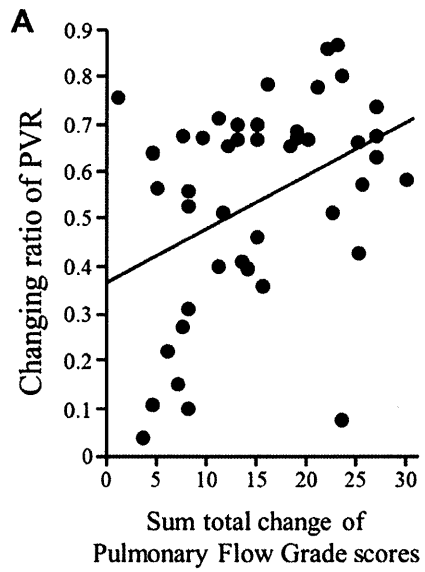
Correlations between Pulmonary Flow Grade scores and the ratio of pressures across the lesions. For all the lesions with Pulmonary Flow Grade 0, it was not possible to measure pressure differences by a pressure wire. Thirty-one measurements of the ratio of the proximal to the distal pressures of the target lesions were performed in a total of 15 target vessels with Pulmonary Flow Grade 1 to 3 in 6 patients. Figure 4 shows the correlation between the Pulmonary Flow Grade score and the pressure ratios, demonstrating a strong correlation ($p < 0.0001$).

Complications other than RPE. Among the 54 enrolled patients, 1 patient with baseline severe right heart failure developed pulmonary hemorrhage as a complication because of perforation by the wire. The perforation was completely sealed, but right heart failure was exacerbated, and the patient died 2 days after the procedure. Therefore, the mortality associated with PTPA was 1.9% in this study.

Table 3. Distribution of Pulmonary Flow Grade Score of Target Vessels in PTPA

Pulmonary Flow Grade Score	Target Vessels Before Angioplasty	Target Vessels After Angioplasty
0	187 (35.6)	26 (5.0)
1	275 (52.4)	33 (6.3)
2	62 (11.8)	100 (19.0)
3	1 (0.2)	366 (69.7)

Values are n (%).
PTPA = percutaneous transluminal pulmonary angioplasty.



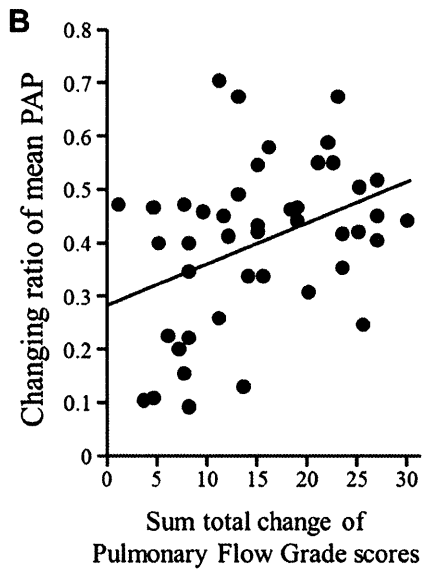


Figure 3. Correlations Between Sum Total Change of Pulmonary Flow Grade Scores and Changes in Hemodynamic Parameters After the Follow-Up Period

The sum total change of Pulmonary Flow Grade scores (based on Table 1) was significantly correlated with changes in PVR **(A)** and mean PAP **(B)** (respectively, p = 0.01, Rs = 0.3636 in PVR, Rs = 0.3495 in mean PAP). Changing ratio of PVR = (baseline PVR − follow-up PVR)/baseline PVR; changing ratio of mean PAP = (baseline mean PAP − follow-up mean PAP)/baseline mean PAP. Abbreviations as in Figure 2.

Among the total of 140 procedures, a dissection occurred in 1 of the targeted pulmonary arteries just after balloon dilation in 2 procedures. The dissections did not expand, and the hemodynamics did not change. Thus, the dissections were left untouched. Extravascular leaks occurred just after balloon dilation in another 4 procedures in which the extravascular leak was stopped by prolonged low-pressure dilation of the balloon in 1 procedure and by insertion of a covered stent in the other cases. Consequently, there were 5 perforations, consisting of 1 case in the deceased patient and 4 cases of extravascular leaks, and 2 dissections in this study, which means that the rate of angiographic complications was 5% (7 of 140 procedures).

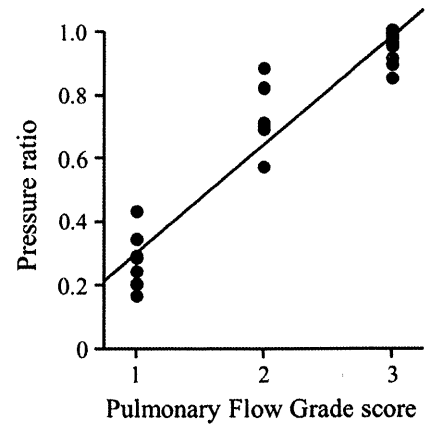


Figure 4. Correlation Between Pulmonary Flow Grade Score and the Ratio of Proximal and Distal Pressures of the Target Lesions

Pulmonary Flow Grade score was strongly correlated with the pressure ratios (p < 0.0001, Rs = 0.9643).

Classification and frequency of RPE. Table 4 lists the definitions of the classification into 5 groups according to the severity of RPE. Figure 5 shows representative chest x-ray and chest computed tomographic images of RPE classified into 5 groups based on the definitions in Table 4.

Table 4. Classification and Frequency of RPE

Grade	Definition of Graded RPE	Number of Procedures
1	No significant recognition of reperfusion pulmonary edema on chest x-ray	87 (62)
2	Mild or small reperfusion pulmonary edema on chest x-ray, but automatic improvement with only a small increase in oxygen for a few days	35 (25)
3	Moderate reperfusion pulmonary edema on chest x-ray that needed elevated concentration of oxygen administered via oxygen mask to maintain arterial saturation at optimum level	9 (6)
4	Moderate to severe reperfusion pulmonary edema on chest x-ray needing non-invasive positive pressure ventilation with high-concentration oxygen inhalation	7 (5)
5	Extremely severe reperfusion pulmonary edema on chest x-ray needing artificial ventilation	2 (1)

Values are n (%).
RPE = reperfusion pulmonary edema.

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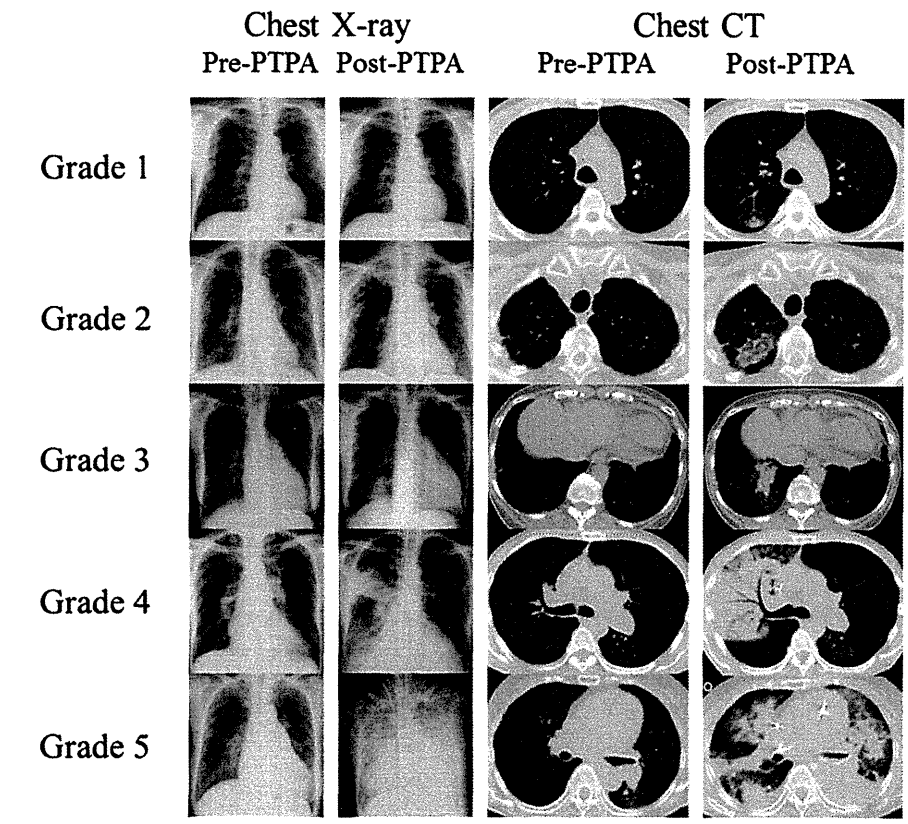

Figure 5. Representative Chest X-Ray and Chest CT Images of RPE

Reperfusion pulmonary edema (RPE) was classified as 5 levels based on the definitions in Table 4. CT = computed tomographic; PTPA = percutaneous transluminal pulmonary angioplasty.

Eighty-seven procedures (62%) belonged to grade 1, defined as no significant findings of pulmonary edema on chest x-ray, and the other 53 procedures (38%) belonged to grade 2 to 5, which indicated the occurrence of RPE. Nine procedures (6.4%) were grade 4 or higher, which indicates the occurrence of severe RPE, and these cases needed noninvasive positive pressure ventilation or artificial respiration. In 1 of the 2 procedures of grade 5, artificial ventilation with a percutaneous cardiopulmonary support (in other words, cardiopulmonary assist device or venoarterial extracorporeal membrane oxygenation) was needed for 5 days.

Comparison between procedures with and without RPE. Table 5 shows a detailed comparison between the procedures with and without RPE of grade 2 or higher. Among the 53 procedures with RPE of grade 2 or higher, 31 procedures (58.5%) were the first-session procedures of each patient. This demonstrates that RPE occurred readily at first-time procedures. Furthermore, mean PAP, PVR, cardiac index, and BNP were more markedly abnormal in the procedures with RPE than in those without.

Significant predictive variables for RPE. We analyzed factors associated with the occurrence of RPE of grade 2 or higher (Table 6). Among the 11 variables, 8 variables (except for the number of target vessels, hemoglobin level, and mean RAP) at baseline were significantly related to the occurrence of RPE according to univariate analysis. Multivariate analysis using variables with a significant correlation of $p < 0.001$ in univariate analysis demonstrated that PEPSI was most strongly related to the occurrence of RPE ($p < 0.0001$).

ROC curve analysis for prediction of RPE. According to the results of the multivariate analysis shown in Table 6, we then analyzed the correlation between PEPSI and the occurrence of RPE of grade 2 or higher. Figure 6A shows the distribution of PEPSI with and without RPE of grade 2 or higher. Figure 6B shows ROC curve analysis, which demonstrated an observed area under the curve of 0.87, cutoff value of 35.4, sensitivity of 88.7% (95% CI: 77 to 96), specificity of 82.8% (95% CI: 73 to 90), positive predictive value of 75.8% (95% CI: 63 to 86), negative predictive value of 92.3% (95% CI: 84 to 97), odds ratio of 37.6 (95% CI: 13.6 to 103.8), likelihood ratio of a positive test of 5.1