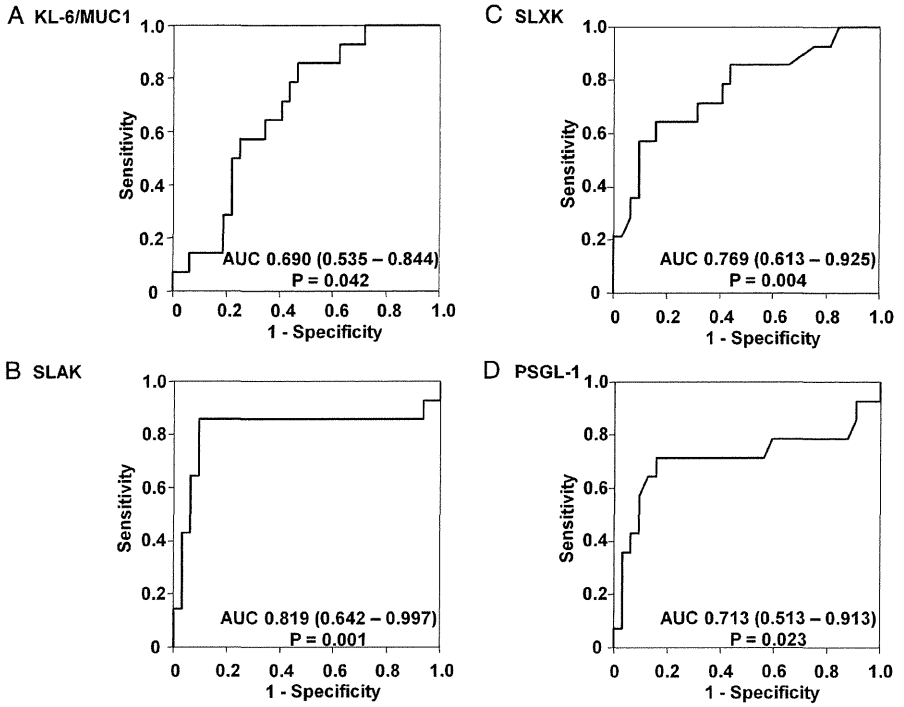

FIGURE 3. Receiver operating characteristic curves concerning DIC complication in ARDS patients. A, KL-6/MUC1. B, SLAK. C, SLXK. D, PSGL-1. Among the analyzed molecules, SLAK showed the largest AUC. Values in parentheses indicate 95% CIs for AUC. AUC = area under the curve. See Figure 1 and 2 legends for expansion of other abbreviations.

higher in ARDS patients complicated with DIC than in patients without DIC, whereas serum levels of PSGL-1 were significantly decreased in ARDS patients complicated with DIC compared with patients without DIC. These differences tended to persist for up to 2 weeks after the diagnosis of ARDS (Fig 2). This result could be explained by differences in the mechanism of elevation between PSGL-1 and KL-6/MUC1. PSGL-1 could be induced by infection, because this molecule is increased in patients with bacterial pneumonia when compared with healthy control subjects (Fig 1). On the other hand, KL-6/MUC1 is not induced by infection, as recently reported.[34] Because of its large molecular size, both alveolar-capillary destruction and enhancement of alveolar-capillary permeability are needed for the elevation of circulating KL-6/MUC1-related molecules.[25] In addition, there are different sites for the production of PSGL-1 and KL-6/MUC1. KL-6/MUC1 is mainly produced by proliferating, regenerating, and injured alveolar type 2 pneumocytes.[22,23,27] On the contrary, PSGL-1, expressed on myeloid cells and lymphocytes, plays a central role, in collaboration with P-selectin, in blood coagulation.[35,36] After it is shed from the cell surface, a soluble form of PSGL-1 is detectable in the bloodstream, which is also capable of binding P-selectin. However, the significance of soluble PSGL-1 in ARDS is unclear. The current findings suggest that soluble PSGL-1 appears to be consumed in the circulation prior to overt DIC development.

We found an association between increases of serum KL-6/MUC1 carrying selectin ligands and future complications of DIC in patients with ARDS, suggesting that KL-6/MUC1 carrying selectin ligands may contribute to enhanced procoagulant activity in ARDS. This notion could be explained in several ways. During a steady state, the selectin-binding sites on the KL-6/MUC1 molecules may be fully occupied by soluble selectins, which are abundant (micrograms per milliliter) in the circulation.[37] When alveolar-capillary destruction occurs and allows the soluble mucins carrying selectin ligand to flow into microcirculation, such released mucins carrying selectin ligands may alter the balance between molecules and cause interactions with cellular selectins, which subsequently initiate the intravascular coagulation process. In accordance with the previous notion, a reduction in soluble L-selectin correlates with susceptibility of ARDS to DIC among at-risk patients and also correlates with the degree of respiratory failure.[9,18] An alternative explanation is that KL-6/MUC1 produced by regenerating type 2 pneumocytes may be accompanied by an alteration in the sugar chain of the molecules, specifically, the selectin binding sites.

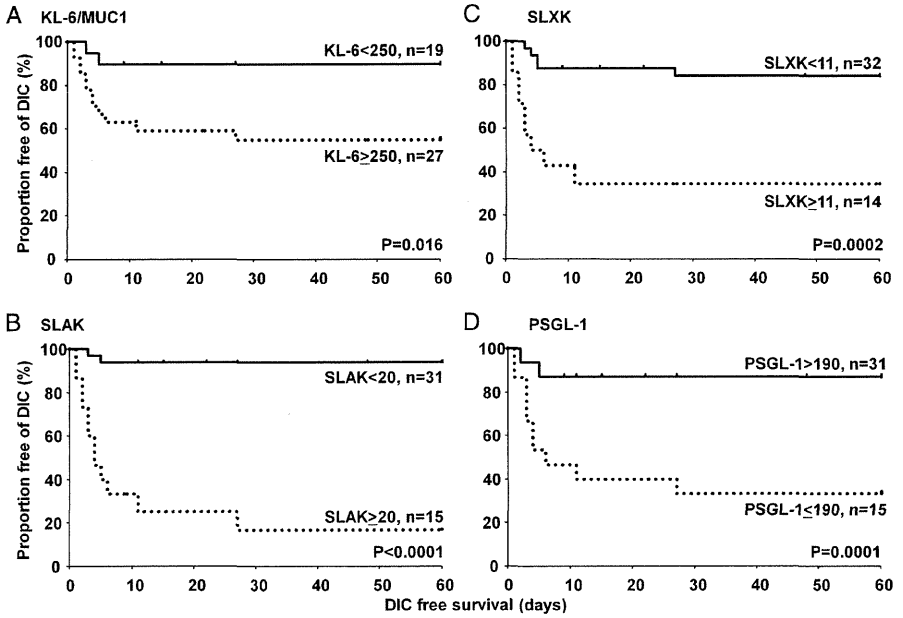

FIGURE 4. Kaplan-Meier analysis of each circulating mucin's high and low groups for development of DIC in ARDS patients. A, KL-6/MUC1. B, SLAK. C, SLXK. D, PSGL-1. See Figure 1 and 2 legends for expansion of abbreviations.

As shown in bacterial pneumonia patients without ALI/ARDS and in healthy subjects, normal circulating KL-6/MUC1 molecules have few ligands for selectins and thus cannot bind to cellular selectins. When produced by regenerating type 2 pneumocytes, KL-6/MUC1 is altered by its character and by added selectin ligands on the molecule. It should be noted that the previously-mentioned theories are speculations and have not been proven. The present study suggests that heterogeneity of KL-6/MUC1 molecules and acute production in KL-6/MUC1 seem to be accompanied by the expression of selectin ligands in patients with ARDS.

This study has several limitations. The sample size was not large enough to allow firm conclusions to be drawn, which may be why we could not replicate our previous results. We demonstrated previously that, at the time of diagnosis of ARDS, elevated levels of KL-6/MUC1 had a significant predictive value for the development of DIC.[10] In the present study, elevated KL-6/MUC was associated with the development of DIC, but this association did not reach statistical significance by univariate analysis ($P = .054$). In addition, we analyzed a diverse study population, which is often problematic in ARDS research. There were significant differences in the patients' baseline characteristics, for example, in age, lung injury, and APACHE II and DIC scores. However, the levels of SLAK were not significantly different among patients with ARDS of different origins, suggesting that measuring the levels of this mucin may be useful regardless of the causes and nature of ARDS. Thus, a prospective study is necessary to validate the identified cutoff levels of the markers in future.

CONCLUSIONS

In conclusion, this study suggests that mucins carrying selectin ligands are indicators for the development of DIC in ARDS patients. Increases in circulating KL-6/MUC1 carrying selectin ligands are more likely to be causally related to intravascular coagulation when compared with the entire amount of KL-6/MUC1. To our knowledge, therapeutic trials of conventional or low-molecular-weight heparin have not been explored in ARDS. Because heparin can block the interactions between selectin-selectin ligands, this study suggests possible therapeutic benefits of heparin in some ARDS patients who have increases in particular mucins such as SLAK. Clinical trials would be needed to determine whether prophylactic administration of heparin would be beneficial, especially if SLAK is increased at diagnosis of ARDS. Nevertheless, our present findings shed light on the novel role of KL-6/MUC1 in the pathophysiology of ARDS.

ACKNOWLEDGMENTS

Author contributions: Dr Yokoyama takes full responsibility for the integrity of all the data and the accuracy of the data analysis.

Dr Nakashima: contributed to designing the study, collecting the data, analyzing the data, and writing the manuscript.
Dr Yokoyama: contributed to designing the study, reanalyzing the data, and revising the manuscript.
Dr Inata: contributed to analyzing the data and revising the manuscript.
Dr Ishikawa: contributed to reanalyzing the data and revising the manuscript.
Dr Haruta: contributed to reanalyzing the data and revising the manuscript.
Dr Hattori: contributed to reanalyzing the data and revising the manuscript.
Dr Kohno: contributed to reanalyzing the data and revising the manuscript.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following conflicts of interest: Dr. Kohno has a royalty for KL-6/MUC1. Drs Nakashima, Yokoyama, Inata, Ishikawa, Haruta, and Hattori have reported that potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Additional Information: The e-Appendix can be found in the Online Supplement at http://chestjournal.chestpubs.org/content/139/2/296/suppl/DC1.

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Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Pulmonary Circulation

Impact of First-Line Sildenafil Monotreatment for Pulmonary Arterial Hypertension

Ryoji Yanagisawa, MD; Masaharu Kataoka, MD; Hiroki Taguchi, MD; Takashi Kawakami, MD; Yuichi Tamura, MD; Keiichi Fukuda, MD; Hideaki Yoshino, MD; Toru Satoh, MD

Background: Sildenafil has been demonstrated as effective for the treatment of pulmonary arterial hypertension (PAH). The purpose of this study was to investigate the occurrence of clinical events after sildenafil monotreatment as a first-line therapy in patients with PAH over a long-term observation period.

Methods and Results: Sildenafil was administered as a first-line drug to 46 patients with PAH (including 24 patients with idiopathic PAH) during 2003–2010. We investigated subsequent clinical events such as the addition of epoprostenol, hospitalization for right-side heart failure, and death. All the hemodynamic parameters and the 6-min walk distance improved significantly in the enrolled patients as a whole receiving sildenafil treatment; 15 (33%) of the 46 patients required the addition of epoprostenol during follow-up. Kaplan-Meier analysis demonstrated that more than 60% of the patients receiving first-line sildenafil treatment did not require the addition of epoprostenol for a 5-year period. Furthermore, the 5-year survival rate after first-line sildenafil treatment was 81%. Finally, more than 75% of the enrolled patients did not reach the composite endpoint of hospitalization for right-side heart failure and death for a 5-year period.

Conclusions: This study describes the long-term outcome of patients with PAH receiving sildenafil monotreatment as a first-line therapy and suggests that it is a promising therapeutic strategy. (*Circ J* 2012; **76:** 1245–1252)

Key Words: Epoprostenol; Hospitalization; Prognosis; Pulmonary hypertension; Sildenafil

Pulmonary arterial hypertension (PAH) is defined as a progressive disease of increasing pulmonary vascular resistance (PVR) that leads to right-side heart failure and a grave prognosis.[1–4] Sildenafil and bosentan have been developed as new treatments for PAH during the past few years. Bosentan, an endothelial receptor antagonist, was the first oral drug shown to have an effect in patients with PAH.[5–9] Sildenafil, a phosphodiesterase-5 inhibitor, is a new effective dilator of pulmonary arteries that is also administered orally. Sildenafil has relatively few adverse effects, compared with other oral drugs for PAH, and is safe for use even in patients with mild-to-moderate renal or hepatic dysfunction; moreover, its use reportedly improves heart failure.[10] Recently, the study on Sildenafil Use in Pulmonary Arterial Hypertension (SUPER)-1 revealed that sildenafil improves exercise capacity, the World Health Organization (WHO) functional class, and the hemodynamics of patients with PAH.[11] Furthermore, SUPER-2 established the safety and tolerability of sildenafil with maintenance of the patient's functional class.[12]

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At the present time, the most powerful and effective treatment for PAH is an ambulatory continuous infusion of epoprostenol. Prior to the introduction of epoprostenol, the 5-year survival rate of patients with idiopathic PAH was 34%.[13] Epoprostenol has increased the 5-year survival rate to 67%, according to a report published in the United States in 1994.[14] However, epoprostenol therapy requires an indwelling catheter attached to an ambulatory infusion pump, limiting the patient's activities and producing the possibility of catheter infection. Thus, if oral drugs, such as bosentan and sildenafil, can be used to inhibit the progression of PAH, the introduction of epoprostenol can be delayed.

Recently, these 3 drugs, epoprostenol, bosentan, and sildenafil, have been used in combination for the treatment of PAH. However, few reports have demonstrated the long-term outcome of first-line sildenafil monotreatment or any evidence regarding the combination of these drugs. Therefore, the ob-

Received October 18, 2011; revised manuscript received December 26, 2011; accepted January 6, 2012; released online February 14, 2012
Time for primary review: 20 days
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ISSN-1346-9843 doi:10.1253/circj.CJ-11-1192

Table 1. Baseline Characteristics of Patients

	All patients (n=46)	Epo(+) group (n=15)	Epo(−) group (n=31)	P value between Epo(+) and Epo(−) groups
Age, years	42±14	35±10	46±15	<0.01
Sex, F/M	38/8	12/3	26/5	NS
NYHA FC I+II/III, n	16/30	3/12	13/18	NS
mRA, mmHg	8.0±5.5	10.1±6.1	7.0±4.9	NS
mPAP, mmHg	52±14	62±15	47±11	<0.01
PVR, Wood unit	14.6±8.7	18±8.7	13±8.2	<0.05
CO, L/min	3.7±1.6	3.4±1.2	3.9±2.9	NS
6MWD, m	349±97	332±94	364±102	NS
BNP, pg/ml	334±349	317±347	345±358	NS

All the data are expressed as the mean±standard deviation.
Epo(+) group, patients who required additional epoprostenol treatment during the observation period; Epo(−) group, patients who did not require additional epoprostenol treatment during the observation period; NS, not significant; NYHA FC, New York Heart Association functional class; mRA, mean right atrial pressure; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; CO, cardiac output; 6MWD, 6-min walk distance; BNP, B-type natriuretic peptide.

jectives of this study were (1) to investigate the clinical efficacy of first-line sildenafil therapy during a long-term observation period, and (2) to examine the relationship of first-line sildenafil therapy and the occurrence of events such as the addition of epoprostenol, hospitalization for right-side heart failure, and death.

Methods

Study Subjects

In this study, we enrolled 57 patients with PAH who visited the Keio and Kyorin University Hospitals. The New York Heart Association functional class (NYHA FC) of enrolled patients was I, II, or III. The patients with NYHA FC IV were excluded because intravenous prostanoid should be the first-line treatment for those patients according to the algorithm proposed at the World Symposium in Venice, Italy, 2003 and revised at Dana Point, USA, in 2008.[15,16] Four patients abandoned sildenafil treatment because of the high cost of off-label use or severe, subjective adverse effects, and 7 patients with Eisenmenger syndrome were excluded because of the differences in their clinical characteristics compared with other patients with PAH. The remaining 46 patients (idiopathic PAH, n=24; secondary to connective tissue disease, n=16; associated with portal hypertension, n=6) were analyzed (age 42±14 years; 38 women, 8 men). Sildenafil was administered as a first-line drug from January 2003 to December 2010. All the patients provided informed consent, and the administration of sildenafil was approved by the institutional review boards of the hospitals.

All the patients enrolled underwent right-side heart catheterization before the administration of sildenafil and during the follow-up period. Furthermore, the 6-min walk distance (6MWD) was determined, and the B-type natriuretic peptide (BNP) level was measured before the administration of sildenafil and during the follow-up period.

Sildenafil Administration

In this study, sildenafil was administered as a first-line drug after the diagnosis of PAH. The maximum dose of sildenafil was 20 mg t.i.d. as long as the adverse effects could be tolerated. Conventional therapies, such as appropriate diuretics and oxygen therapy, were administered to all patients if such therapies were judged as being necessary based on the severity of the PAH and right-side heart failure.

Indication of Additional Epoprostenol and Bosentan

After the administration of sildenafil, the most appropriate treatment for each patient was instituted based on the algorithm.[15,16] If epoprostenol was added, the dosage was started at 1 $ng \cdot min^{-1} \cdot kg^{-1}$ and gradually increased to a dose of approximately 30 $ng \cdot min^{-1} \cdot kg^{-1}$ at 6 months.

Bosentan was administered when the efficacy of sildenafil was insufficient in terms of the clinical symptoms and objective findings or when the patient refused epoprostenol because of the need to insert an indwelling catheter and having a preference for oral treatment. The maximum dose of bosentan was 125 mg b.i.d. as long as all the adverse effects were tolerable.

Division of Patients Into 2 Groups According to the Addition of Epoprostenol

All the enrolled patients were divided into 2 groups according to the addition of epoprostenol. The patients given additional epoprostenol were designated as the Epo(+) group, and those without were designated as the Epo(−) group.

Statistical Analysis

The baseline characteristics, hemodynamic variables, and observation periods were compared between the 2 groups using Student's unpaired t-test. The proportion of each baseline NYHA FC was compared by the chi-square test. Comparisons of the time course of parameters between the 2 groups were made by 2-way analysis of variance for repeated measures, followed by Newman-Keuls test. The curves of the event-free rates according to the addition of epoprostenol, the event-free rates according to the composite endpoint of hospitalization for right-side heart failure and death, and the estimated survival rates were derived using the Kaplan-Meier method and compared using the log-rank test. A univariate analysis based on the proportional hazards model was used to examine the relationship between events such as death or hospitalization or the addition of epoprostenol and parameters such as the baseline characteristics and hemodynamics. The results were expressed as hazard ratios with 95% confidence intervals. A multivariate analysis based on the Cox proportional hazards regression model was used to examine the independent effect

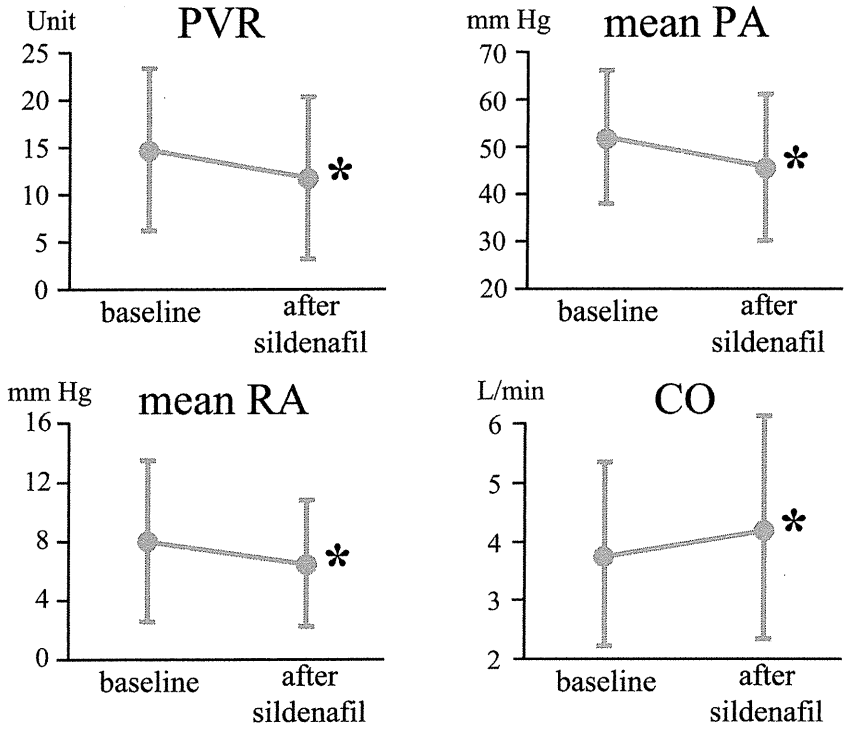

Figure 1. Hemodynamic changes during the observation period of sildenafil monotreatment in the enrolled patients as a whole. Pulmonary vascular resistance (PVR), mean pulmonary arterial pressure (mean PAP), mean right atrial pressure (mean RA), and cardiac output (CO) improved significantly with first-line sildenafil therapy. Data are the mean±standard deviation (SD). *P<0.05 vs. baseline.

of each variable on the events. The comparison of the proportion of underlying diseases between the younger group and the older group was made using chi-square test for independence. All the data are expressed as the mean±standard deviation. A value of P<0.05 was considered statistically significant.

Results

Baseline Characteristics and Changes in Hemodynamics, BNP, 6MWD, and NYHA FC in the Enrolled Patients as a Whole After Sildenafil Monotreatment

The baseline characteristics of all the patients enrolled in the study are shown in Table 1. The follow-up examinations, including right-side heart catheterization, were performed just before the addition of epoprostenol or bosentan to the treatment regimen. The patients who did not require additional treatment during the observation period were analyzed using the final follow-up data until December 2010. Therefore, our follow-up data for the hemodynamics, 6MWD, and BNP were obtained during sildenafil monotreatment. The average observation period was 21±22 months, and none of the patients were lost to follow-up.

A comparison of the hemodynamics at baseline and after sildenafil treatment is presented in Figure 1. The hemodynamic parameters, such as the PVR (14.6±8.7 vs. 11.6± 8.6 Wood units, P<0.05), mean pulmonary arterial pressure (PAP: 52.1±14.0 vs. 45.7±15.7 mmHg, P<0.01), mean right atrial pressure (RA: 8.0±5.5 vs. 6.4±4.4 mmHg, P<0.05), and cardiac output (CO: 3.7±1.6 vs. 4.2±1.9 L/min, P<0.05), improved significantly after sildenafil treatment in the enrolled patients as a whole.

Furthermore, the BNP and 6MWD at baseline and after sildenafil treatment were also compared. Some 6MWD and BNP follow-up data were missing, and some patients refused the 6MWD examination because of the presence of a gait disorder or dyspnea. The BNP (n=30) tended to be lower after sildenafil treatment, although the difference was not significant (332± 362 vs. 247±382 pg/ml, P=NS). The 6MWD results (n=16) improved significantly (352±104 vs. 422±102 m, P<0.05).

During the observation period of sildenafil monotreatment, the NYHA FC either improved (n=12, 26.1%) or was maintained (n=30, 65.2%) in 42 of 46 patients, and worsened in 4 patients (8.7%) (Table 2).

Table 2. Change in NYHA FC Between Baseline and After First-Line Sildenafil Monotreatment

Change in NYHA FC	n (%)
Improved 2 classes	0 (0)
Improved 1 class	12 (26.1)
No change	30 (65.2)
Worsened 1 class	4 (8.7)

NYHA FC, New York Heart Association functional class.

Baseline Characteristics and Hemodynamic Changes in Patients Treated With or Without Epoprostenol

The patients were divided into 2 groups based on their clinical course. The Epo(−) group (n=31; 67% of all the enrolled patients) comprised patients who did not receive epoprostenol (3 of the 31 patients additionally received bosentan), and the average follow-up period was 25±23 months. The Epo(+) group (n=15; 33% of all the enrolled patients) comprised patients who were additionally treated with intravenous epoprostenol (4 of those 15 patients additionally received bosentan), and the average follow-up period was 12±18 months. The baseline characteristics of the Epo(−) and Epo(+) groups are shown in Table 1. The age of the Epo(+) group was significantly younger than that of the Epo(−) group.

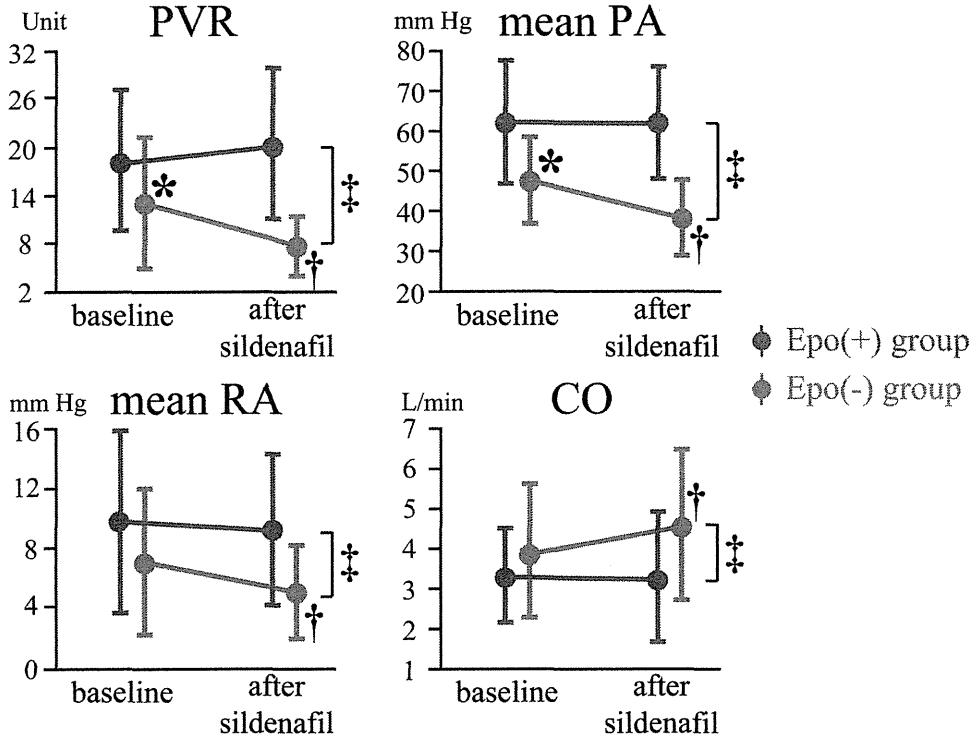

Figure 2. Hemodynamic changes during the observation period of sildenafil monotreatment among patients grouped according to the addition of epoprostenol (Epo) treatment. The red circles show the hemodynamic changes in the Epo(+) group, comprising patients treated with additional epoprostenol, and the blue circles show the hemodynamic changes in the Epo(−) group, comprising patients without additional epoprostenol treatment. At baseline, the mean PAP and PVR of the Epo(+) group were significantly higher than those of the Epo(−) group. The PVR, mean PAP, mean RA, and CO all improved significantly with sildenafil treatment in the Epo(−) group. However, these parameters did not change significantly in the Epo(+) group. The data are the mean±SD. *P<0.05 vs. baseline Epo(+) group; †P<0.05 between baseline and after sildenafil; ‡P<0.05 between the 2 groups in the time-course changes. CO, cardiac output; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance;

The hemodynamics at baseline, before the administration of sildenafil, of the 2 groups is presented in Figure 2. No significant differences in the mean RA or CO were observed at baseline. However, the mean PAP and the PVR were significantly higher in the Epo(+) group than in the Epo(−) group at baseline. All the hemodynamic parameters improved significantly after sildenafil treatment, compared with the baseline values, in the Epo(−) group (mean PAP, 47.4±10.8 vs. 38.0±9.4 mmHg, P<0.01; mean RA, 7.0±4.9 vs. 5.0±3.1 mmHg, P<0.05; PVR, 12.8±8.2 vs. 7.4±3.6 Wood units, P<0.01; CO, 3.9±1.7 vs. 4.6±1.9 L/min, P<0.05). On the other hand, no significant differences in any of the hemodynamic parameters were observed after sildenafil treatment, compared with the baseline values, in the Epo(+) group (mean PAP, 61.8± 15.3 vs. 61.7±13.9 mmHg, P=NS; mean RA, 10.1±6.1 vs. 9.3± 5.1 mmHg, P=NS; PVR, 18.2±8.7 vs. 20.3±9.4 Wood units, P=NS; CO, 3.4±1.2 vs. 3.3±1.6 L/min, P=NS). There were significant differences between the 2 groups in the time-course of changes of all 4 parameters. However, there was a significant difference in the observation period between the 2 groups, so the possibility cannot be ruled out that this difference may have affected the statistical results.

Event-Free Rate According to the Addition of Epoprostenol

"Event" was defined as the addition of epoprostenol therapy. The Kaplan-Meier event-free curve was then determined according to the addition of epoprostenol, as shown in Figure 3A. The observation period was 33±27 months. The percentage of patients treated without the addition of epoprostenol was 80%, 70%, and 63% at 1, 3, and 5 years, respectively.

During the observation period, 15 patients were treated with additional epoprostenol. In 7 of them, epoprostenol was added because of right-side heart failure. In remaining 8 patients, it was added because of deterioration in NYHA FC, worsening of clinical symptoms or objective findings, and rapid progression of PAH, although without right-side heart failure.

Furthermore, we analyzed factors associated with the addition of epoprostenol. Age, mean PAP, and PVR at baseline were related to the addition of epoprostenol according to univariate analysis, and multivariate analysis demonstrated that only age at baseline was independently related to the addition of epoprostenol (Table 3). The median age of all the patients was 40 years. The Kaplan-Meier event-free curves according to the median age demonstrated that more of the patients aged less than 40 years required the addition of epoprostenol at an earlier stage, compared with the older patients (age >40 years) (log-rank test, P<0.05) (Figure 3B). In particular, at 2 years after the start of first-line sildenafil therapy, epoprostenol was added to the treatment of approximately 20% of the patients who were older than 40 years old, but 40% of the patients who were younger than 40 years required the addition of epoprostenol. Meanwhile, we compared the proportion of underlying

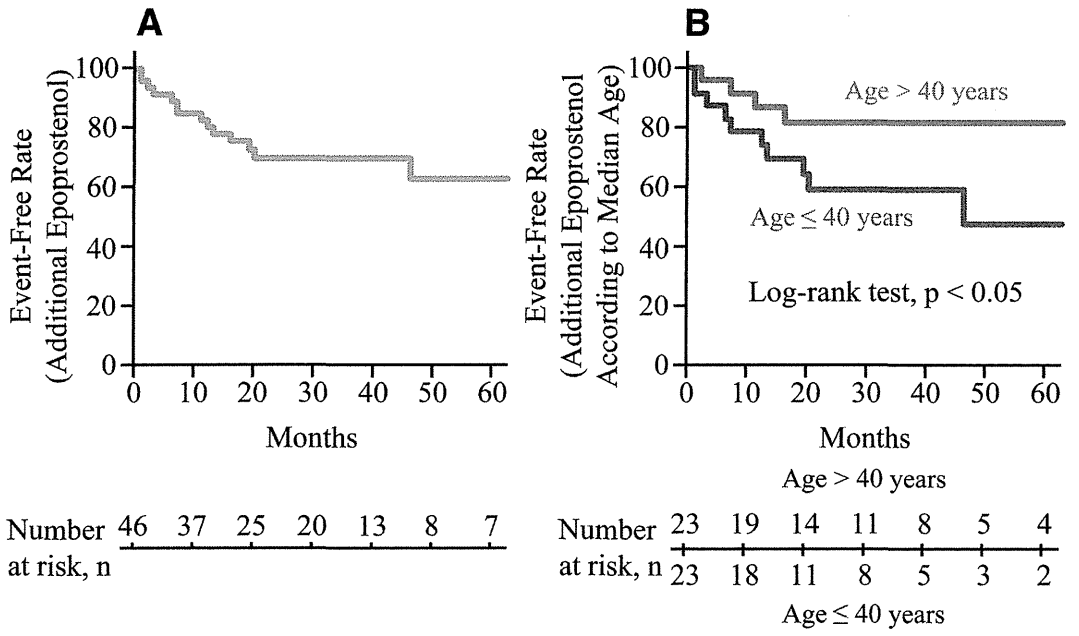

Figure 3. (A) Kaplan-Meier estimates according to the addition of epoprostenol treatment. The 1-, 3-, and 5-year rates for patients treated without the addition of epoprostenol were approximately 80%, 70%, and 63%, respectively. (B) Kaplan-Meier estimates according to the addition of epoprostenol treatment among patients grouped according to age. The overall median age was 40 years. The event-free rate among older patients (>40 years) (blue line) was significantly higher than that among younger patients (≤40 years) (red line) (P<0.05, log-rank test).

Table 3. Statistical Analysis of Variables Correlated With the Addition of Epoprostenol Treatment

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Age	0.95 (0.91–0.99)	<0.05	0.94 (0.90–0.99)	<0.05
Sex	1.15 (0.32–4.12)	NS	–	–
NYHA FC I+II/III	0.38 (0.11–1.35)	NS	–	–
mRA	1.09 (0.99–1.19)	NS	–	–
mPAP	1.07 (1.03–1.12)	P<0.05	1.05 (1.00–1.10)	NS
PVR	1.06 (1.01–1.11)	P<0.05	1.05 (0.96–1.13)	NS
CO	0.78 (0.53–1.17)	NS	–	–
6MWD	0.99 (0.99–1.00)	NS	–	–
BNP	1.00 (0.99–1.00)	NS	–	–

HR, hazard ratio; CI, confidence interval. Other abbreviations see in Table 1.

diseases between the younger group (idiopathic PAH, n=15; secondary to connective tissue disease, n=5; associated with portal hypertension, n=3) and the older group (idiopathic PAH, n=9; secondary to connective tissue disease, n=11; associated with portal hypertension, n=3). There was no significant difference between the 2 groups in the proportions of the underlying diseases of PAH.

Survival Rate

In this study, 5 patients died during the observation period; 2 of them had refused epoprostenol therapy. The estimated survival rate is shown in Figure 4A. The observation period was 44±26 months. The 5-year survival rate after first-line sildenafil treatment was approximately 81%. We analyzed the factors associated with survival. Univariate analysis demonstrated that only the mean RA was related to death (Table 4). All the patients who died during the observation period were female, and their baseline NYHA FC was III. Therefore, sex and NYHA functional class were not included in the analysis.

Event-Free Rate According to the Composite Endpoint

The event-free rate for the composite endpoint of hospitalization for right-side heart failure and death is shown in Figure 4B. The observation period was 40±26 months. More than 75% of the patients had not reached the composite endpoint at 5 years. There were no significant variables related to the event in univariate analysis.

Nine of the enrolled patients needed hospitalization because of right-side heart failure; 7 needed additional epoprostenol because of right-side heart failure and the remaining 2 patients,

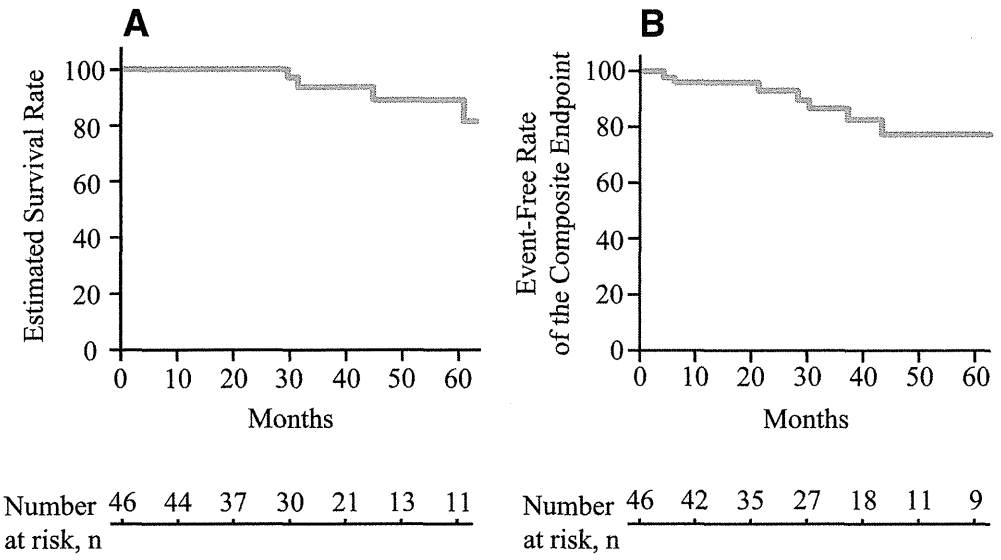

Figure 4. (A) Kaplan-Meier survival estimates for patients with pulmonary arterial hypertension (PAH) treated with first-line sildenafil therapy. (B) Kaplan-Meier estimates according to the composite endpoint of hospitalization for right-side heart failure and death.

Table 4. Statistical Analysis of Variables Correlated With Overall Survival

	HR (95%CI)	P value
Age	0.98 (0.92–1.05)	NS
mRA	1.26 (1.06–1.49)	<0.05
mPAP	1.01 (0.96–1.06)	NS
PVR	1.02 (0.92–1.13)	NS
CO	0.84 (0.32–2.18)	NS
6MWD	0.98 (0.96–1.01)	NS
BNP	1.00 (0.99–1.00)	NS

Abbreviations see in Tables 1,3.

who did not have additional epoprostenol, died because of rapid progression of right-side heart failure in the short term after hospitalization.

Discussion

This study demonstrated the long-term outcome of sildenafil administration as a first-line therapy. We found that: (1) all hemodynamic parameters improved significantly after sildenafil treatment in the enrolled patients as a whole; (2) more than 60% of the enrolled patients did not require the addition of epoprostenol for 5 years; (3) the patients who required additional epoprostenol were younger and had more severe hemodynamic characteristics at baseline; and (4) more than 75% of the patients did not reach the composite endpoint of hospitalization for right-side heart failure and death for 5 years.

Previous studies have demonstrated the efficacy of sildenafil for the treatment of PAH.[11,12,17–24] In the evidence-based algorithm established at Dana Point in 2008, sildenafil was defined as a first-line drug for PAH in patients with WHO functional class II or III.[16] In the present study, all the hemodynamic parameters and exercise capacity, as evaluated using the 6MWD, improved significantly after sildenafil treatment in the enrolled patients as a whole, and the BNP level tended to decrease. These results suggest that sildenafil is effective for the treatment of PAH, even when it is administered as a first-line therapy, and are consistent with the evidence-based algorithm. Furthermore, we analyzed the changes of NYHA FC during the observation period of sildenafil monotreatment (Table 2). The SUPER-2 study reported that the majority of patients who entered the SUPER-1 trial improved or maintained their FC and 6MWD.[12] Similar to the results of SUPER-2 study, the present study demonstrated that sildenafil monotreatment resulted in maintenance or improvement of NYHA FC in the majority of all enrolled patients (91.3%). Therefore, we consider that these results demonstrate the superiority of sildenafil as a first-line drug for PAH. Moreover, we analyzed the changes in hemodynamic parameters according to the addition of epoprostenol. In our results, all the hemodynamic parameters improved significantly after sildenafil treatment in the Epo(−) group, whereas no significant differences in any of the hemodynamic parameters were observed in the Epo(+) group. The baseline PVR and mean PA were significantly higher in the Epo(+) group compared with the Epo(−) group. These results suggest that first-line sildenafil monotreatment only was not sufficient to improve hemodynamics in patients who were more severe at baseline. However, this can lead to the suggestion that any hemodynamic parameter in the Epo(+) group was not significantly worsened, meaning that sildenafil treatment contributes to maintenance of clinical stability even in the baseline severe patients. It is consistent with maintenance of NYHA FC shown in Table 2.

Furthermore, in the present study, we focused on the occurrence of events, such as the addition of epoprostenol and the composite endpoint of hospitalization for right-side heart failure and death. Epoprostenol is recognized as the most powerful and effective treatment for PAH.[25,26] However, epoprostenol requires continuous infusion via an indwelling catheter, limiting the quality of life of the patient and a risk of

catheter infection. Thus, analyzing the clinical course of additional treatment with epoprostenol after first-line sildenafil monotreatment and investigating the characteristics of high-risk patients are important. In the present study, the age of the patients who required additional treatment with epoprostenol was significantly younger than the other patients. The baseline hemodynamics suggest that the severity of PAH among the patients who required additional treatment with epoprostenol was more severe than that of other patients. Furthermore, in the multivariate analysis, age at baseline was the only variable that correlated with the addition of epoprostenol. More patients under the age of 40 years (the median age) required the addition of epoprostenol treatment at an earlier stage, compared with the older patients. Thus, the severity of the disease may progress more rapidly among younger patients. There was no significant difference in the proportions of underlying causes of PAH between the younger and older patients. These findings suggest that patients who are younger or whose severity assessment at baseline is severe have a strong possibility of requiring the addition of epoprostenol treatment, and therapeutic efficacy may need to be frequently evaluated after the start of first-line sildenafil treatment among these high-risk patients to ensure timely introduction of epoprostenol treatment. Baseline NYHA FC did not influence the requirement of additional epoprostenol therapy in the present study, which suggests that the introduction of epoprostenol is prescribed by the degree of progression of disease rather than by the baseline disease status.

In this study, more than 75% of the patients did not reach the composite endpoint of hospitalization for right-side heart failure and death for 5 years after the start of first-line sildenafil therapy. In our study, 20%, 30%, and 37% of the enrolled patients received additional treatment with epoprostenol at 1, 3, and 5 years, respectively, after the start of first-line sildenafil therapy. These findings raise the possibility that combination therapy should be considered for patients who fail to improve or whose condition deteriorates after the start of first-line sildenafil therapy and that a fairly good prognosis can be expected if the severity assessment and the timing of epoprostenol introduction are appropriate.

The estimated 5-year survival rate after the start of first-line sildenafil therapy was approximately 81%. Several studies have demonstrated the survival in patients with PAH treated in the modern management era.[27–30] Compared with the recent studies, survival in this study was relatively better and was obtained when sildenafil was used as a first-line monotherapy. Therefore, it cannot be compared simply with the survival data of recent studies in the modern management era. However, the baseline NYHA FC III/IV in our study was 65% (there were no patients with NYHA FC IV in this study), whereas that in the recent studies was approximately 80%.[27,28,30] The difference in baseline NYHA FC may explain the difference between the survival in our study and that in other recent studies. In the present study, all of the patients who died were in NYHA FC III at baseline, demonstrating that baseline NYHA FC is generally a strong prognostic factor in the mortality of PAH patients. Our statistical analysis of variables associated with overall death demonstrated that only the mean RA at baseline was related to outcome, consistent with the results of several previous reports demonstrating that the mean RA strongly correlated with the outcome of patients with PAH.[29,31] Variables arising from right-side overload, such as the mean RA, may be better prognostic indicators, even when sildenafil is used as a first-line therapy.

Study Limitations

The study limitations are the insufficient observation period and small population. A study with a longer observation period and a larger number of patients is needed to confirm the present results and to ensure their accuracy.

Conclusions

We have shown the long-term outcome of sildenafil when used as a first-line therapy for patients with PAH. Our results suggest that sildenafil is emerging as a promising first-line drug for the treatment of PAH.

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●原 著

間質性肺炎における肺気腫の合併と肺高血圧，%FEV_1との関連

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要旨：特発性肺線維症（idiopathic pulmonary fibrosis；IPF）は予後が悪く，肺高血圧を合併すると予後がさらに悪くなる．IPFの重症度の示標としてFVCがよく用いられるが，肺気腫を合併するとFVCが比較的保たれ重症例を見落とす可能性もある．本研究において，心エコーによって得られる三尖弁圧較差（PG）を肺高血圧の指標とし，IPFにおけるPGと呼吸機能パラメーターとの相関を検討した．肺気腫を合併していない間質性肺炎群（35例）ではPGと%FVCとの間に有意な逆相関があったが，肺気腫を合併した7例を含めた42例で解析すると相関が消失した．またPGと%FEV_1との間には，肺気腫を合併していない症例の解析では有意な相関はなかったが，肺気腫合併例を含む全例の解析では有意な逆相関を認めた．以上より，慢性経過のIPFの診療において，FVCのみならず，%FEV_1にも注目し，肺気腫や肺高血圧の合併を検索することが重要であると考えられた．

キーワード：特発性肺線維症，肺気腫合併間質性肺炎，%1秒量，三尖弁圧較差，肺高血圧
Idiopathic pulmonary fibrosis, Combined pulmonary fibrosis and emphysema, %FEV_1, Pressure gradient maximum in tricuspid valve (PG), Pulmonary hypertension

緒　言

特発性肺線維症（idiopathic pulmonary fibrosis；IPF）の重症度や重症度の経時的変化をみるには肺活量（vital capacity；VC）や努力肺活量（forced vital capacity；FVC）を用いることが一般的であるが[1)~4)]，肺高血圧の合併がある場合にはCO肺拡散能力（diffusing capacity of carbon monoxide；DL_{CO}）の測定が有用と言われている[5)~7)]．最近，肺気腫合併のIPFの報告が増えた[8)~10)]．その予後は悪く，その原因として肺高血圧を合併する頻度が高いことが大きな要因となっている．

IPFに肺気腫を合併すると，VCやFVCは病態の重症度に比較して保たれていることが多く[8)10)]，重症度を知るためにはDL_{CO}を測定することが重要である．しかしDL_{CO}の測定はVCやFVCほど容易ではなく，制約を受けることがある．IPFでは1秒率（FEV_1/FVC）はむしろ正常人より高値であるが，IPFに肺気腫を合併した場合は閉塞性障害が加わり%VCや%FVCよりも対標準1秒量（%FEV_1）の方が病態や重症度をより正確に反映している可能性がある．しかし%FEV_1に関して検討した報告はない．今回，IPFの重症度の指標を肺高血圧に求め，肺気腫を合併するIPF（IP with emphysema）と肺気腫を合併していないIPF（IP without emphysema）における肺高血圧と%FEV_1の関連を検討し，重症度評価における%FEV_1の有用性を検討した．

対象および方法

症例の選択

2007年4月から2010年3月まで当院に間質性肺炎（interstitial pneumonia；IP）の精査目的で入院した全症例の中から，①CT所見から通常型間質性肺炎（usual interstitial pneumonia；UIP）が考えられる，②fine cracklesを聴取する，③明らかな環境曝露歴がない，④膠原病や薬剤をはじめとして間質性肺炎の原因となる要因を見出せない，⑤スパイロメトリーと肺気量分画を測定している，⑥心エコー検査を行っている，⑦肺癌や肺炎を合併していない，⑧間質性肺炎の急性増悪を認めず病態が安定している，という8項目を満たす42名を選択し，clinical-IPFとして検討対象とした．

呼吸機能，心機能～IP with emphysema群とIP without emphysema群との比較

入院中の安定した状態で呼吸機能検査，心エコー検査，胸部CT検査を行った．呼吸機能検査は肺気量分画，スパイログラムを全症例で行い，検査可能な症例にはDL_{CO}を測定した．心エコー検査により三尖弁圧較差（pressure gradient maximum in tricuspid valve；PG）を測定した．

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（受付日平成23年2月3日）

Table 1 Clinical features, respiratory function data and echo cardiographic data

	whole cohort of patients (n=42)	IP without emphysema (n=35)	IP with emphysema (n=7)	p values*
Number of patients (male/female)	30/12	23/12	7/0	
age	69±13	68±14	74±3	0.17
Body Height (cm)	159±7.4	159±7.4	160±7.8	0.65
Body Weight (kg)	55±11	55±11	57±11	0.43
FVC (absolute volume, L)	2.19±0.69	2.10±0.64	2.61±0.83	0.11
FVC % predicted	73±21	71±20	83±27	0.14
FEV_1 (absolute volume, L)	1.78±0.53	1.76±0.54	1.9±0.53	0.64
FEV_1 % predicted	74±20	74±20	75±18	0.87
FEV_1/FVC (%)	82±11	84±10	75±15	0.15
DL_{CO} (mL/min/mmHg)	8.76±3.65 (n=35)	9.25±3.59 (n=29)	6±2.78 (n=6)	0.035
DL_{CO} % predicted	57±21 (n=35)	61±20 (n=29)	42±18 (n=6)	0.06
DL_{CO}/V_A (mL/min/mmHg/L)	3.35±1.20 (n=35)	3.65±1.05 (n=29)	1.88±0.67 (n=6)	0.001
DL_{CO}/V_A % predicted	75±26 (n=35)	81±23 (n=29)	44±16 (n=6)	0.0016
EF (%)	67±7	67±7	69±8	0.3
PG (mmHg)	16.4±16.1	14.8±15.7	24±17	0.14

Data show means and standard deviations. *Mann-Whitney's U test (IP without emphysema vs. IP with emphysema).
EF; ejection fraction, PG; pressure gradient maximum in tricuspid valve

推定肺動脈収縮期圧はPG＋10 mmHgであるが，今回はPGを肺高血圧の指標とした．また駆出率（ejection fraction；EF）を測定し心機能が正常であることを確認した．

胸部CTにて上肺野の任意スライスにおいて低吸収域が25%以上分布するものを気腫性変化と定義し，気腫性変化を伴わないIPF（IP without emphysema）群と気腫性変化を伴うIPF（IP with emphysema）群の2群に分け上述の項目について2群間の差異を検討した．

肺高血圧と呼吸機能，重症度スコア，CTスコアとの相関

肺高血圧の程度と呼吸機能パラメーターとの関連を検討するために，PGと呼吸機能（%FVC，%FEV_1，%DL_{CO}）との相関の強さをIP without emphysema群，IP with emphysemaとIP without emphysemaを一緒にしたIP全症例群でそれぞれ検討した．IP with emphysema群は症例数（n=7）が少なかったため，IP with emphysema群単独ではPGと呼吸機能の相関を検討することはできなかった．

呼吸機能の他に，日本呼吸器学会（JRS）によるIPFの重症度分類[11]やKazeroonilらによるIPFのCTスコア[12]を用いて症例を群分けし，それぞれについてPGとの相関を検討した．

統計解析

IP with emphysema群とIP without emphysema群における年齢，体重，呼吸機能検査パラメーターやPG値などの数値データは平均値±標準偏差で表記し，群間の有意差はMann-WhitneyのU検定を用いた．またPGと呼吸機能検査との相関分析はPearson積率法によった．PGとJRSの重症度スコア，CTスコアとの相関はSpearman's rank correlation testを用いて検討した．

結　果

IP without emphysema群とIP with emphysema群との比較

IP without emphysema群は35名よりなり，男性23名，女性12名であった．IP with emphysema群は男性7名であり女性はいなかった．両群の年齢，身長，体重，呼吸機能検査成績，EF，PGをTable 1に示している．

IP without emphysema群における年齢，身長，体重はそれぞれ68±14歳，身長159±7.4 cm，体重55±11 kgであった．一方IP with emphysema群ではそれぞれ74±3歳，160±7.8 cm，57±11 kgであり，両群間に差はなかった．

FVC，%FVCに両群間の有意差はないものの，IP with emphysema群で大きい傾向があった．FEV_1/FVCも両群間で有意差はなかったがIP with emphysema群において低い傾向があった．しかし%FEV_1は両群間でほとんど差がなかった．%DL_{CO}がIP with emphysema群で低下していたが，有意差はなかった．しかし%DL_{CO}/VAはIP with emphysema群で有意に低値であった．

EFは両群間で差を認めなかった．三尖弁圧較差（PG＞0）を認めた症例はIP without emphysema群で23例（55%），IP with emphysema群では5例（71%）あり，PG＋10 mmHgで求められる推定肺動脈収縮期圧が40 mmHg以上の肺高血圧を示す症例はそれぞれ6例（14%），4例（57%）であった．PGはIP with emphysema群で高い傾向があった（Table 1，Fig. 1）．

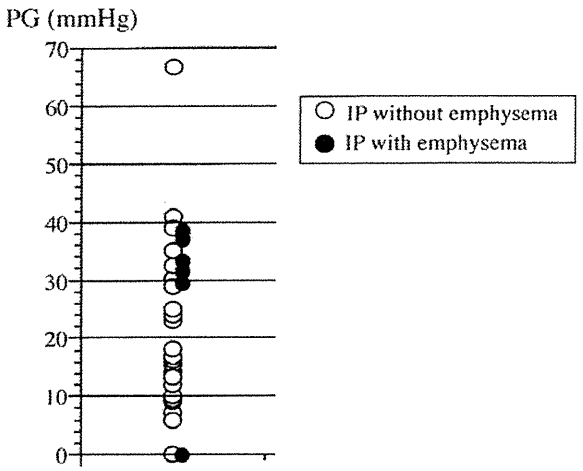

Fig. 1 Distribution of maximum pressure gradient (PG) in the tricuspid valve. In IP without emphysema, PG>0 mmHg was noted in 23 patients (55%), and pulmonary hypertension (40 mmHg or more of systolic pulmonary pressure estimated by PG plus 10 mmHg) was observed in 6 (14%). In IP with emphysema, PG>0 mmHg was noted in 5 patients (71%), and pulmonary hypertension was observed in 4 patients (57%).

PG と呼吸機能との相関

IP without emphysema 群では PG と %FVC との間に有意な逆相関を認めたが(r=−0.352, p<0.05), IP without emphysema 群と IP with emphysema 群を含めた全体で解析すると相関がより緩やかになった(r=−0.281, p=0.07) (Fig. 2a). PG と $\%FEV_1$ との相関をみると, IP without emphysema 群のみでは有意差のない緩やかな逆相関 (r=−0.319, p=0.061) であったが, IP with emphysema 群を含めた全体では有意な逆相関(r=−0.313, p<0.05) になった (Fig. 2b). 次に PG と $\%DL_{CO}$ との相関を検討した. IP without emphysema 群のみの解析では相関がみられなかった (r=−0.031, p=0.874). また IP with emphysema 群を含めた全体で解析しても, 有意な負の相関関係はなかった (r=−0.193, p=0.267) (Fig. 2c).

PG と JRS 重症度スコア, CT スコアとの相関

IPF の重症度を JRS に従い分類すると, 重症度 I：17 例 (IP without emphysema 14 例, IP with emphysema 3 例), 重症度 II：9 名 (9 例, 0 例), 重症度 III：6 例 (5 例, 1 例), 重症度 IV：10 例 (7 例, 3 例) であった.

一方 Kazerooni らの CT スコアを用いて分類すると, fibrosis score 0：なし, fibrosis socre 1：7 例(IP without emphysema 7 例, IP with emphysema 0 例), fibrosis score 2：23 例 (19 例, 4 例), fibrosis score 3：10 例 (7 例, 3 例), fibrosis score 4：2 例 (2 例, 0 例), fibrosis score 5 はなかった. GGO score 0：なし, GGO score 1：13 例(IP without emphysema 10 例, IP with emphysema 3 例), GGO score 2：23 例(20 例, 3 例), GGO score 3：6 例 (5 例, 1 例), GGO score 4 と 5：なし, という結果であった.

以上のように群分けした JRS 重症度スコア, CT score と PG との相関を検討したが有意な相関は認めなかった.

予後

2010 年 12 月までの追跡調査で 15 例の死亡が確認された. 内訳は間質性肺炎の増悪 10 例, 肺癌 2 例, 大腸癌 2 例, 脳血管障害 1 例であった. 生存者中の 2 例は肺癌を発症し外科手術が行われた. 対象患者のエントリー期間が 2007 年 4 月から 2010 年 3 月までであり, 予後の調査期間が 2010 年 12 月まで(平均追跡期間 2 年 4 カ月, IP without emphysema 群 2 年 5 カ月, IP with emphysema 群 1 年 10 カ月) であったため調査期間の差が大きく, 生命予後との関連性を見いだすことはできなかった.

考　察

IPF は予後が悪く, 肺高血圧を合併するとさらに予後が悪くなることが知られている[5)6)13)14)]. また肺気腫を合併した IPF も予後が悪い. その理由として, 肺高血圧の合併が予後と関連していることが明らかになってきた[8)9)]. 従って IPF の診療において, 肺気腫や肺高血圧の合併の有無を把握することが特に重要である. 本論文において, IPF の重症度の指標として肺高血圧をとりあげ, ルーチンで行われる呼吸機能検査のどのパラメーターと相関しているのか検討することにした. 相関を検討するに当たって今回の検討対象とした IPF を, 肺気腫を合併した IP 群と肺気腫を合併していない IP 群とに分け, 肺高血圧とより関連の深い呼吸機能パラメーターが何であるのか, また何れの群にその傾向があるのかを明らかにすることを本研究の主題とした.

肺高血圧の診断は右心カテーテル検査がゴールドスタンダードである[5)]が, 侵襲が大きく, 心エコー検査で代用[6)]されることが多い. 本研究においても心エコー検査で得られる PG を肺高血圧の定量的評価に用いた.

IPF の重症度とその経時的変化をみる呼吸機能検査としては VC や FVC, DL_{CO} などが一般的であり, %VC や %FVC は最も信頼性の高い予後因子とされている[1)~5)]. また VC や FVC は簡便な検査法であり, 設備投資も少なくてすみ, 小規模の病院でも容易に行える利点がある. しかし IPF に気腫性変化を伴うと VC や FVC が比較的に保たれ重症度を見落とす可能性がある[8)10)]. IPF は牽引性気管支拡張のため FEV_1/FVC がむしろ正

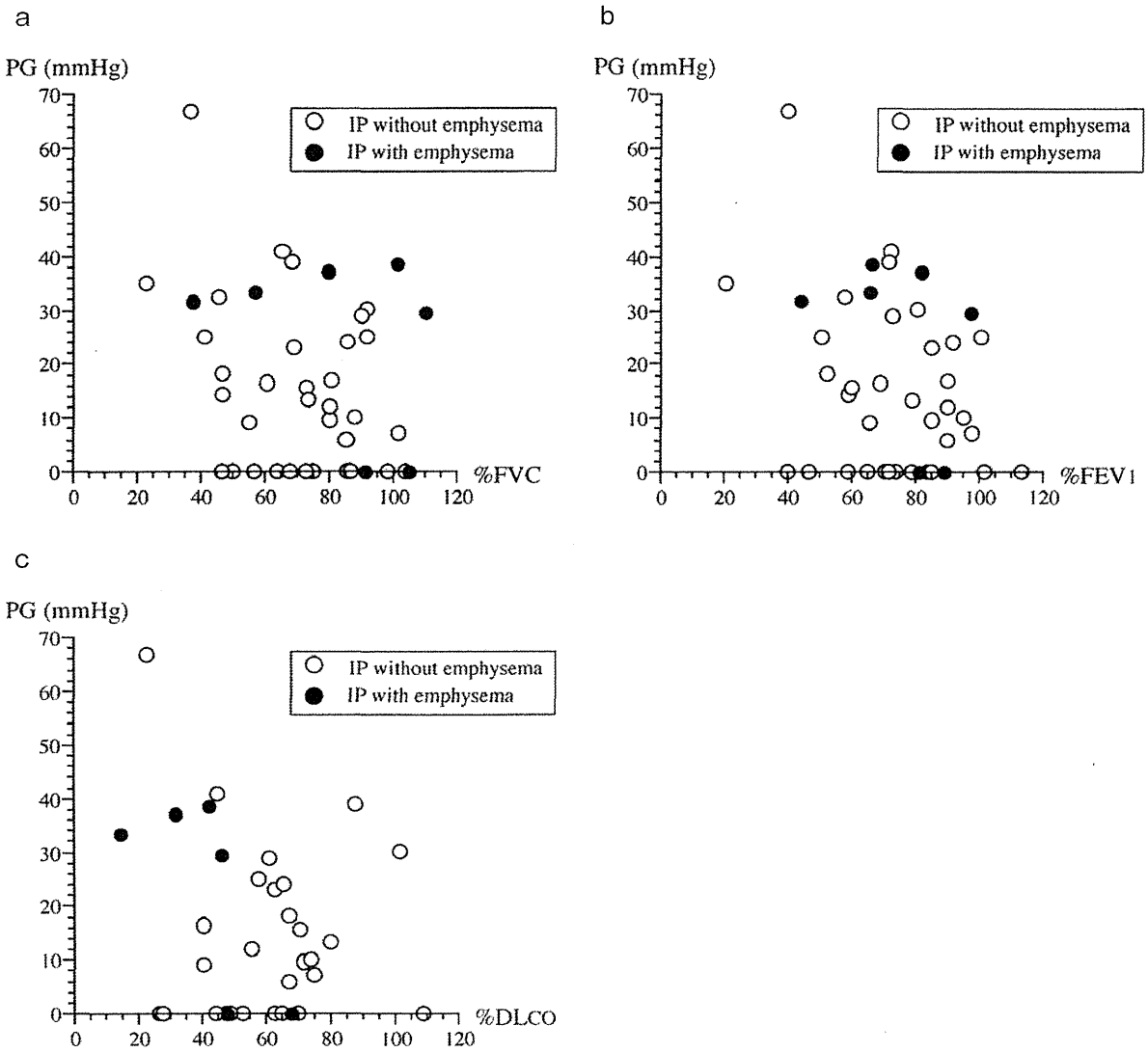

Fig. 2 Correlation between PG and %FVC, $\%FEV_1$, and %DLco. In patients with IP without emphysema, PG was inversely correlated with %FVC (Fig. 2a). However, when analyzed in the whole cohort of patients (patients with IP with or without emphysema), the inverse correlation between PG and %FVC became weak without significance (Figs. 2a). Patients with IP without emphysema had a weak and inverse correlation between PG and $\%FEV_1$, but without significance (Fig. 2b). When analyzed using the whole cohort of patients, there was an inverse and significant correlation between PG and $\%FEV_1$ (Fig. 2b). There was no significant correlation between PG and %DLco in the analysis using patients with IP without emphysema as well as using the whole cohort of patients (Fig. 2c).

常人より高値であるが，気腫性変化が加わると$\%FEV_1$は低下すると考えられる．

今回の検討でも，気腫性変化を含まないIP群のみでは%FVCはPGと有意な逆相関の関係にあったが，気腫性変化を含んだ群が加わると相関がより緩やかになった．一方%FVCと同様に簡便に算出できる$\%FEV_1$は気腫性変化を含まないIP群においてPGとの間に有意な相関は無かったが，気腫性変化を含んだ群が加わると逆相関が有意になった．すなわちIP without emphysema群とIP with emphysema群ではPGと$\%FEV_1$の分布パターンが異なり，両者を併せることにより，全体の分布が形作られていることを示している．これは一般臨床の場において%FVCが保たれていても$\%FEV_1$を注意深く見る必要性を示している．

確認されたPGと$\%FEV_1$との間の逆相関は，IP without emphysema群とIP with emphysema群との患者比に依存するのかもしれない．今回の患者比は35：7であったがこれが変わることによって相関も変化する可能性がある．今後さらに検討を要する課題である．何れにせよ%FVCが保たれていても$\%FEV_1$が低いIPF患者

は気腫性変化の合併を考え胸部CT検査や，肺高血圧の精査などを積極的に行っていくべきであると考えられた．

今回の検討対象はCT上，非特異性間質性肺炎（non-specific interstitial pneumonia；NSIP）よりもUIPをより考えやすい症例に絞っている．UIPとその他の慢性経過のIPの鑑別には外科生検による病理組織の検討がのぞましいが，今回は症例数に限りがあるので，病理診断をエントリーの基準にしなかった．従って今回の検討にNSIPや剝離性間質性肺炎などの症例が含まれている可能性は否定できない．しかし慢性経過の線維化型間質性肺炎が肺気腫を合併した際に生じる生理学的特徴は，肺気腫を合併していない場合と同様にUIPに類似していると考えて差し支えないだろう．

IPFにおいて肺高血圧とよく相関する呼吸機能検査はDL_{CO}といわれている[5][6]が，DL_{CO}はどの病院でも簡単に行える検査ではなく，また極端に肺気量が低下した重症例では実施できない．今回提示したデータにおいて，IP without emphysema群の三尖弁圧較差を認めない症例(PG＝0)をみると$\%DL_{CO}$のバラツキが大きく(Fig. 2c)，肺高血圧と$\%DL_{CO}$の間に有意な負の相関を検出できなかった．

PGとJRSの重症度スコアとの間に有意な相関が認められなかったが，JRSの重症度には肺高血圧を含め複数の因子が関与しているためと考えられた．PGとCT scoreの間にも有意な相関がなかったが，今回の症例ではCT scoreにおける症例数のバラツキが大きかったことが一因と考えられた．

まとめ

慢性経過のIPFを気腫の有無に拘わらず，両者をまとめて検討すると肺高血圧が進むと$\%FEV_1$が低下するという相関関係を見いだした．日常臨床のIPFの診療においては，%FVCの低下のみならず，$\%FEV_1$の低下にも注目し，気腫性変化や肺高血圧の存在を想定し，積極的に胸部CTや心エコー検査を行う必要がある．

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Abstract

Relationship between combined emphysema, pulmonary hypertension and %FEV$_1$ in patients with idiopathic interstitial pneumonia

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The prognosis of idiopathic pulmonary fibrosis (IPF) is poor, and it deteriorates when it is complicated with pulmonary hypertension (PH). Forced vital capacity (FVC) is a useful parameter for evaluating the disease status of interstitial pneumonia (IP). However, in patients with IP complicated with emphysema, the disease severity can be overlooked because of relatively well preserved FVC. We investigated the correlation between the maximum pressure gradient (PG) in the tricuspid valve using echocardiographic measurements and pulmonary function tests in patients with IP without emphysema and in those with IP with emphysema. There was an inverse correlation between PG and %FVC in patients with IP without emphysema. However, the above inverse correlation between PG and %FVC mentioned above disappeared when analyzed in the whole cohort of patients (n = 42) consisting of IP without emphysema (n = 35) and IP with emphysema (n = 7). Patients with IP without emphysema did not show a correlation between PG and %FEV$_1$, but when analyzed using the whole cohort of patients an inverse correlation between PG and %FEV$_1$ was observed ($p < 0.05$). In clinical practice, not only FVC, but also %FEV$_1$ is a valuable parameter in investigating the complication of emphysema and PH in patients with chronic idiopathic interstitial pneumonia.

厚生労働科学研究費補助金難治性疾患克服研究事業

呼吸不全に関する調査研究

平成 23 年度～ 25 年度　総合研究報告書
研究成果の刊行物・別刷

発　　行　平成 26 年 3 月 26 日
厚生労働科学研究費補助金
難治性疾患克服研究事業
呼吸不全に関する調査研究
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印　　刷　ユニバース印刷