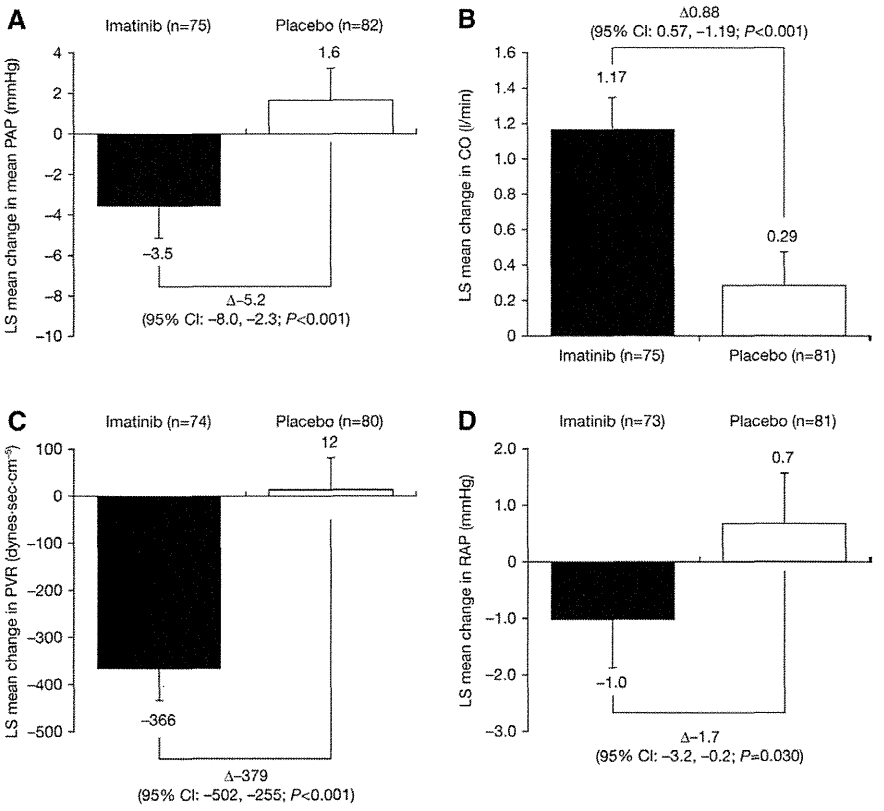


Figure 3. Least squares (LS) mean changes from baseline to end of study in mean pulmonary artery pressure (PAP; **A**), cardiac output (CO; **B**), pulmonary vascular resistance (PVR; **C**), and right atrial pressure (RAP; **D**). Δ indicates LS mean difference between groups; and CI, confidence interval. Patients included in analyses of hemodynamic parameters include those who completed the study plus those who discontinued early but had a right heart catheterization performed at discontinuation.

medication. A sizable proportion of the worsening events in the imatinib group were transient events associated with known imatinib side effects rather than events reflecting disease progression. Of those with clinical worsening events who continued on imatinib, improvements in 6MWD and PVR at 24 weeks were consistent with long-term improvement with imatinib therapy as opposed to PAH disease progression. The analysis method used for time to clinical worsening assumes a noninformative missing data mechanism (ie, that censoring is not related to the end point of interest). It is difficult to confirm this in the IMPRES trial because of the difficulty in distinguishing AEs from true clinical worsening events or signs of disease progression. Further investigations are needed to assess the effects of imatinib therapy on outcome in patients with PAH.

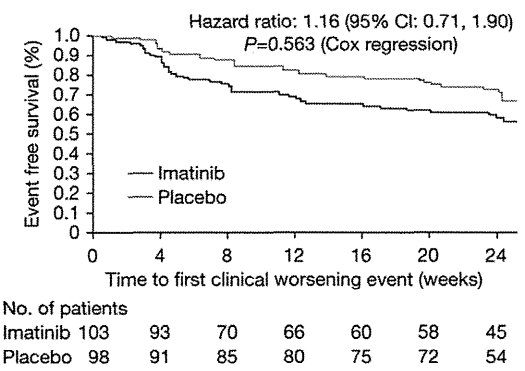


Figure 4. Time to clinical worsening. CI indicates confidence interval. Values below the graph are the number of patients remaining in the study at each time point.

Most of the AEs reported in the study were similar to those observed previously in association with the use of imatinib in patients with other approved indications. The most frequent AEs were nausea, peripheral edema, diarrhea, vomiting, and periorbital edema. There were no indications of liver toxicity or impaired renal function. However, particular note should be taken of the safety profile of imatinib in PAH because certain early AEs could be mistaken for progression of right heart failure, whereas progressive venous congestion in conjunction with worsening PAH could be interpreted erroneously as an imatinib side effect.

Study-drug discontinuations were comparatively high in the present study compared with previous studies with imatinib for malignant diseases (12% to 44% in studies up to 24 months in duration).[30,31] The exact reasons for this observation are unknown, but potential causes may include effects of the underlying disease and comedications as well as a lack of experience with the use of imatinib among PAH specialists.

Subdural hematomas occurred in 4.2% of the patients treated with imatinib in the extension study, all of them in patients receiving concomitant anticoagulation. The incidence of subdural hematomas in patients receiving imatinib for oncological indications is reported to vary between 0.2% and 5.8%.[32] A recent study by Henkens et al[33] showed a relatively high incidence of bleeding complications in patients receiving oral anticoagulants for PAH, but there was only 1 case of central nervous system bleeding in this series. A recent review of cases of subdural hematoma was reported from the 12-week Sildenafil Use in Pulmonary Arterial Hypertension (SUPER)-1 (277 treatment-naive patients) and the 16-week Pulmonary arterial hypertension combination study of epoprostenol and

Table 3. Frequency of Adverse Events

	Imatinib (n=103)	Placebo (n=98)
Adverse event, n (%)*	100 (97)	94 (96)
Nausea	57 (55)	23 (24)
Peripheral edema	45 (44)	20 (20)
Diarrhea	36 (35)	19 (19)
Vomiting	31 (30)	10 (10)
Periorbital edema	30 (29)	7 (7)
Headache	25 (24)	22 (22)
Dyspnea	19 (18)	13 (13)
Nasopharyngitis	18 (18)	19 (19)
Hypokalemia	16 (16)	3 (3)
Anemia	14 (14)	3 (3)
Cough	11 (11)	15 (15)
Fatigue	11 (11)	7 (7)
Face edema	10 (10)	1 (1)
Muscle spasms	10 (10)	2 (2)
Serious adverse event, n (%)†	45 (44)	29 (30)
Worsening of pulmonary hypertension	6 (6)	8 (8)
Anemia	7 (7)	1 (1)
Dyspnea	6 (6)	2 (2)
Peripheral edema	6 (6)	0
Presyncope	5 (5)	0
Diarrhea	3 (3)	2 (2)
Device-related infection	3 (3)	0
Syncope	1 (1)	5 (5)
Subdural hematoma	2 (2)	0 (0)
Total patients with clinical worsening, n (%)	37 (36)	32 (33)
Death (all deaths)	3 (3)	3 (3)
Hospitalization for worsening of PAH (adjudicated events)	17 (17)	13 (13)
Worsening of WHO functional class by at least 1 level	15 (15)	11 (11)
15% reduction of 6MWD on 2 consecutive occasions compared with baseline	12 (12)	17 (17)
Worsening of WHO functional class by at least 1 level and 15% reduction in 6MWD on 2 consecutive occasions compared with baseline	2 (2)	3 (3)

6MWD indicates 6-minute walk distance; PAH, pulmonary arterial hypertension; and WHO, World Health Organization.
*Individual adverse events are shown if they occurred in >10% in the imatinib group (see online-only Data Supplement for full listing).
†Individual serious adverse events are shown if they occurred in ≥3 patients in either group.

sildenafil (PACES-1) (267 patients stable on intravenous epoprostenol) clinical trials, performed among patients with mean baseline PVR of 810.5 and 952.0 dyne·s·cm^{-5}, respectively.[34] Patients in both trials received open-label sildenafil for ≥3 years. The report identified only 2 cases of subdural hematoma (1 in each open-label extension), both in patients receiving oral anticoagulants. Thus, the incidence of subdural hematomas in the present study was unexpectedly high. However, the patient population was different from that of PACES-1 and SUPER-1 in terms of both hemodynamic severity and background treatment at baseline. The mechanism by which imatinib might cause subdural hematoma is unclear and requires further evaluation.

Limitations of this study include the short observation period, the relatively high dropout rates in both treatment arms, and the differential dropout rates on imatinib and placebo. However, the patient population was highly selected for disease severity, and the study duration was longer than in most previous trials in the field of pulmonary hypertension. Differential dropout was anticipated and was taken into account in the prespecified statistical analysis plan by the choice of primary analysis method and sensitivity analyses. Our statistical analyses also followed the principles identified by the National Research Council for drawing inferences from incomplete data,[35] but the possibility cannot be excluded that the higher discontinuation rate in the imatinib group may have led to an overestimation of the treatment effect. In addition, because 75% of the study population had idiopathic or heritable PAH, our findings are not necessarily applicable to all PAH subgroups.

The target dose of 400 mg once daily was selected because this dose is widely used in patients receiving imatinib for malignant disorders. The same target dose was also used in the phase II study of imatinib in PAH.[23] The present study protocol allowed dose reduction in patients not tolerating imatinib at 400 mg/d. Approximately half of the patients receiving imatinib were able to remain on the 400-mg dose. Although the number of patients was too small for a formal dose-effect analysis, the largest treatment effects were observed in patients who received a dose of 400 mg/d (Appendix III and Table XIV in the online-only Data Supplement), although this is a nonrandomized comparison. There was no difference in AEs between the patients who received 400 mg/d for ≥50% versus <50% of the study. However, the minimum efficacious dose of imatinib in PAH remains unknown and needs to be determined in future trials.

Finally, the present study did not further assess the mechanisms by which imatinib acts in PAH. Understanding these mechanisms is of key importance not only to predict the response to therapy but also to design more targeted tyrosine kinase inhibitors for this disease. These are crucial aspects for further research, particularly because broad-spectrum tyrosine kinase inhibition may have pleiotropic effects on the cardiopulmonary system. Sorafenib, for instance, had detrimental effects on cardiac output in patients with PAH,[36] and dasatinib has been identified as a potential cause of PAH.[37]

In conclusion, this study provides evidence that imatinib, as the first representative of a new class of drugs for the treatment of PAH, improves exercise capacity and hemodynamics in patients with advanced PAH who remain symptomatic on at least 2 drugs of the currently available 3 drug classes. Discontinuations of study medication and serious AEs, including subdural hematomas, were more common in the imatinib group, and further studies are required to assess the risk-benefit profile of imatinib in patients with advanced PAH. Until further data are available, the off-label use of imatinib for this indication is strongly discouraged.

Acknowledgments

We thank all site investigators involved in conducting the IMPRES trial, as follows: Austria: Christian Kaehler, Irene Lang; Belgium: Marion Delcroix, Jean-Luc Vachiéry; Canada: Douglas Helmersen, Sanjay Mehta, Evangelos Michelakis; France: Gérald Simonneau; Germany: Jürgen Behr, Leonhard Bruch, Ardeschir Ghofrani, Ekkehard Gruenig, Gert Hoeffken, Marius Hoeper, Hans Klose, Christian Opitz, Theo Pelzer, Michael Pfeifer, Stephan Rosenkranz, Henrieke Wilkens; Italy: Stefano Ghio, Carmine Vizza; Japan: Yoshihiro Fukumoto, Hiromi Matsubara, Norifumi Nakanishi, Toru Satoh, Hiroshi Watanabe, Atsushi Yao; Netherlands: Antonie Vonk-Noordegraaf; South Korea: Hyukjae Chang, Dukkyung Kim, Chungil Noh; Spain: Joan Barbera Mir, Miguel Gomez Sanchez, Antonio Roman, Vicente Roig, Julio Sanchez Roman, Jose Luis Velasco, Felipe Zurbano; Sweden: Björn Ekmehag; Switzerland: Martin Brutsche; United Kingdom: Gerry Coghlan, Paul Corris, David Kiely, Andrew Peacock, Joanna Pepke-Zaba; United States: Tahir Ahmed, David Badesch, Raymond Benza, Robert Bourge, Murali Chakinala, Teresa DeMarco, Raed Dweik, Peter Engel, Jeremy Feldman, Robert Franz, Adaani Frost, Mardi Gomberg-Maitland, Paul Hassoun, Jonathan Ilowite, Gary Kinasewitz, Catherine Markin, Michael Mathier, Ajith Nair, Frank Rahagi, Rajan Saggar, Dan Schuller, Victor Tapson, Fernando Torres, Sheila Weaver, Dianne Zwicke. Paul Hutchin, PhD, a professional medical writer funded by Novartis, assisted in the preparation of the manuscript. Helen Venables, BA(Hons) (CircleScience), an editorial assistant funded by Novartis, provided additional editorial support including the preparation of figures. The primary statistical analyses were performed by DATAMAP, an independent clinical research organization contracted by the sponsor.

Sources of Funding

This work was funded by Novartis Pharma AG.

Disclosures

Dr Hoeper has received honoraria for consultations and/or speaking at conferences from Actelion, Bayer, Gilead, GlaxoSmithKline, Lilly, Novartis, and Pfizer. Dr Barst has received honoraria for consultations/scientific advisory board activity from Actelion, Bayer, Eli Lilly, Gilead, GlaxoSmithKline, Ikaria, Merck, Novartis, Pfizer, and VentriPoint. Dr Bourge reports grant support, scientific advisory board activity, and/or speaker's honoraria from Actelion, Bayer, Gilead, Novartis, Pfizer, Lilly, United Therapeutics, and GeNO. Dr Feldman has received honoraria for consultations and/or speaking at conferences from Gilead and United Therapeutics. Dr Frost has received honoraria for consultations and/or speaking about a product or about pulmonary hypertension from Actelion, Pfizer, United Therapeutics, Gilead, Novartis, Bayer, and Pfizer. Dr Galié has been involved with Steering Committee activities for Eli Lilly and Company, Actelion, Pfizer, Bayer-Schering, GlaxoSmithKline, and Novartis. He has been a paid lecturer for Actelion, Eli Lilly and Company, Pfizer, Bayer-Schering, and GlaxoSmithKline. He has also done contract research for Actelion, Pfizer, United Therapeutics, Bayer-Schering, and GlaxoSmithKline. Dr Gómez-Sánchez has received honoraria for consultations and/or speaking at conferences from Actelion, Bayer, GlaxoSmithKline, Lilly, Novartis Pfizer, and United Therapeutics. Dr Grimminger has received honoraria for consultations and/or speaking at conferences from Bayer HealthCare AG, Actelion, Lilly, and Pfizer. He is a member of advisory boards for Bayer HealthCare AG and Pfizer. He has also received governmental grants from the German Research Foundation, Excellence Cluster Cardiopulmonary Research, State Government of Hessen, and German Ministry for Education and Research. Dr Grünig has received honoraria for consultations and/or speaking at conferences from Actelion, Bayer, Gilead, GSK, Lilly, Milteney, Novartis, Pfizer, and Rotex Medica and funding for clinical trials by Actelion, Bayer, GSK, Encysive, Lilly, and Pfizer. Dr Hassoun has received honoraria for consultations and/or scientific advisory board activities for Gilead, Pfizer, Novartis, and Merck. Dr Morrell has received a research grant from Novartis and has received honoraria for speaking at conferences from Novartis, Actelion, and Pfizer. Dr Peacock has received honoraria for consultations and/or speaking at conferences from Actelion, Bayer, GlaxoSmithKline, Lilly, Novartis Pfizer, and United Therapeutics and educational grants for research from Pfizer, Bayer, and Actelion. Dr Satoh has no conflicts of interest to declare. Dr Simonneau has received honoraria for consultations and/or speaking at conferences from Actelion, Bayer, GlaxoSmithKline, Lilly, Novartis, and Pfizer. Dr Tapson has received research grants from Actelion, Bayer, Gilead, GlaxoSmithKline, Novartis, and United Therapeutics and fees for consulting/lecturing from Actelion, Bayer, Gilead, Novartis, and United Therapeutics. Dr Torres participates in research, on advisory boards, or as a speaker for the following companies: Gilead, Actelion, Pfizer, Bayer, iNO, United Therapeutics, and Novartis. Drs Lawrence and Quinn are employees of Novartis. Dr Ghofrani has received honoraria for consultations and/or speaking at conferences from Bayer HealthCare AG, Actelion, Encysive, Pfizer, Ergonex, Lilly, and Novartis. He is a member of advisory boards for Bayer HealthCare AG, Pfizer, GlaxoSmithKline, Actelion, Ergonex, Lilly, Merck, Encysive, and Ergonex. He has also received governmental grants from the German Research Foundation, Excellence Cluster Cardiopulmonary Research, State Government of Hessen, and German Ministry for Education and Research.

References

1. Farber HW, Loscalzo J. Pulmonary arterial hypertension. *N Engl J Med.* 2004;351:1655–1665.
2. Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. *N Engl J Med.* 2004;351:1425–1436.
3. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, Elliott CG, Gaine SP, Gladwin MT, Jing ZC, Krowka MJ, Langleben D, Nakanishi N, Souza R. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol.* 2009;54(suppl 1):S43–S54.
4. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kernis JT. Survival in patients with primary pulmonary hypertension: results from a national prospective registry. *Ann Intern Med.* 1991;115:343–349.
5. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, Groves BM, Tapson VF, Bourge RC, Brundage BH, Koerner SK, Langleben D, Keller CA, Murali S, Uretsky BF, Clayton LM, Jöbsis MM, Blackburn SD, Shortino D, Crow JW; Primary Pulmonary Hypertension Study Group. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N Engl J Med.* 1996;334:296–301.
6. Barst RJ, Langleben D, Badesch D, Frost A, Lawrence EC, Shapiro S, Naeije R, Galie N; STRIDE-2 Study Group. Treatment of pulmonary arterial hypertension with the selective endothelin-A receptor antagonist sitaxsentan. *J Am Coll Cardiol.* 2006;47:2049–2056.
7. Galiè N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, Fleming T, Parpia T, Burgess G, Branzi A, Grimminger F, Kurzyna M, Simonneau G; Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med.* 2005;353:2148–2157.
8. Galiè N, Olschewski H, Oudiz RJ, Torres F, Frost A, Ghofrani HA, Badesch DB, McGoon MD, McLaughlin VV, Roecker EB, Gerber MJ, Dufton C, Wiens BL, Rubin LJ; Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Studies (ARIES) Group. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy (ARIES) study 1 and 2. *Circulation.* 2008;117:3010–3019.
9. Galiè N, Brundage BH, Ghofrani HA, Oudiz RJ, Simonneau G, Safdar Z, Shapiro S, White RJ, Chan M, Beardsworth A, Frumkin L, Barst RJ; Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) Study Group. Tadalafil therapy for pulmonary arterial hypertension. *Circulation.* 2009;119:2894–2903.
10. Rubin LJ, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A, Pulido T, Frost A, Roux S, Leconte I, Landzberg M, Simonneau G. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med.* 2002;346:896–903.
11. Humbert M, Sitbon O, Yaïci A, Montani D, O'Callaghan DS, Jaïs X, Parent F, Savale L, Natali D, Günther S, Chaouat A, Chabot F, Cordier JF, Habib G, Gressin V, Jing ZC, Souza R, Simonneau G; French Pulmonary Arterial Hypertension Network. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. *Eur Respir J.* 2010;36:549–555.
12. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaïci A, Weitzenblum E, Cordier JF, Chabot F, Dromer C, Pison C, Reynaud-Gaubert M, Haloun A, Laurent M, Hachulla E, Cottin V, Degano B, Jaïs X, Montani D, Souza R, Simonneau G. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation.* 2010;122:156–163.
13. Morrell NW, Adnot S, Archer SL, Dupuis J, Jones PL, MacLean MR, McMurtry IF, Stenmark KR, Thistlethwaite PA, Weissmann N, Yuan JX, Weir EK. Cellular and molecular basis of pulmonary arterial hypertension. *J Am Coll Cardiol.* 2009;54(suppl 1):S20–S31.
14. Humbert M, Monti G, Fartoukh M, Magnan A, Brenot F, Rain B, Capron F, Galanaud P, Duroux P, Simonneau G, Emilie D. Platelet-derived growth factor expression in primary pulmonary hypertension: comparison of HIV seropositive and HIV seronegative patients. *Eur Respir J.* 1998;11:554–559.
15. Montani D, Perros F, Gambaryan N, Girerd B, Dorfmuller P, Price LC, Huertas A, Hammad H, Lambrecht B, Simonneau G, Launay JM, Cohen-Kaminsky S, Humbert M. C-kit-positive cells accumulate in remodeled vessels of idiopathic pulmonary arterial hypertension. *Am J Respir Crit Care Med.* 2011;184:116–123.
16. Perros F, Montani D, Dorfmüller P, Durand-Gasselin I, Tcherakian C, Le Pavec J, Mazmanian M, Fadel E, Mussot S, Mercier O, Hervé P, Emilie D, Eddahibi S, Simonneau G, Souza R, Humbert M. Platelet-derived growth factor expression and function in idiopathic pulmonary arterial hypertension. *Am J Respir Crit Care Med.* 2008;178:81–88.
17. Schermuly RT, Dony E, Ghofrani HA, Pullamsetti S, Savai R, Roth M, Sydykov A, Lai YJ, Weissmann N, Seeger W, Grimminger F. Reversal of experimental pulmonary hypertension by PDGF inhibition. *J Clin Invest.* 2005;115:2811–2821.
18. Abe K, Toba M, Alzoubi A, Koubsky K, Ito M, Ota H, Gairhe S, Gerthoffer WT, Fagan KA, McMurtry IF, Oka M. Tyrosine kinase inhibitors are potent acute pulmonary vasodilators in rats. *Am J Respir Cell Mol Biol.* 2011;45:804–808.
19. Nakamura K, Akagi S, Ogawa A, Kusano KF, Matsubara H, Miura D, Fuke S, Nishii N, Nagase S, Kohno K, Morita H, Oto T, Yamanaka R, Otsuka F, Miura A, Yutani C, Ohe T, Ito H. Pro-apoptotic effects of imatinib on PDGF-stimulated pulmonary artery smooth muscle cells from patients with idiopathic pulmonary arterial hypertension. *Int J Cardiol.* 2012;159:100–106.
20. Ghofrani HA, Seeger W, Grimminger F. Imatinib for the treatment of pulmonary arterial hypertension. *N Engl J Med.* 2005;353:1412–1413.
21. Patterson KC, Weissmann A, Ahmadi T, Farber HW. Imatinib mesylate in the treatment of refractory idiopathic pulmonary arterial hypertension. *Ann Intern Med.* 2006;145:152–153.
22. Souza R, Sitbon O, Parent F, Simonneau G, Humbert M. Long term imatinib treatment in pulmonary arterial hypertension. *Thorax.* 2006;61:736.
23. Ghofrani HA, Morrell NW, Hoeper MM, Olschewski H, Peacock AJ, Barst RJ, Shapiro S, Golpon H, Toshner M, Grimminger F, Pascoe S. Imatinib in pulmonary arterial hypertension patients with inadequate response to established therapy. *Am J Respir Crit Care Med.* 2010;182:1171–1177.
24. Rich S, ed. Executive summary from the World Symposium on Primary Pulmonary Hypertension; September 6–10, 1998; Evian, France; cosponsored by the World Health Organization.
25. McGoon M, Gutterman D, Steen V, Barst R, McCrory DC, Fortin TA, Loyd JE; American College of Chest Physicians. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest.* 2004;126(suppl 1):14S–34S.
26. American Thoracic Society. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med.* 2002; 166:111–117.
27. McLaughlin VV, Oudiz RJ, Frost A, Tapson VF, Murali S, Channick RN, Badesch DB, Barst RJ, Hsu HH, Rubin LJ. Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. *Am J Respir Crit Care Med.* 2006;174:1257–1263.
28. McLaughlin VV, Benza RL, Rubin LJ, Channick RN, Voswinckel R, Tapson VF, Robbins IM, Olschewski H, Rubenfire M, Seeger W. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. *J Am Coll Cardiol.* 2010;55:1915–1922.
29. Mathai SC, Puhan MA, Lam D, Wise RA. The minimal important difference in the 6-minute walk test for patients with pulmonary arterial hypertension. *Am J Respir Crit Care Med.* 2012;186:428–433.
30. Verweij J, Casali PG, Zalcberg J, LeCesne A, Reichardt P, Blay JY, Issels R, van Oosterom A, Hogendoorn PC, Van Glabbeke M, Bertulli R, Judson I. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. *Lancet.* 2004;364:1127–1134.
31. O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, Cornelissen JJ, Fischer T, Hochhaus A, Hughes T, Lechner K, Nielsen JL, Rousselot P, Reiffers J, Saglio G, Shepherd J, Simonsson B, Gratwohl A, Goldman JM, Kantarjian H, Taylor K, Verhoef G, Bolton AE, Capdeville R, Druker BJ; IRIS Investigators. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med.* 2003;348:994–1004.
32. Song KW, Rifkind J, Al-Beirouti B, Yee K, McCrae J, Messner HA, Keating A, Lipton JH. Subdural hematomas during CML therapy with imatinib mesylate. *Leuk Lymphoma.* 2004;45:1633–1636.
33. Henkens IR, Hazenoot T, Boonstra A, Huisman MV, Vonk-Noordegraaf A. Major bleeding with vitamin K antagonist anticoagulants in pulmonary hypertension [published online ahead of print August 30, 2012]. *Eur Respir J.* doi:10.1183/09031936.00039212.

34. Simonneau G, Hwang LJ, Teal S, Galie N. Incidence of subdural hematoma in patients with pulmonary arterial hypertension (PAH) in two randomized controlled clinical trials. *Eur Respir J.* 2012; 40(suppl 56):941.
35. Little RJ, D'Agostino R, Cohen ML, Dickersin K, Emerson SS, Farrar JT, Frangakis C, Hogan JW, Molenberghs G, Murphy SA, Neaton JD, Rotnitzky A, Scharfstein D, Shih WJ, Siegel JP, Stern H. The prevention and treatment of missing data in clinical trials. *N Engl J Med.* 2012;367:1355–1360.
36. Gomberg-Maitland M, Maitland ML, Barst RJ, Sugeng L, Coslet S, Perrino TJ, Bond L, Lacouture ME, Archer SL, Ratain MJ. A dosing/cross-development study of the multikinase inhibitor sorafenib in patients with pulmonary arterial hypertension. *Clin Pharmacol Ther.* 2010;87:303–310.
37. Montani D, Bergot E, Günther S, Savale L, Bergeron A, Bourdin A, Bouvaist H, Canuet M, Pison C, Macro M, Poubeau P, Girerd B, Natali D, Guignabert C, Perros F, O'Callaghan DS, Jaïs X, Tubert-Bitter P, Zalcman G, Sitbon O, Simonneau G, Humbert M. Pulmonary arterial hypertension in patients treated by dasatinib. *Circulation.* 2012;125:2128–2137.

CLINICAL PERSPECTIVE

Pulmonary arterial hypertension (PAH) is a progressive and frequently fatal condition. Platelet-derived growth factor and c-KIT signaling are important in vascular smooth muscle cell proliferation and hyperplasia, which are cardinal features of the pathophysiology underlying the disease. Imatinib is an inhibitor of platelet-derived growth factor receptor α and β kinases and c-KIT and may have a role in the treatment of PAH. The Imatinib in Pulmonary Arterial Hypertension, a Randomized, Efficacy Study (IMPRES) was a double-blind, placebo-controlled, randomized, 24-week trial evaluating the efficacy and safety of imatinib in PAH patients with high pulmonary vascular resistance (≥800 dyne·s·cm^{-5}) receiving ≥2 PAH therapies (endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and/or prostacyclin analogues). Compared with placebo, imatinib significantly improved exercise capacity and hemodynamic parameters in patients with advanced PAH who remained symptomatic on at least 2 of the currently available drug classes. Discontinuations of study medication and serious adverse events, including subdural hematoma, were more common in the imatinib group. The results suggest that the efficacy profile of imatinib is promising for the treatment of PAH patients who are still symptomatic despite receiving ≥2 PAH therapies, although clinicians should take note of its safety profile, which continues to be assessed in ongoing studies.

JACC: CARDIOVASCULAR INTERVENTIONS
© 2013 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.
VOL. 6, NO. 7, 2013
ISSN 1936-8798/$36.00
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

Takumi Inami, MD,* Masaharu Kataoka, MD,*† Nobuhiko Shimura, MD,* Haruhisa Ishiguro, MD,* Ryoji Yanagisawa, MD,* Hiroki Taguchi, MD,* Keiichi Fukuda, MD,† Hideaki Yoshino, MD,* Toru Satoh, MD*

Tokyo, Japan

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

From the *Division of Cardiology, Second Department of Internal Medicine, Kyorin University School of Medicine, Tokyo, Japan; and the †Department of Cardiology, Keio University School of Medicine, Tokyo, Japan. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Inami and Kataoka contributed equally to this work.

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

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

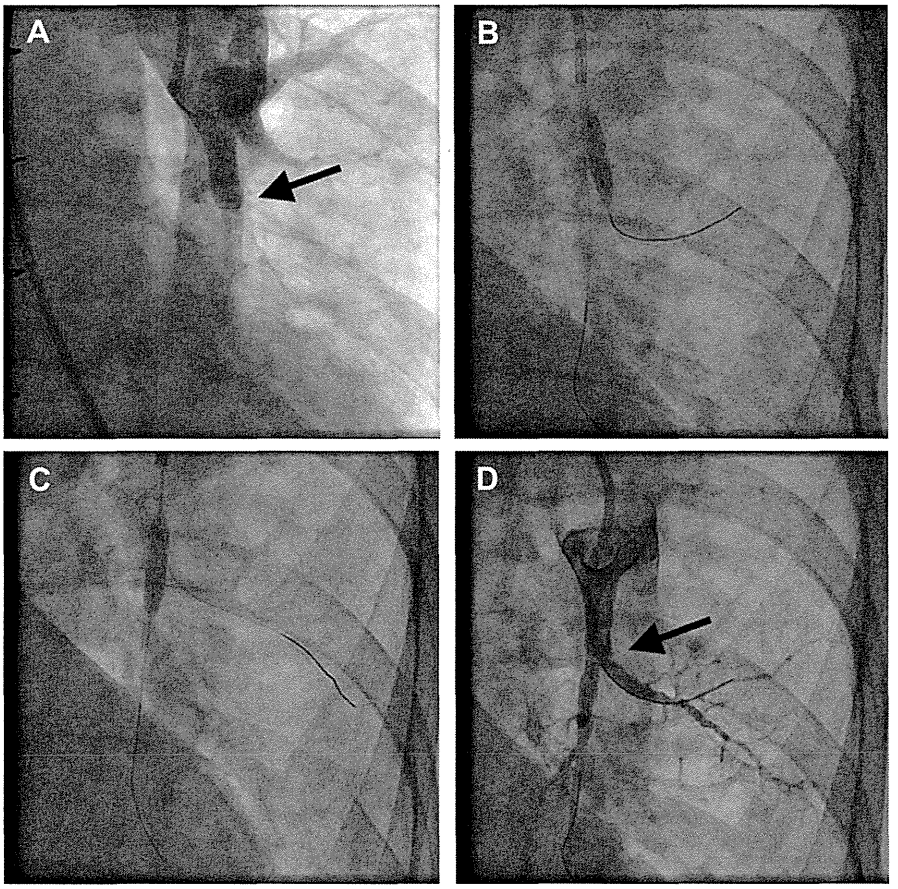


Figure 1. Representative Angiogram of PTPA

(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

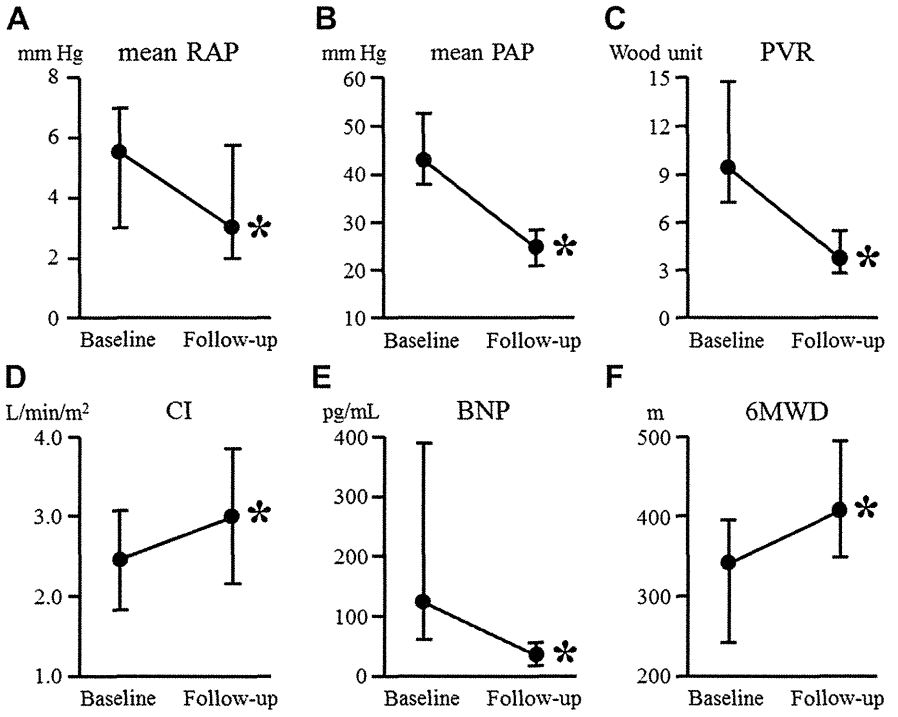


Figure 2. Therapeutic Efficacy of PTPA

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).

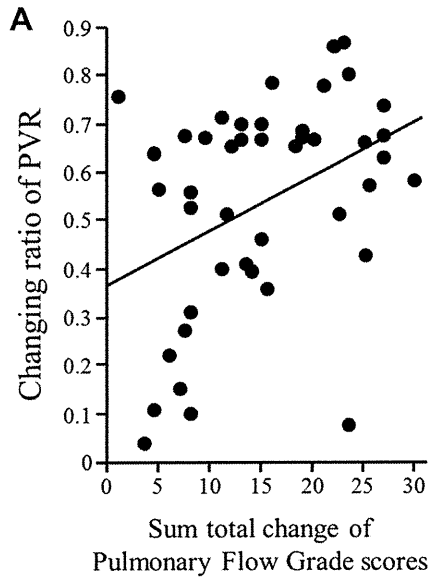
Correlations between Pulmonary Flow Grade scores and the ratio of pressures across the lesions. For all the lesions with Pulmonary Flow Grade 0, it was not possible to measure pressure differences by a pressure wire. Thirty-one measurements of the ratio of the proximal to the distal pressures of the 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.



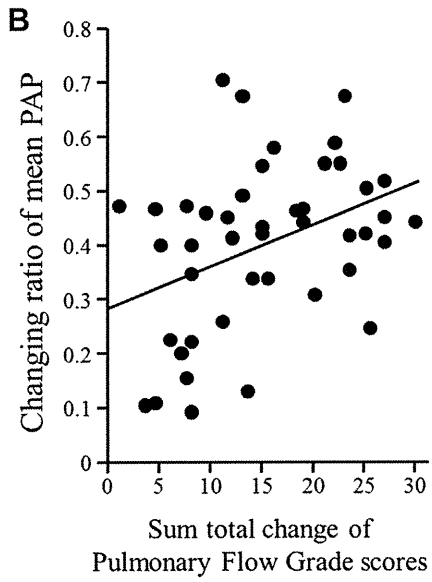


Figure 3. Correlations Between Sum Total Change of Pulmonary Flow Grade Scores and Changes in Hemodynamic Parameters After the Follow-Up Period

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).

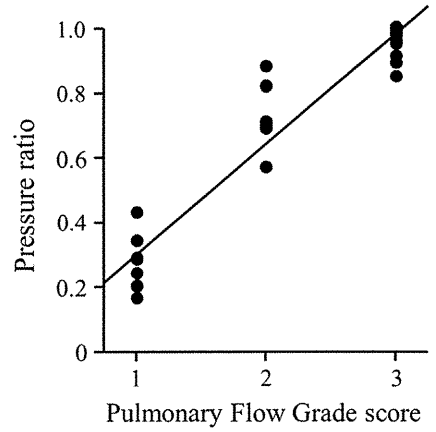


Figure 4. Correlation Between Pulmonary Flow Grade Score and the Ratio of Proximal and Distal Pressures of the Target Lesions

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.

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

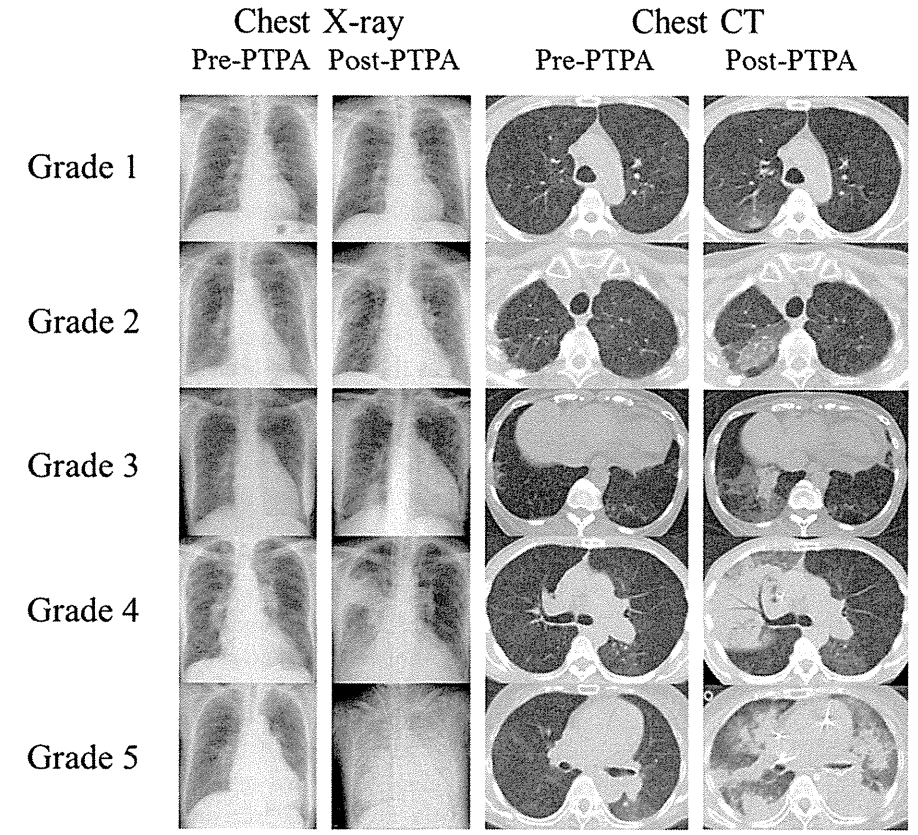


Figure 5. Representative Chest X-Ray and Chest CT Images of RPE

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

Table 5. Comparison of Variables Between Procedures With RPE and Those Without It

	Procedures With RPE of Grade 2 or Higher (n = 53)	Procedures Without RPE (n = 87)	p Value
First session	31 (58.5)	23 (26.4)	0.0003*
Mean RAP, mm Hg	4 (3 to 7)	4 (2 to 6)	0.2022
Mean PAP, mm Hg	42 (38 to 50)	33 (28 to 41)	<0.0001*
Cardiac index, l/min/m^2	2.5 (1.9 to 2.7)	2.6 (2.4 to 3.3)	0.0060*
PVR, Wood units	9.2 (7.0 to 14.6)	6.1 (3.9 to 8.7)	<0.0001*
Number of target vessels	4 (3 to 5)	3 (2 to 5)	0.1128
Sum total change of Pulmonary Flow Grade scores	6.0 (5.0 to 8.5)	4.0 (3.0 to 6.3)	<0.0001*
PEPSI	54.6 (41.9 to 81.5)	24.5 (17.7 to 33.2)	<0.0001*
Hemoglobin, g/dl	12.3 (11.3 to 13.5)	12.2 (10.6 to 13.6)	0.3353
eGFR, ml/min/1.73 m^2	63.4 (52.0 to 80.0)	74.4 (62.6 to 90.3)	0.0186*
BNP, pg/ml	125 (48 to 365)	42 (22 to 70)	<0.0001*

Values are n (%) or median (25th to 75th percentiles). PEPSI (Pulmonary Edema Predictive Scoring Index) = (sum total change of Pulmonary Flow Grade scores in percutaneous transluminal pulmonary angioplasty) × baseline PVR (Wood units). First session, number of procedures performed as first session. *p < 0.05.

EGFR = estimated glomerular filtration rate; RPE = reperfusion pulmonary edema; other abbreviations as in Table 2.

(95% CI: 2.9 to 9.6), and likelihood ratio of a negative test of 0.14 (95% CI: 0.04 to 0.32).

Discussion

We proposed Pulmonary Flow Grade scores for the classification of the angiographic flow appearances of target vessels in PTPA, and PEPSI as a marker connecting the Pulmonary Flow Grade scores with the baseline hemodynamic severity of CTEPH. This study demonstrates that the sum total change in Pulmonary Flow Grade scores is a good marker for predicting hemodynamic improvement at follow-up, and that PEPSI is useful to predict the risk of RPE in PTPA.

The present study found significant improvement in hemodynamic parameters, exercise capacity as indicated by 6-min-walk distance, and plasma BNP level after PTPA. In combination with some previous studies (17–20), these findings demonstrate that PTPA is clinically effective for the treatment of CTEPH. Some previous reports have demonstrated that about 45% to 55% of mean PAP and 65% to 70% of PVR decrease by pulmonary endarterectomy (22–24). Furthermore, the outcomes of patients treated medically have been reported sporadically (25–35), suggesting that the clinical efficacy of medical treatment tends to be lower than that of invasive surgical treatment. Meanwhile, in the results of our study, 42% of the mean PAP and 60% of the PVR decreased at about 6 months after PTPA. These findings suggest that the hemodynamic outcomes by PTPA are improved, but are not superior to, the outcomes by pulmonary endarterectomy. A large multicenter collaborative study is required in the future to compare the therapeutic efficacy, mortality, and complications of PTPA with those of pulmonary endarterectomy performed in experienced centers.

We proposed Pulmonary Flow Grade scores, which classify selective pulmonary angiography flow grade based on the flow appearance of the pulmonary veins perfused by the targeted pulmonary arteries. In the present study, the sum total change in Pulmonary Flow Grade scores was significantly correlated with hemodynamic changes of PVR and mean PAP at follow-up. In particular, our previous report demonstrated that the benefits of PTPA cannot be estimated by any immediate hemodynamic changes at the time of the procedure (17), suggesting that the performance guided by Pulmonary Flow Grade could more easily predict

Table 6. Statistical Analysis of Variables Correlated With the Occurrence of RPE

	Univariate Analysis			Multivariate Analysis		
	Odds Ratio	95% CI	p Value	Odds Ratio	95% CI	p Value
First session	3.920	1.918–8.215	0.0002*	1.958	0.692–5.578	0.2037
Mean RAP	1.093	0.970–1.242	0.1423	—	—	—
Mean PAP	1.075	1.038–1.116	<0.0001*	1.117	1.027–1.224	0.0088*
Cardiac index	0.417	0.225–0.723	0.0013*	—	—	—
PVR	1.220	1.120–1.344	<0.0001*	0.571	0.367–0.834	0.0029*
Number of target vessels	1.123	0.925–1.372	0.239	—	—	—
Sum total change of Pulmonary Flow Grade scores	1.284	1.124–1.487	0.0002*	0.642	0.364–1.056	0.0827
PEPSI	1.074	1.048–1.106	<0.0001*	1.162	1.078–1.274	<0.0001*
Hemoglobin	1.138	0.938–1.390	0.1899	—	—	—
eGFR	0.977	0.958–0.995	0.0143*	—	—	—
BNP	1.005	1.002–1.008	<0.0001*	1.002	0.998–1.008	0.2479

Multivariate analysis was made using variables with significant correlation of p < 0.001 in univariate analysis. *p < 0.05.

CI = confidence intervals; other abbreviations as in Tables 2 and 5.

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

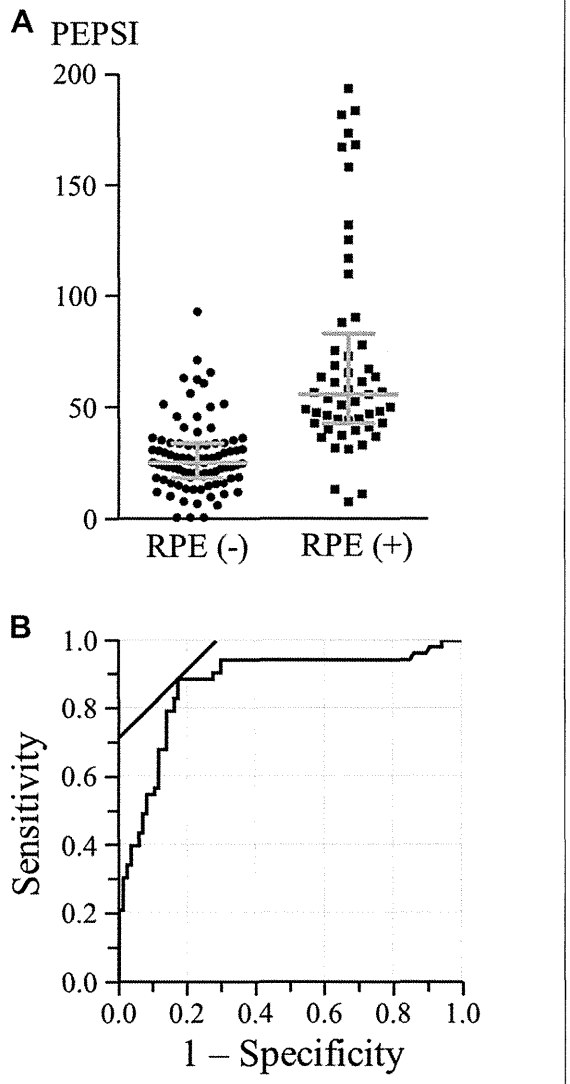


Figure 6. Correlation Between PEPSI and the Occurrence of RPE

(A) Distribution of PEPSI (Pulmonary Edema Predictive Scoring Index) in the presence [RPE (+)] and absence of reperfusion pulmonary edema [RPE (–)]. **(B)** Receiver-operating characteristic curve analysis of PEPSI for prediction of RPE.

the therapeutic efficacy at follow-up. Furthermore, in our results, Pulmonary Flow Grade score was strongly correlated with the ratio of the proximal to the distal pressures of the target lesions obtained by a pressure wire, suggesting that the practical utility of Pulmonary Flow Grade scores is substantiated by these pressure ratios, which is an objective method of measurement of stenosis.

RPE remains the most important complication of PTPA. Indeed, Feinstein et al. (20) experienced RPE in 11 of 18 enrolled patients (61%). In this study, RPE was graded into 5 groups according to severity. As shown in Figure 5, the RPE was recognized even in the opposite lung without angioplasty, in particular in grade 3 or higher. These findings raise the possibility that the occurrence of RPE is mediated, not only by the direct injury or direct exposure of high pressure in pulmonary arteries, but also by the indirect spreading effect of inflammation via cytokines. A more detailed exploration of mechanisms of RPE is desirable. Among the 140 total procedures in this study, 53 procedures (38%) were classified as grade 2 to 5, which indicates clear occurrence of RPE, and all 9 cases with RPE of grade 4 or higher, which indicates severe RPE, needed noninvasive positive-pressure ventilation or artificial respiration. Therefore, it would be highly risky to increase the sum total change of Pulmonary Flow Grade scores blindly without concern for the occurrence of RPE.

Comparison between the procedures with and without RPE of grade 2 or higher demonstrated that the sum total change in Pulmonary Flow Grade scores in cases with RPE was significantly higher than that in those without, and that procedures in cases with greater clinical severity at baseline had a higher risk of RPE. These findings confirm that PTPA should be performed based on the index reflecting both angiographic flow change and baseline severity of pulmonary hypertension so as to obtain maximum therapeutic efficacy and minimal risk of RPE at the same time. The PEPSI, which is calculated by multiplying the sum total change in Pulmonary Flow Grade scores by baseline PVR, could therefore provide a new and useful index in clinical settings. In this study, PEPSI was the strongest factor related to the occurrence of RPE by multivariate analysis, and ROC curve analysis demonstrated that the negative predictive value of the PEPSI for the occurrence of RPE was 92.3% when the cutoff value was 35.4, suggesting the possibility that PEPSI is a useful predictor of RPE.

These findings presuppose the usefulness of PTPA performed based on PEPSI. To cite a case with baseline PVR of 12 Wood units, the targeted value of sum total change in Pulmonary Flow Grade scores is 2.95, because the optimal cutoff value of PEPSI, 35.4, divided by a PVR of 12 Wood units equals 2.95. Thus, in such a case, if the Pulmonary Flow Grade score is changed from 0 to 2 after angioplasty of the first target vessel, the procedure should be stopped without angioplasty of the second target vessel because it would be difficult to maintain the change in Pulmonary Flow Grade score within 0.95 (i.e., 2.95 – 2). Alternatively, the procedure should be carefully continued so as to control the change in Pulmonary Flow Grade score of the second target vessel within 1 (for example, change in Pulmonary Flow Grade score from 0 to 1, 1 to 2, or 2 to 3). To cite another case with a baseline PVR of 5.0 Wood units, the targeted value of the sum total change in Pulmonary Flow Grade scores is 7.1 (i.e., 35.4/5.0). In such a case, if the Pulmonary Flow Grade score is changed from 0 to 3 after angioplasty of the first target vessel and is changed from 0 to 2 after angioplasty of the second target vessel, the change in Pulmonary Flow Grade score of the third target vessel should

be controlled within 2 (for example, change in Pulmonary Flow Grade score from 0 to 2 or 1 to 3). Additionally, because PEPSI is calculated using the baseline PVR, in the patients with lower PVR at baseline, it appears that it is possible to treat more target lesions or reach more changes of Pulmonary Flow Grade scores within 1 procedure, leading to more benefits in reduction in PVR and mean PAP.

Study limitations. The average observation period was not very long, and the number of patients was relatively small. Therefore, a study based on a longer observation period following a greater number of patients is needed to confirm our results. Furthermore, a prospective study should be performed to further demonstrate the predictive value of the PEPSI. This is also a nonrandomized study with no control arm, and these data are subject to selection bias.

Conclusions

PTPA is effective for the treatment of CTEPH, and the sum total change in Pulmonary Flow Grade scores is very useful for predicting the therapeutic efficacy at follow-up. With RPE recognized as the most important complication of PTPA, PEPSI, which reflects both angiographic flow change and the baseline severity of pulmonary hypertension due to CTEPH, could be a useful predictor of RPE. Our findings lead to the following hypothesis: if PTPA is performed guided by PEPSI, the risk of RPE will be minimized and therapeutic efficacy maximized, making PTPA a safe and common therapeutic strategy for CTEPH. However, the usefulness of PEPSI in this study is just a retrospective finding and would need to be tested prospectively to see whether clinical outcome is improved by using the PEPSI as a guide for PTPA.

Reprint requests and correspondence: Dr. Toru Satoh or Dr. Masaharu Kataoka, Division of Cardiology, Second Department of Internal Medicine, Kyorin University School of Medicine, 6-20-2, Shinkawa, Mitaka, Tokyo 181-8611, Japan. E-mail: tsatoh@ks.kyorin-u.ac.jp (T.S.); m.kataoka09@gmail.com (M.K.).

REFERENCES

1. Piazza G, Goldhaber SZ. Chronic thromboembolic pulmonary hypertension. N Engl J Med 2011;364:351–60.
2. Fedullo P, Kerr KM, Kim NH, Auger WR. Chronic thromboembolic pulmonary hypertension. Am J Respir Crit Care Med 2011;183:1605–13.
3. Auger WR, Kim NH, Trow TK. Chronic thromboembolic pulmonary hypertension. Clin Chest Med 2010;31:741–58.
4. Humbert M. Pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: pathophysiology. Eur Respir Rev 2010;19:59–63.
5. Lang IM, Klepetko W. Chronic thromboembolic pulmonary hypertension: an updated review. Curr Opin Cardiol 2008;23:555–9.
6. Bonderman D, Skoro-Sajer N, Jakowitsch J, et al. Predictors of outcome in chronic thromboembolic pulmonary hypertension. Circulation 2007; 115:2153–8.
7. McNeil K, Dunning J. Chronic thromboembolic pulmonary hypertension (CTEPH). Heart 2007;93:1152–8.
8. Hoeper MM, Mayer E, Simonneau G, Rubin LJ. Chronic thromboembolic pulmonary hypertension. Circulation 2006;113:2011–20.
9. Dartevelle P, Fadel E, Mussot S, et al. Chronic thromboembolic pulmonary hypertension. Eur Respir J 2004;23:637–48.
10. Seyfarth HJ, Halank M, Wilkens H, et al. Standard PAH therapy improves long term survival in CTEPH patients. Clin Res Cardiol 2010;99:553–6.
11. Hoeper MM, Barberà JA, Channick RN, et al. Diagnosis, assessment, and treatment of non-pulmonary arterial hypertension pulmonary hypertension. J Am Coll Cardiol 2009;54 Suppl:S85–96.
12. Pepke-Zaba J, Delcroix M, Lang I, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation 2011;124:1973–81.
13. Mayer E, Jenkins D, Lindner J, et al. Surgical management and outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. J Thorac Cardiovasc Surg 2011;141:702–10.
14. Freed DH, Thomson BM, Berman M, et al. Survival after pulmonary thromboendarterectomy: effect of residual pulmonary hypertension. J Thorac Cardiovasc Surg 2011;141:383–7.
15. Jensen KW, Kerr KM, Fedullo PF, et al. Pulmonary hypertensive medical therapy in chronic thromboembolic pulmonary hypertension before pulmonary thromboendarterectomy. Circulation 2009;120:1248–54.
16. Keogh AM, Mayer E, Benza RL, et al. Interventional and surgical modalities of treatment in pulmonary hypertension. J Am Coll Cardiol 2009;54 Suppl:S67–77.
17. Kataoka M, Inami T, Hayashida K, et al. Percutaneous transluminal pulmonary angioplasty for the treatment of chronic thromboembolic pulmonary hypertension. Circ Cardiovasc Interv 2012;5:756–62.
18. Mizoguchi H, Ogawa A, Munemasa M, Mikouchi H, Ito H, Matsubara H. Refined balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension. Circ Cardiovasc Interv 2012;5:748–55.
19. Sugimura K, Fukumoto Y, Satoh K, et al. Percutaneous transluminal pulmonary angioplasty markedly improves pulmonary hemodynamics and long-term prognosis in patients with chronic thromboembolic pulmonary hypertension. Circ J 2012;76:485–8.
20. Feinstein JA, Goldhaber SZ, Lock JE, Ferndandes SM, Landzberg MJ. Balloon pulmonary angioplasty for treatment of chronic thromboembolic pulmonary hypertension. Circulation 2001;103:10–3.
21. Sheehan FH, Braunwald E, Canner P, et al. The effect of intravenous thrombolytic therapy on left ventricular function: a report on tissue-type plasminogen activator and streptokinase from the Thrombolysis in Myocardial Infarction (TIMI Phase I) trial. Circulation 1987;75: 817–29.
22. Corsico AG, D'Armini AM, Cerveri I, et al. Long-term outcome after pulmonary endarterectomy. Am J Respir Crit Care Med 2008;178:419–24.
23. Piovella F, D'Armini AM, Barone M, Tapson VF. Chronic thromboembolic pulmonary hypertension. Semin Thromb Hemost 2006;32:848–55.
24. Matsuda H, Ogino H, Minatoya K, et al. Long-term recovery of exercise ability after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. Ann Thorac Surg 2006;82:1338–43.
25. Condliffe R, Kiely DG, Gibbs JS, et al. Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. Am J Respir Crit Care Med 2008;177:1122–7.
26. Ulrich S, Fischler M, Speich R, Popov V, Maggiorini M. Chronic thromboembolic and pulmonary arterial hypertension share acute vasoreactivity properties. Chest 2006;130:841–6.
27. Jais X, D'Armini AM, Jansa P, et al. Bosentan for treatment of inoperable chronic thromboembolic pulmonary hypertension: BENEFiT (Bosentan Effects in iNopErable Forms of chronic Thromboembolic pulmonary hypertension), a randomized, placebo-controlled trial. J Am Coll Cardiol 2008;52:2127–34.
28. Reichenberger F, Voswinckel R, Enke B, et al. Long-term treatment with sildenafil in chronic thromboembolic pulmonary hypertension. Eur Respir J 2007;30:922–7.
29. Skoro-Sajer N, Bonderman D, Wiesbauer F, et al. Treprostinil for severe inoperable chronic thromboembolic pulmonary hypertension. J Thromb Haemost 2007;5:483–9.

30. Voswinckel R, Enke B, Reichenberger F, et al. Favorable effects of inhaled treprostinil in severe pulmonary hypertension: results from randomized controlled pilot studies. J Am Coll Cardiol 2006;48:1672–81.
31. Vizza CD, Badagliacca R, Sciomer S, et al. Mid-term efficacy of beraprost, an oral prostacyclin analog, in the treatment of distal CTEPH: a case control study. Cardiology 2006;106:168–73.
32. Oudiz RJ, Galie N, Olschewski H, et al. Long-term ambrisentan therapy for the treatment of pulmonary arterial hypertension. J Am Coll Cardiol 2009;54:1971–81.
33. Galie N, Brundage BH, Ghofrani HA, et al. Tadalafil therapy for pulmonary arterial hypertension. Circulation 2009;119:2894–903.
34. Barst RJ, Langleben D, Badesch D, et al. Treatment of pulmonary arterial hypertension with the selective endothelin-A receptor antagonist sitaxsentan. J Am Coll Cardiol 2006;47:2049–56.
35. Kim NH. Riociguat: an upcoming therapy in chronic thromboembolic pulmonary hypertension? Eur Respir Rev 2010;19:68–71.

Key Words: chronic thromboembolic pulmonary hypertension ■ flow appearance ■ percutaneous transluminal pulmonary angioplasty ■ reperfusion pulmonary edema.

●シンポジウム：我が国における肺高血圧症の最新治療の現状 6

肺動脈性肺高血圧症に対するチロシンキナーゼ抑制剤

杏林大学循環器内科
佐藤　徹

はじめに

多剤投与にても治療抵抗性の肺動脈性肺高血圧症（PAH）に対して，本来抗がん剤であるチロシンキナーゼ抑制剤の imatinib が 2005 年に初めて使用された。ドイツの Dr. Ghofrani によるもので，epoprostenol を含めた複数薬によってもNYHA Ⅳ の特発性肺動脈性肺高血圧症（IPAH）患者が，著明な血行動態および症状の改善を示したのであった。その後，単施設からの報告が続いたあと，phase Ⅱ および phase Ⅲ の治験が全世界の施設を対象に行われ，対象患者を肺血管抵抗（PVR）1000 dyn・sec・cm^{-5}以上とすると他剤に不応例に対しても効果があることが示された（IMPRES Study）[1]。しかし，約 30%強が副作用で中止となったことや硬膜下出血が数例で発生したことなどから結局は認可されず幻の薬となってしまった。しかし，わが国では現在，imatinib の長期投与治験を継続している症例が 9 例あり，いずれも良好な経過を示している。一方，われわれは別種のチロシンキナーゼ抑制剤 sorafenib を早期より使用してきたが，副作用の発生は imatinib より低いと感じ（imatinib の副作用発生率は日本人では 30%よりさらに高い），multiple channel inhibitor のため効果も高いともされている[2]。本報告では，imatinib（研究 1：imatinib の適応外使用，研究 2：imatinib の治験）と sorafenib（研究 3：sorafenib の適応外使用）の使用経験をまとめてみたい。

1　対象と方法

1）研究 1

3 系統の PAH 治療薬すべてを使用してもNYHA Ⅳ の PAH 5 例に適応外で使用した。imatinib を 100 mg より開始し 2 週後に 200 mg へ増量した。血液検査，胸部 X 線，心電図は週に 1 回，心エコー検査を 3 ヵ月ごと，右心カテーテル検査を 6 ヵ月後に施行した。必要なら適宜追加検査を行った。

2）研究 2

2 系統の PAH 治療薬すべてを使用してもPVR 10 単位以上の PAH 6 例に治験で使用した。imatinib を 200 mg より開始し，2 週後に 400 mg へ増量した。血液検査，胸部 X 線，心電図は 2 週に 1 回，心エコー検査を 3 ヵ月ごと，右心カテーテル検査を 6 ヵ月後に施行した。

3）研究 3

3 系統の PAH 治療薬すべてを使用してもNYHA Ⅲ，Ⅳ の PAH 11 例（IPAH 8 例，肺静脈閉塞症 PVOD 3 例）に適応外で使用した。sorafenib を 200 mg より開始し 1〜2 週後に 400 mg へ増量した。血液検査，胸部 X 線，心電図は週に 1 回，心エコー検査を 3 ヵ月ごと，右心カテーテル検査を 6 ヵ月後に施行した。必要なら適宜追加検査した。

2　結　　果

1）研究 1

5 例全例で臨床的改善がみられたが，そのう

Toru Satoh：Tyrosine kinase inhibitor for pulmonary arterial hypertension

ち 4 例では副作用（中毒疹 2 例，血小板減少，強い嘔気）のため 2 ヵ月以内に中止となり，中止後には元の状態に戻った。1 例は低心拍出量のため血圧低下して尿量減少したが，imatinib 投与により退院可能となり，その後約 1 年生存した。

2）研究 2

6 例中 3 例は副作用（血小板減少 3 例）のため中断となった。残りの 3 例の平均肺動脈圧（mPA）の経過を図 1 に示す。28 歳女性例（Sjogren 症候群）では血小板が 5 万以下に減少して，中止すると悪化するが，血小板が回復して投与を再開すると mPA は低下した。

3）研究 3

年齢 43±16 歳，男/女＝2/9 であった。血行動態（mPA）の変化を図 2 に示す。全体および PVOD では mPA は有意に改善したが，PAH 8 例では有意な改善は認められなかった。

非侵襲的指標については表 1 で左側の四つの指標のうち，PVOD 3 例は三つ以上の改善がみられ，IPAH の 8 例中症例 Ⅱ，Ⅴ，Ⅵ で二つ以上の指標の改善がみられており，これらは改善例とした。また，表 1 の右端の列に示したように，11 例中 IPAH では症例 Ⅱ，Ⅴ，Ⅵ，Ⅶ，Ⅷ の 5 例で，PVOD では症例①，②で，血圧低下，尿量減少を起こし，いわゆる「terminal shock state」となって入院加療をしたが，sorafeniv の投与で安定して外来通院治療が可能となった。

表 2 に sorafeniv による副作用と sorafeniv 開始後の生存期間を示した。11 例中 6 例で手足の発疹を認めたが，5 例は手足のみに限局し薬剤中止は不要で対症療法で悪化せずに安定した。1 例は全身に拡大したため，投与を中止して PSL

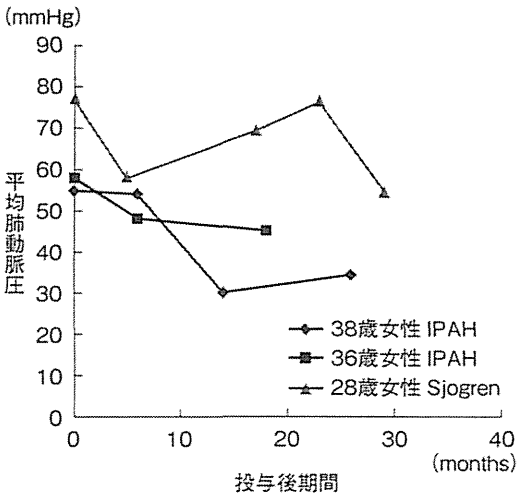


図 1　Imatinib 長期投与症例の経過

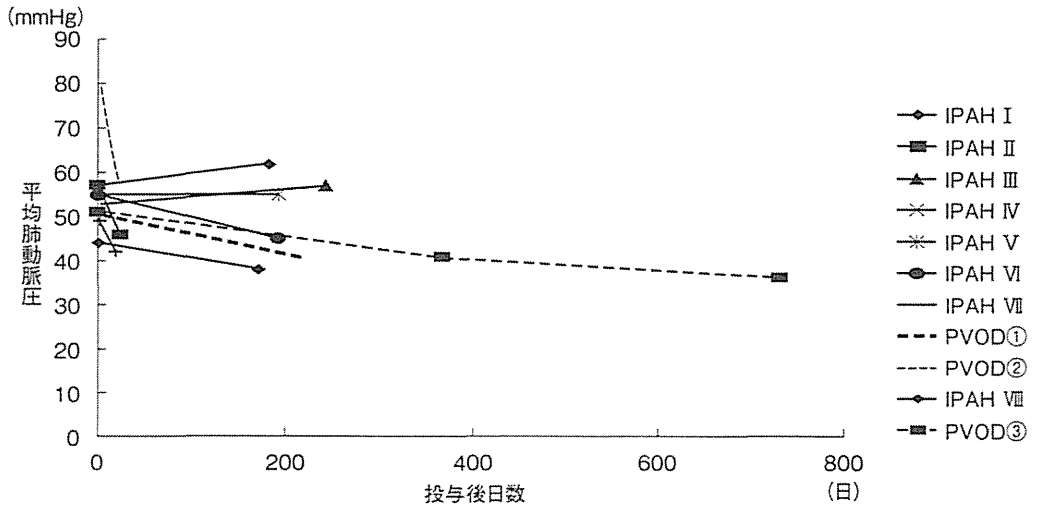


図 2　Sorafenib 投与後の mPA の変化
実線は IPAH，点線は PVOD を示す。

表 1　非侵襲的指標の変化

患者	BNP	尿酸	心胸郭比	NYHA	血圧低下，腎機能悪化
IPAH I	×	×	×	×	
IPAH II	○4	×	○21	○	○
IPAH III	○30	×	×	×	
IPAH IV	×	×	×	×	
IPAH V	×	○14	×	○	○
IPAH VI	×	○21	○21	○	○
PVOD①	○14	○14	○14	○	○
IPAH VII	×	×	×	×	○
PVOD②	×	○30	○14	○	○
IPAH VIII				×	○
PVOD③	○	○	○	○	

○：改善，10%以上改善して 1 ヵ月以上継続
×：不変あるいは無効
算用数字：sorafenib 開始から改善がみられるまでの日数

表 2　副作用と予後

患者	副作用	生死	sorafenib 投与後生存期間（日）
IPAH I	なし	死亡	219
IPAH II	全身の発疹	死亡	262
IPAH III	なし	死亡	306
IPAH IV	なし	生存	989
IPAH V	手足の発疹	死亡	129
IPAH VI	手足の発疹	死亡	443
PVOD①	手足の発疹	死亡	176
IPAH VII	なし	死亡	691
PVOD②	手足の発疹	死亡	405
IPAH VIII	なし	生存	355
PVOD③	手足の発疹	生存	790

などによる治療を必要とした。

3　考　　察

2 剤から 3 剤の PAH 薬投与にもかかわらず治療不応性に乏しい重症 PAH 症例に対し，チロシンキナーゼ抑制剤を投与した結果を呈示した。imatinib は研究 1，2 を合わせて 11 例に投与したが，長期投与できた症例は 4 例のみで，中止率は 6 割に達した。しかし，研究 1 の 2 例は皮膚生検で中毒疹とされたが，imatinib による中毒疹の出現は極めて少ないため epoprostenol による毛細血管拡張性発疹を見誤られていた可能性も否定できなかった。研究 1 の長期使用症例は「血圧低下，尿量低下などのショック状態」となってから使用したためか長期生存は難しかったが，研究 2 の長期使用例 3 例は NYHA III の状態で開始したためか 3 年以上安定した状態で生存している。一方，sorafeniv の副作用は有痛性の手足を中心とした発疹，高血圧が主なもので比較的重篤な臓器障害は少ない。そこで，われわれはある時期より sorafeniv を治療抵抗性の PAH に対して主に使用するようになった。sorafeniv は適応外使用となるため，IPAH では NYHA IV となって使用した。そのためか，結果的に延命が投与の目的の中心となった。「血圧低下，尿量低下などのショック状態」に陥った 7 例では全員が回復し，退院およびしばらくは外来通院が可能となった。PVOD の 1 例は NYHA IV の安定した時期に開始したためか約 3 年間安定して経過している。副作用は手足の発疹が中心だが，日々確認できる副作用のため大部分の症例で安定してコントロールすることができた。しかし，1 例は悪化しても我慢していたため全身に広がり PSL の投与を必要としており，厳しい患者教育の必要性を感じた。

結　　語

チロシンキナーゼ抑制剤は他剤抵抗性難治性肺動脈性肺高血圧症の一つの治療選択肢になると考えられた。

文　　献

1) Hoeper MM, et al. Imatinib mesylate as add-on therapy for pulmonary arterial hypertension: results of the randomized IMPRES Study. Circulation 2013; 127:1128-38.
2) Klein M, et al. Combined tyrosine and serine/threonine kinase inhibition by sorafenib prevents progression of experimental pulmonary hypertension and myocardial remodeling. Circulation 2008;118:2081-90.