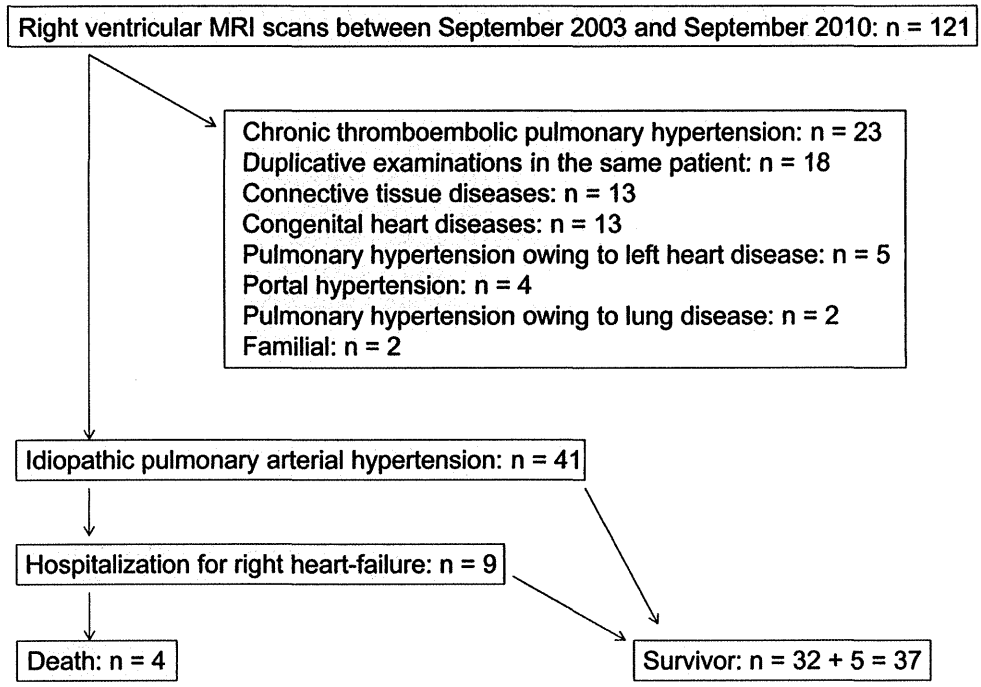

Figure. Study profile.

correcting for the patient's body surface area. The RVEF and LVEF were determined by dividing the systolic volume by the right and left end-diastolic volumes, respectively.

Right Heart Catheterization

A diagnostic right-heart catheterization was performed using a balloon-tipped, flow-directed 7F Swan-Ganz catheter. The patient was stable, lay supine, and breathed room air. The PAP, right atrial pressure, PCWP, cardiac output, PVR index and mixed venous oxygen saturation were measured. Blood was sampled with the catheter positioned inside the main pulmonary artery. The arterial oxygen saturation was measured using blood sampled from the radial or femoral artery. The cardiac output was assessed using the Fick method, and the PVR was calculated using the following formula: (mPAP−PCWP)/cardiac output. All of the eligible patients had right-heart catheterization examinations within 6 months of their CMR examinations.

Statistical Analysis

All data are expressed as the mean±standard deviation (SD). The hazard ratios of the factors potentially associated with a first hospitalization (primary endpoint) or death after hospitalization (secondary endpoint), such as age, sex, NYHAFC, biochemical markers and the CMR measures, were calculated using a Cox proportional-hazards model. First, the hazard ratio and 95% confidence interval (CI) for each factor were estimated using a univariate model. The following variables were tested: age, sex, the NYHAFC, the distance in a 6-min walk test (6MWT), the plasma brain natriuretic peptide (BNP) level,[14] the serum uric acid level,[15] the cardiac index, the stroke volume index (SVI), the RV mass index (RVMI), the LV mass index (LVMI), RVEF, LVEF, the RV end-systolic volume index (RVESVI), the RV end-diastolic volume index (RVEDVI), the LV end-systolic volume index (LVESVI) and the LV end-diastolic volume index (LVEDVI). Catheterization was not performed on the same day as the CMR examination, so the right heart catheterization variables were not tested. To examine the robustness of the univariate results, multivariate Cox regression analyses with step-wise variable selection were performed. A multivariate Cox model with time-dependent covariates was also used to evaluate the effects of any concomitant medications during the follow-up period.

We added exploratory analyses with respect to the endpoint of clinical worsening, including all clinical events (additional therapies in response to clinical worsening, hospitalization and death) with a univariate Cox regression model.

All of the confidence intervals were estimated at the 95% confidence level, and significance was set at a $P<0.05$ (2-tailed). All of the data were analyzed using a commercially available software program (SAS version 9.1, Cary, NC, USA).

Results

Patients' Characteristics

The patients' demographic and baseline CMR data are summarized in **Table 1**. The right heart catheterization measurements collected within 6 months of each CMR examination are also shown in **Table 2**. Over a mean follow-up period of 1,350±769 (range: 196–2,654) days, 9 of the 41 patients were hospitalized for right heart failure; 4 of the 9 hospitalized patients died and none died from non-cardiopulmonary causes (**Figure**). In 29 patients (71%), the medical therapy was changed because of clinical worsening. Intravenous prostacyclin, endothelin-receptor antagonists and sildenafil were added in 14, 13 and 18 patients, respectively (**Table 1**). All the patients were

Table 3. Univariate Analysis of Factors With Cox Regression Model for Hospitalization and Mortality

	Hospitalization for right HF				Mortality			
	HR	95%CI		P value	HR	95%CI		P value
		Lower	Upper			Lower	Upper	
Demographic variables								
Age (year)	1.01	0.97	1.05	0.716	1.04	0.98	1.12	0.193
Sex (M/F)	2.00	0.54	7.48	0.301	2.36	0.33	16.73	0.392
CMR measurements								
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	0.81	0.33	1.98	0.645	0.46	0.09	2.43	0.358
SVI (ml/m^2)	1.01	0.97	1.05	0.645	0.98	0.91	1.06	0.681
RVMI (g/m^2)	0.96	0.88	1.06	0.444	0.96	0.88	1.05	0.401
LVMI (g/m^2)	1.07	1.02	1.12	0.008*	1.03	0.97	1.10	0.386
RVEF (%)	0.97	0.92	1.03	0.351	0.96	0.87	1.05	0.369
LVEF (%)	0.95	0.88	1.02	0.175	0.97	0.86	1.08	0.527
RVEDVI (ml/m^2)	1.02	1.00	1.03	0.012*	1.02	1.00	1.04	0.028*
RVESVI (ml/m^2)	1.02	1.00	1.03	0.014*	1.03	1.00	1.05	0.021*
LVEDVI (ml/m^2)	1.03	1.00	1.05	0.019*	1.00	0.95	1.04	0.932
LVESVI (ml/m^2)	1.04	1.00	1.07	0.027*	1.00	0.92	1.08	0.907
Functional status								
NYHAFC	4.61	1.69	12.55	0.003*	6.23	1.29	30.13	0.023*
6MWT (m)	1.00	0.99	1.01	0.467	1.00	0.98	1.02	0.799
Biochemical markers								
Plasma BNP (pg/ml)	1.00	1.00	1.00	0.129	1.00	1.00	1.00	0.197
Serum uric acid (mg/dl)	1.25	0.98	1.59	0.075	1.38	0.95	2.00	0.087

*P<0.05.
HF, heart failure; HR, hazard ratio; CI, confidence interval. Other abbreviations as in Table 1.

Table 4. Multivariate Analysis of the Factors for Hospitalization Using a Cox Regression Model

	Hospitalization for right HF			
	HR	95%CI		P value
		Lower	Upper	
RVEDVI (ml/m^2)	1.02	1.00	1.03	0.010*
LVEDVI (ml/m^2)	1.02	1.00	1.05	0.052
NYHAFC	7.66	2.05	28.61	0.002*

*P<0.05.
Abbreviations as in Tables 1,3.

Table 5. Multivariate Analysis of the Factors for Mortality Using a Cox Regression Model

	Mortality			
	HR	95%CI		P value
		Lower	Upper	
RVEDVI (ml/m^2)	1.03	1.00	1.05	0.020*
NYHAFC	21.85	1.46	328.14	0.023*

*P<0.05.
Abbreviations as in Tables 1,3.

Table 6. Univariate Analysis of the Therapies Using Cox Regression Models for Hospitalization and Mortality

Therapy	Hospitalization for right HF				Mortality			
	HR	95%CI		P value	HR	95%CI		P value
		Lower	Upper			Lower	Upper	
Intravenous prostacyclin	2.87	0.77	10.72	0.117	2.09	0.29	14.90	0.461
Endothelin-receptor antagonists	0.52	0.14	1.96	0.334	0.23	0.02	2.24	0.207
Sildenafil†	–	–	–	(0.994)	–	–	–	(0.996)
Calcium antagonists	1.02	0.21	4.92	0.981	1.18	0.12	11.36	0.885

†All hospitalized or deceased patients were treated with sidenafil.
Abbreviations as in Table 3.

treated with oral anticoagulants.

Predictors of Hospitalization for Right Heart Failure or Mortality

The univariate Cox regression analyses suggested that LVMI, LVEDVI, LVESVI, RVEDVI, RVESVI and NYHAFC were associated with the time to hospitalization (primary endpoint) in the IPAH patients and that RVEDVI, RVESVI and NYHAFC were associated with the time to death (secondary endpoint) (**Table 3**). The RVEDVI was closely related to the RVESVI, and the LVEDVI was closely related to the LVESVI and LVMI; therefore, multivariate Cox regression analyses were performed using RVEDVI, LVEDVI and NYHAFC as predictors of the hazard of hospitalization and RVEDVI and

Table 7. Multivariate Cox Model for Hospitalization With Time-Dependent Covariates

Therapy/Variable	Hospitalization for right HF			
	HR	95%CI		P value
		Lower	Upper	
Intravenous prostacyclin				
RVEDVI (ml/m²)	1.02	1.01	1.04	0.008*
NYHAFC	5.02	1.17	21.54	0.030*
Time-dependent covariate (intravenous prostacyclin)	4.60	0.96	21.92	0.055
Endothelin-receptor antagonists				
RVEDVI (ml/m²)	1.02	1.01	1.03	0.005*
NYHAFC	9.24	2.16	39.43	0.003*
Time-dependent covariate (endothelin-receptor antagonists)	2.47	0.47	12.98	0.286
Sildenafil†				
RVEDVI (ml/m²)	1.02	1.00	1.03	0.009*
NYHAFC	5.21	1.51	18.02	0.009*
Time-dependent covariate (sildenafil)†	–†	–†	–†	(0.995)†
Calcium antagonists				
RVEDVI (ml/m²)	1.02	1.00	1.03	0.009*
NYHAFC	8.01	2.11	30.49	0.002*
Time-dependent covariate (calcium antagonists)	0.52	0.10	2.70	0.438

*P<0.05. †Because of a high percentage of patients treated with sildenafil (88%), it was impossible to evaluate the effect of sildenafil by means of multivariate Cox model with time-dependent covariate.
Abbreviations as in Tables 1,3.

NYHAFC as predictors of mortality. The multivariate analyses using step-wise variable selection showed that the RVEDVI and NYHAFC were independent predictors of the hazards of both hospitalization and mortality (**Tables 4,5**).

There was no significant relationship between the endpoints and the type of therapy (ie, intravenous prostacyclin, endothelin-receptor antagonist, sildenafil and calcium antagonists; **Table 6**). Furthermore, the effects of RVEDVI and NYHAFC on hospitalization were not substantially changed in a time-dependent Cox model with additional adjustments for any concomitant medications during the follow-up period (**Table 7**). However, because of the large percentage of patients treated with sildenafil (88%), it was impossible to evaluate the effects of sildenafil using this statistical model.

Results of Exploratory Data Analyses

Clinical worsening, including all clinical events (additional therapies in response to clinical worsening, hospitalization and death), occurred in 32 of 41 patients. In the univariate Cox regression model, there was no significant association between clinical worsening and any variables including age, sex, NYHAFC, 6MWT, BNP level, serum uric acid level and CMR measurements.

Discussion

In this study, we investigated the prognostic significance of CMR measurements in patients with IPAH before initiating intravenous prostacyclin therapy. We found that increased RVEDVI and NYHAFC were associated with both hospitalization for right heart failure and mortality.

In our study, we only focused on patients with IPAH. Some previous studies have included multiple types of PAH patients (category 1 of the Venice or Dana Point classification[11]) in their cohorts and subsequent analyses. Although this approach may be appropriate for some therapeutic studies,[16] the validity of this practice is questionable when evaluating prognostic factors.[17] It is well known that survival curves are not comparable across all subgroups of category 1 PAH,[18] and therefore it should not be assumed that the prognostic variables will be identical in the various populations.

Compared with other diagnostic tools, the advantages of CMR are its noninvasiveness, non-ionizing safety, excellent spatial and temporal resolution, and repeatability. CMR is more reproducible than echocardiography when measuring RV function.[19] There have been few previous studies that have addressed the relationships between CMR measures and clinical outcomes in IPAH patients. Previous studies have demonstrated that an increased RVEDVI, a large right atrium, and a low RVSVI are associated with a poor prognosis.[9,20,21] However, to the best of our knowledge, the associations between hospitalization for heart failure because of IPAH and the CMR results have not yet been reported. We found that the RVEDVI and RVESVI were associated with both hospitalization for right heart failure and mortality. This finding is clinically important because CMR provides a direct RV parameter for predicting early RV failure (before the initiation of intravenous prostacyclin therapy). Measures of increased RVEDVI and RVESVI could be used to predict treatment failure and, thus, could offer an opportunity to change the patient's treatment or add the patient to the transplant list before RV failure leads to death.[9] It is well known that the RV compensates for increased afterload via enlargement and hypertrophy. At some point, the RV is unable to further adapt to the increased afterload, and RV failure occurs, leading to hospitalization for heart failure or imminent death.

A previous study enrolling 64 IPAH patients revealed a significantly better survival in the patients with RVEDVI <84 ml/m² than in those with RVEDVI ≥84 ml/m².[9] In our post hoc analysis by means of a Cox regression, treating the RVEDVI as a binary variable, no event was observed in patients with RVEDVI <84 ml/m² during a longer mean follow-up period (32±16 vs. 45±26 months), which is consistent with the previous finding; however, we did not observe enough events in the

patients with RVEDVI ≥84 ml/m² to establish a significant difference between the groups (**Figure S1**). Thus, in the statistical analyses presented here, we treated each factor (eg, RVEDVI) as a continuous variable to avoid the loss of information associated with creating binary variables.

In our study, the NYHAFC was an independent predictor of both hospitalization and mortality. Previous studies have reported that this classification is a prognostic factor for mortality in IPAH patients.[22–24] Sitbon et al have reported that the survival of primary pulmonary hypertension patients treated with intravenous prostacyclin is associated with the NYHAFC at baseline,[23] and our results are consistent with that.

Our univariate analyses also found that LVEDVI, LVESVI and LVMI were associated with hospitalization; however, these 3 parameters were not associated with mortality. The reason for the discrepancy in P-values between hospitalization and death events may have been related to the difference in the numbers of events; that is, the statistical power of the death-event data (4 events) is lower than that of the hospitalization-event data (9 events). In the multivariate model, these 3 parameters did not predict our patients' prognoses, which may have been related to the strong effect of the RVEDVI on the severity of the IPAH. Additional large-scale studies are warranted.

The exploratory analyses showed no significant association between clinical worsening (all clinical events, including additional therapies, hospitalization and death) and any variables in our study. One explanation is that too many events (32 out of 41 patients) may have resulted in a low statistical power in the exploratory analyses of our patient population. Furthermore, hospitalization and death were more clinically relevant than the total of all clinical events (new additional therapies, hospitalization and death) and would have a higher power to detect associations between the MRI findings and the patients' prognoses in this study.

Study Limitations

First, this was an observational study with a cohort limited to a 45-month period. Second, our single measurement of the CMR parameters at the time of study entry and our inability to evaluate the longitudinal trends in these parameters may have led to an underestimation of the relationships between the CMR measures and our endpoints because of regression-dilution bias. Third, because our study had an observational design, the IPAH therapies were not controlled. However, there was no significant relationship between the endpoints and the medications used. Furthermore, the effects of RVEDVI and NYHAFC on hospitalization were consistent when the concomitant medications were included as time-dependent covariates. Finally, our data were obtained from a single center and should be evaluated in other centers.

Conclusions

In IPAH patients, the RVEDVI obtained from CMR measurements predicts both hospitalization for right heart failure and mortality before initiating intravenous prostacyclin therapy.

Acknowledgment

The authors acknowledge Yohei Ohno for important suggestions.

Disclosures

Funding/Support: None.

References

1. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol* 2009; **53:** 1573–1619.
2. Badesch DB, Abman SH, Simonneau G, Rubin LJ, McLaughlin VV. Medical therapy for pulmonary arterial hypertension: Updated ACCP evidence-based clinical practice guidelines. *Chest* 2007; **131:** 1917–1928.
3. Fukumoto Y, Shimokawa H. Recent progress in the management of pulmonary hypertension. *Circ J* 2011; **75:** 1801–1810.
4. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Survival in patients with primary pulmonary hypertension: Results from a national prospective registry. *Ann Intern Med* 1991; **115:** 343–349.
5. Lang IM, Plank C, Sadushi-Kolici R, Jakowitsch J, Klepetko W, Maurer G. Imaging in pulmonary hypertension. *JACC Cardiovasc Imaging* 2010; **3:** 1287–1295.
6. Marrone G, Mamone G, Luca A, Vitulo P, Bertani A, Pilato M, et al. The role of 1.5T cardiac MRI in the diagnosis, prognosis and management of pulmonary arterial hypertension. *Int J Cardiovasc Imaging* 2010; **26:** 665–681.
7. Benza R, Biederman R, Murali S, Gupta H. Role of cardiac magnetic resonance imaging in the management of patients with pulmonary arterial hypertension. *J Am Coll Cardiol* 2008; **52:** 1683–1692.
8. Kang KW, Chang HJ, Kim YJ, Choi BW, Lee HS, Yang WI, et al. Cardiac magnetic resonance imaging-derived pulmonary artery distensibility index correlates with pulmonary artery stiffness and predicts functional capacity in patients with pulmonary arterial hypertension. *Circ J* 2011; **75:** 2244–2251.
9. van Wolferen SA, Marcus JT, Boonstra A, Marques KM, Bronzwaer JG, Spreeuwenberg MD, et al. Prognostic value of right ventricular mass, volume, and function in idiopathic pulmonary arterial hypertension. *Eur Heart J* 2007; **28:** 1250–1257.
10. Gan CT, Lankhaar JW, Westerhof N, Marcus JT, Becker A, Twisk JW, et al. Noninvasively assessed pulmonary artery stiffness predicts mortality in pulmonary arterial hypertension. *Chest* 2007; **132:** 1906–1912.
11. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2009; **54:** S43–S54.
12. Badesch DB, Champion HC, Sanchez MA, Hoeper MM, Loyd JE, Manes A, et al. Diagnosis and assessment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2009; **54:** S55–S66.
13. Galie N, Torbicki A, Barst R, Dartevelle P, Haworth S, Higenbottam T, et al. Guidelines on diagnosis and treatment of pulmonary arterial hypertension: The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. *Eur Heart J* 2004; **25:** 2243–2278.
14. Nagaya N, Nishikimi T, Uematsu M, Satoh T, Kyotani S, Sakamaki F, et al. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. *Circulation* 2000; **102:** 865–870.
15. Nagaya N, Uematsu M, Satoh T, Kyotani S, Sakamaki F, Nakanishi N, et al. Serum uric acid levels correlate with the severity and the mortality of primary pulmonary hypertension. *Am J Respir Crit Care Med* 1999; **160:** 487–492.
16. Satoh T, Saji T, Watanabe H, Ogawa S, Takehara K, Tanabe N, et al. A phase III, multicenter, collaborative, open-label clinical trial of sildenafil in Japanese patients with pulmonary arterial hypertension. *Circ J* 2011; **75:** 677–682.
17. Swiston JR, Johnson SR, Granton JT. Factors that prognosticate mortality in idiopathic pulmonary arterial hypertension: A systematic review of the literature. *Respir Med* 2010; **104:** 1588–1607.
18. McLaughlin VV, Presberg KW, Doyle RL, Abman SH, McCrory DC, Fortin T, et al. Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004; **126:** 78S-92S.
19. McLure LE, Peacock AJ. Imaging of the heart in pulmonary hypertension. *Int J Clin Pract Suppl* 2007; **61**(Suppl156): 15–26.
20. Gan CT, Holverda S, Marcus JT, Paulus WJ, Marques KM, Bronzwaer JG, et al. Right ventricular diastolic dysfunction and the acute effects of sildenafil in pulmonary hypertension patients. *Chest* 2007; **132:** 11–17.
21. Kovacs G, Reiter G, Reiter U, Rienmuller R, Peacock A, Olschewski

H. The emerging role of magnetic resonance imaging in the diagnosis and management of pulmonary hypertension. *Respiration* 2008; **76:** 458–470.
22. Barst RJ, Galie N, Naeije R, Simonneau G, Jeffs R, Arneson C, et al. Long-term outcome in pulmonary arterial hypertension patients treated with subcutaneous treprostinil. *Eur Respir J* 2006; **28:** 1195–1203.
23. Sitbon O, Humbert M, Nunes H, Parent F, Garcia G, Herve P, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: Prognostic factors and survival. *J Am Coll Cardiol* 2002; **40:** 780–788.
24. Raymond RJ, Hinderliter AL, Willis PW, Ralph D, Caldwell EJ, Williams W, et al. Echocardiographic predictors of adverse outcomes in primary pulmonary hypertension. *J Am Coll Cardiol* 2002; **39:** 1214–1219.

Supplementary Files

Supplementary File 1

Figure S1. Kaplan-Meier plots showing survival in patients with IPAH categorized according to RVEDVI <84 ml/m^2 or ≥84 ml/m^2.

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-11-1237

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

Second Department of Internal Medicine, Kyorin University School of Medicine, Tokyo (R.Y., M.K., H.T., H.Y., T.S.); Department of Cardiology, Keio University School of Medicine, Tokyo (M.K., T.K., Y.T., K.F.), Japan

The first two authors contributed equally to this work (R.Y., M.K.).

Mailing address: Toru Satoh, MD, 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

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·min^{-1}·kg^{-1} and gradually increased to a dose of approximately 30 ng·min^{-1}·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

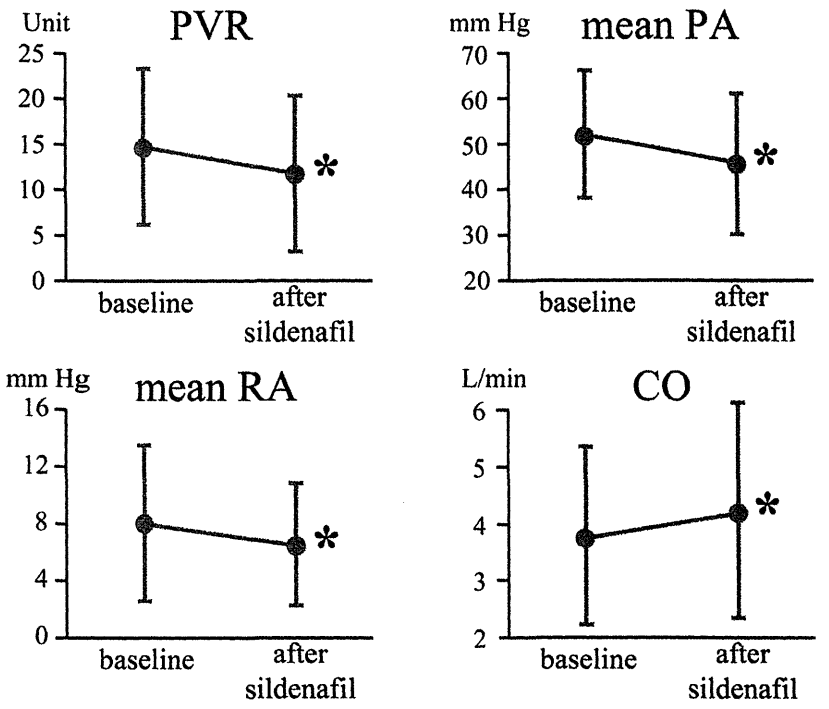

Figure 1. Hemodynamic changes during the observation period of sildenafil monotreatment in the enrolled patients as a whole. Pulmonary vascular resistance (PVR), mean pulmonary arterial pressure (mean PAP), mean right atrial pressure (mean RA), and cardiac output (CO) improved significantly with first-line 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).

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.

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**).

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.

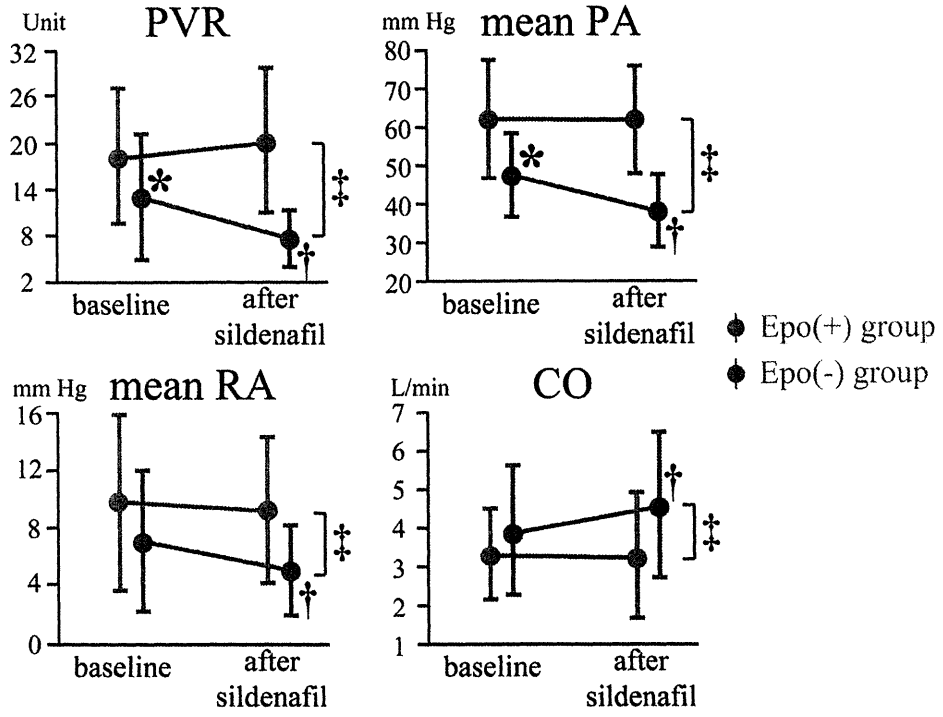

Figure 2. Hemodynamic changes during the observation period of sildenafil monotreatment among patients grouped according to the addition of epoprostenol (Epo) treatment. The red circles show the hemodynamic changes in the Epo(+) group, comprising patients treated with additional epoprostenol, and the 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

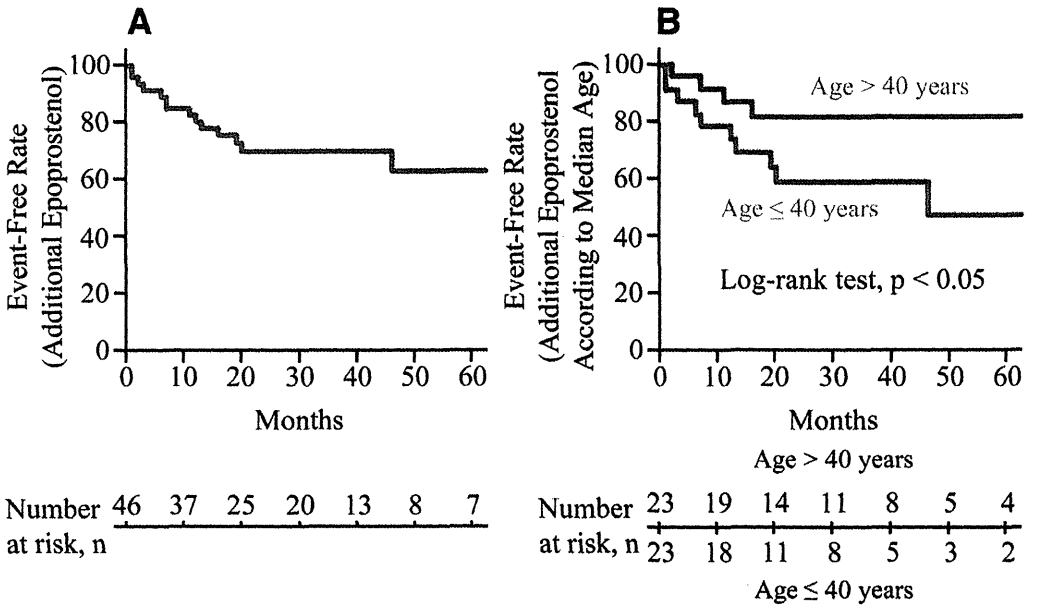

Figure 3. (**A**) Kaplan-Meier estimates according to the addition of epoprostenol treatment. The 1-, 3-, and 5-year rates for patients treated without the addition of epoprostenol were approximately 80%, 70%, and 63%, respectively. (**B**) Kaplan-Meier estimates according to the addition of epoprostenol 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,

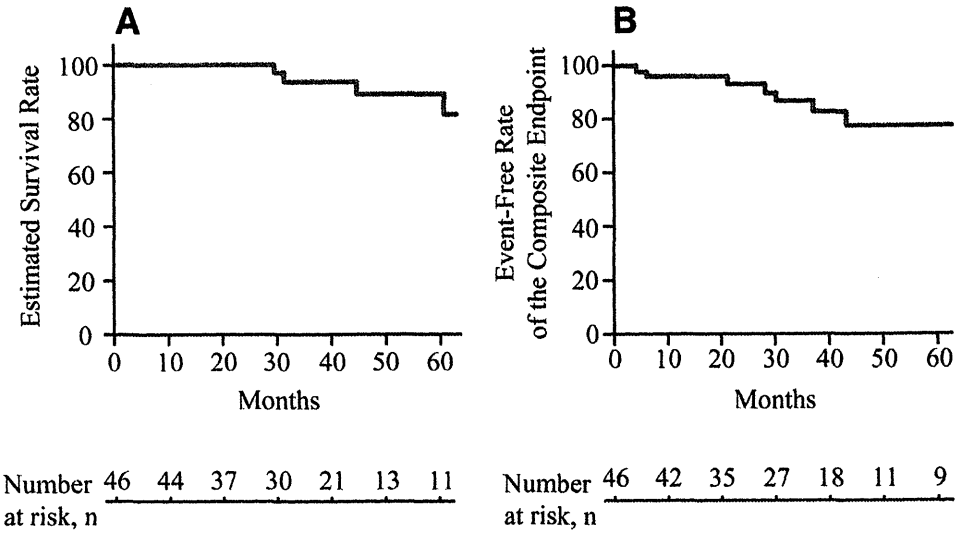

Figure 4. (A) Kaplan-Meier survival estimates for patients with pulmonary arterial hypertension (PAH) treated with first-line sildenafil therapy. (B) Kaplan-Meier estimates according to the composite endpoint of hospitalization for right-side heart failure and death.

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.

References

1. Galiè N, Manes A, Negro L, Palazzini M, Bacchi-Reggiani ML, Branzi A. A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. *Eur Heart J* 2009; **30:** 394–403.
2. Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2009; **34:** 1219–1263.
3. Badesch DB, Champion HC, Sanchez MA, Hoeper MM, Loyd JE, Manes A, et al. Diagnosis and assessment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2009; **54:** 55S–66S.
4. Fukumoto Y, Shimokawa H. Recent progress in the management of pulmonary hypertension. *Circ J* 2011; **75:** 1801–1810.
5. Channick RN, Simonneau G, Sitbon O, Robbins IM, Frost A, Tapson VF, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: A randomized placebo controlled study. *Lancet* 2001; **358:** 1119–1123.
6. Rubin LJ, Badesch DB, Barst RJ, Galiè N, Black CM, Keogh A, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002; **346:** 896–903.
7. McLaughlin VV, Sitbon O, Badesch DB, Barst RJ, Black C, Galiè N, et al. Survival with first-line bosentan in patients with primary pulmonary hypertension. *Eur Respir J* 2005; **25:** 244–249.
8. Provencher S, Sitbon O, Humbert M, Cabrol S, Jaïs X, Simonneau G. Long-term outcome with first-line bosentan therapy in idiopathic pulmonary arterial hypertension. *Eur Heart J* 2006; **27:** 589–595.
9. Galiè N, Rubin LJ, Hoeper M, Jansa P, Al-Hiti H, Meyer G, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): A double-blind, randomised controlled trial. *Lancet* 2008; **371:** 2093–2100.
10. Archer SL, Michelakis ED. Phosphodiesterase type 5 inhibitors for pulmonary hypertension. *N Engl J Med* 2009; **361:** 1864–1871.
11. Galiè N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, et al; Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2005; **353:** 2148–2157.
12. Rubin LJ, Badesch DB, Fleming TR, Galiè N, Simonneau G, Ghofrani HA, et al; on behalf of the SUPER-2 study group. Long-term treatment with sildenafil citrate in pulmonary arterial hypertension: SUPER-2. *Chest* 2011; **140:** 1274–1283.
13. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Survival in patients with primary pulmonary hypertension: Results from a national prospective registry. *Ann Intern Med* 1991; **115:** 343–349.
14. Barst RJ, Rubin LJ, McGoon MD, Caldwell EJ, Long WA, Levy PS. Survival in primary pulmonary hypertension with long-term continuous intravenous prostacyclin. *Ann Intern Med* 1994; **121:** 409–415.
15. Galiè N, Seeger W, Naeije R, Simonneau G, Rubin LJ. Comparative analysis of clinical trials and evidence-based treatment algorithm in pulmonary arterial hypertension. *J Am Coll Cardiol* 2004; **43:** 81S–88S.
16. Barst RJ, Gibbs JSR, Ghofrani HA, Hoeper MM, McLaughlin VV, Rubin LJ, et al. Updated evidence-based treatment algorithm in pulmonary arterial hypertension. *J Am Coll Cardiol* 2009; **54:** 78S–84S.
17. Michelakis E, Tymchak W, Lien D, Webster L, Hashimoto K, Archer S. Oral sildenafil is an effective and specific pulmonary vasodilator in patients with pulmonary arterial hypertension: Comparison with inhaled nitric oxide. *Circulation* 2002; **105:** 2398–2403.
18. Watanabe H, Ohashi K, Takeuchi K, Yamashita K, Yokoyama T, Tran QK, et al. Sildenafil for primary and secondary pulmonary hypertension. *Clin Pharmacol Ther* 2002; **71:** 398–402.
19. Michelakis ED, Tymchak W, Noga M, Webster L, Wu XC, Lien D,

et al. Long-term treatment with oral sildenafil is safe and improves functional capacity and hemodynamics in patients with pulmonary arterial hypertension. *Circulation* 2003; **108:** 2066–2069.
20. Sastry BK, Narasimhan C, Reddy NK, Raju BS. Clinical efficacy of sildenafil in primary pulmonary hypertension: A randomized, placebo-controlled, double-blind, crossover study. *J Am Coll Cardiol* 2004; **43:** 1149–1153.
21. Kataoka M, Satoh T, Manabe T, Anzai T, Yoshikawa T, Mitamura H, et al. Oral sildenafil improves primary pulmonary hypertension refractory to epoprostenol. *Circ J* 2005; **69:** 461–465.
22. Wilkins MR, Paul GA, Strange JW, Tunariu N, Gin-Sing W, Banya WA, et al. Sildenafil versus endothelin receptor antagonist for pulmonary hypertension (SERAPH) study. *Am J Respir Crit Care Med* 2005; **171:** 1292–1297.
23. Hoeper MM, Welte T. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2006; **354:** 1091–1093.
24. Satoh T, Saji T, Watanabe H, Ogawa S, Takehara K, Tanabe N, et al. A phase III, multicenter, collaborative, open-label clinical trial of sildenafil in Japanese patients with pulmonary arterial hypertension. *Circ J* 2011; **75:** 677–682.
25. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: The impact of epoprostenol therapy. *Circulation* 2002; **106:** 1477–1482.
26. Sitbon O, Humbert M, Nunes H, Parent F, Garcia G, Hervé P, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: Prognostic factors and survival. *J Am Coll Cardiol* 2002; **40:** 780–788.
27. Thenappan T, Shah SJ, Rich S, Tian L, Archer SL, Gomberg-Maitland M. Survival in pulmonary arterial hypertension: A reappraisal of the NIH risk stratification equation. *Eur Respir J* 2010; **35:** 1079–1087.
28. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation* 2010; **122:** 156–163.
29. Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS, et al. Predicting survival in pulmonary arterial hypertension: Insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation* 2010; **122:** 164–172.
30. Humbert M, Sitbon O, Yaïci A, Montani D, O'Callaghan DS, Jaïs X, et al. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. *Eur Respir J* 2010; **36:** 549–555.
31. Sandoval J, Bauerle O, Palomar A, Gómez A, Martínez-Guerra ML, Beltrán M, et al. Survival primary pulmonary hypertension: Validation of a prognostic equation. *Circulation* 1994; **89:** 1733–1744.

連関疾患を考慮した診察のすすめかた

呼吸器疾患・肺高血圧と心不全(右心不全)

佐藤　徹
杏林大学医学部循環器内科／さとう・とおる

はじめに●

当稿では右心不全および肺高血圧症(PAH)の，診察所見を主に記載してみたい．循環器内科を専門としているので呼吸器疾患患者さんを普段診療する機会は少なく，これに関しての詳述は省略したい．

疫　学●

急性の肺高血圧症はほぼ肺塞栓症に限られるといってよく，高齢者にも多発し右心不全の原因ともなる．慢性の肺高血圧症の原因は，最近は大きく五つに分類される(**表1**)．分類1の肺動脈性肺高血圧症は発症の年齢ピークが30歳代と50歳代にあり，分類4の慢性肺血栓塞栓症(CTEPH)では50歳代となる(**図1**)．分類1の肺動脈性肺高血圧症で頻度の最も多い特発性肺動脈性肺高血圧症(IPAH)は図1で30歳代のピークを形成し，ほとんどが60歳までに発症する．肺動脈性肺高血圧症の50歳代のピークは膠原病が主体となる．したがって高齢者で肺高血圧症を認めると，急性の肺塞栓症，肺動脈性肺高血圧症の膠原病，慢性肺血栓塞栓症と，分類2の左心疾患によるもの，分類3の肺疾患によるものが原因疾患の主なものとなる．

自覚症状●

右心不全の症状は低心拍出による全身倦怠感，静脈うっ血による下肢や顔面のむくみ，肝うっ血による右上腹部の張った感じ，食事摂取不良があげられる．右上腹部膨満感は急速に生じて程度も強い場合には急性腹症と紛らわしい．食欲不振は消化管や肝臓のうっ血によるもので，食欲そのものはあるけれどすぐに満腹となり易満腹感ともいえる．食事摂取不良が持続すると体重減少に至り，消化器症状が悪化すると嘔気を認めるようになる．

表1　肺高血圧症の分類(ダナポート分類2008)

1. 肺動脈性高血圧症(PAH)
   1) 特発性IPAH
   2) 遺伝性
   3) 薬物と毒物
   4) 各種疾患に伴う肺動脈性肺高血圧症
      ① 膠原病性
      ② 先天性心疾患
      ③ 肝臓病
      ④ エイズ
      ⑤ 住血吸虫
      ⑥ 溶血性貧血
   5) 新生児遷延性肺高血圧症
      1' 肺静脈および/または肺毛細管閉塞
      肺静脈閉塞性疾患(PVOD)，肺毛細血管症(PCH)
2. 左心性心疾患に伴う肺高血圧症
   1) 収縮障害
   2) 拡張障害
   3) 弁膜症
3. 肺疾患および/または低酸素血症に伴う肺高血圧症
   1) 慢性閉塞性肺疾患
   2) 間質性肺疾患
   3) 混合性障害
   4) 睡眠呼吸障害
   5) 肺胞低換気障害
   6) 高所への慢性曝露
   7) 発育障害
4. 慢性血栓性および/または塞栓性疾患による肺高血圧症
5. その他の肺高血圧症
   1) 血液疾患：骨髄増殖性疾患，脾摘出
   2) 全身疾患：サルコイドーシス，ヒスチオサイトーシスX，リンパ管腫症，神経鞘腫，血管炎
   3) 代謝疾患：甲状腺疾患，糖原病，ゴーシェ病
   4) その他：肺血管の圧迫(リンパ節腫脹，腫瘍，線維性縦隔炎)

(第4回世界シンポジウム，Danaport, USA, 2008より引用)

診察所見●

右房圧が上昇すると頸静脈の怒張を認め，静脈うっ血の所見として，肝腫大を生じ下腿浮腫を認める．参考となる所見としては，右室圧が上がると右室拍動を触知し，右室の拡張により三尖弁閉鎖不全を生じこの雑音を聴取するようになるとと

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- 右心不全では頸静脈怒張，肝腫大，浮腫を認める．
- 内頸静脈が観察される最高点から右房圧を推定できる．

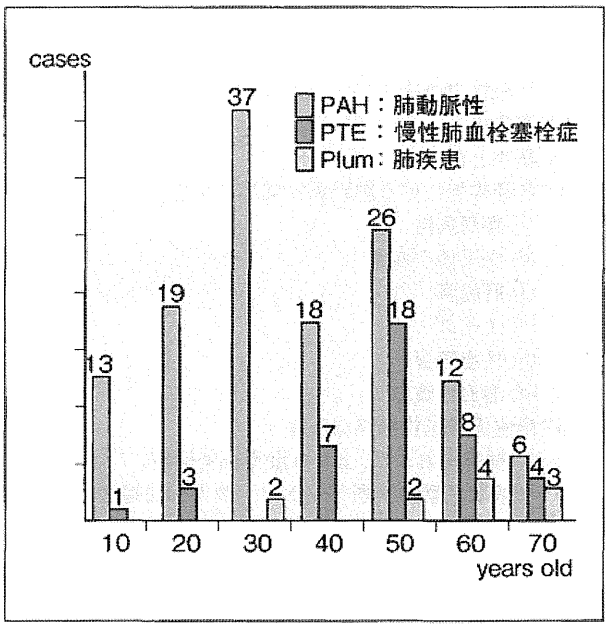


図1　肺高血圧症の年齢分布
対象は慶應大学病院へ入院の上右心カテーテル検査を施行した症例 1999～2007

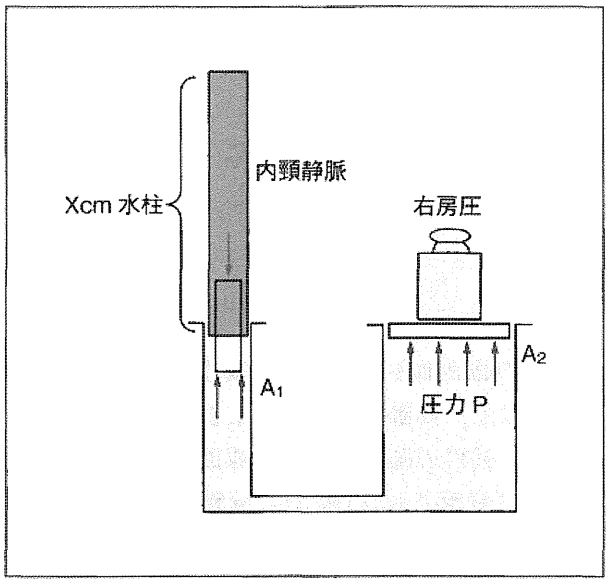


図2　内頸静脈視診による右房圧推定の原理
右房圧と釣り合う内頸静脈の血液の水柱の高さまで，内頸静脈の拍動が見える．

もに頸静脈拍動でｖ波が増高し，肝臓に拍動を触れるようになる．右室拡張末期圧が上昇すると右心性のⅣ音を聴取するようになる．右心不全が重症となると右心性のⅢ音が聞かれる．その他，右心不全の原因として肺高血圧症があることが多いため，Ⅱ音の肺動脈成分が亢進したり，肺動脈弁閉鎖不全雑音を認めることもある．

1.　右心不全の所見

a.　頸静脈の怒張

右心不全になると頸静脈を視診しやすくなるため，それを怒張と呼んでも良いかもしれないが，右房圧上昇により頸静脈が高い位置まで見えるようになる．内頸静脈と外頸静脈が観察されるが内頸静脈は9割近くで視診できる．外頸静脈も拍動していれば以下の情報収集に使用される．下顎を挙上すると頸部が伸展されて頸静脈が見やすくなる．静脈には拍動は本来ないが右房近傍の静脈では右房の拍動が伝達して頸静脈の拍動を観察できる．右房圧に内頸静脈の血液の柱が釣り合う位置まで拍動が観察されるため(図2)，逆に内頸静脈の観察される最高点が右房圧に一致する．経験的には，拍動がはっきりと観察される最高点が平均右房圧に近い．実際に右房圧を推定するためには右房の位置を同定しここから頸静脈が見える点までの垂直距離を測定する必要がある．右房の位置の決定方法としては，胸骨角より一定の距離下に右房が存在するとする方法がよく用いられる(図3)．右房圧の高さにより内頸静脈が観察される場所が異なるため，座位，45° 座位，仰臥位の三つの体位で視診され，おのおの右房の推定位置は胸骨角より約10 cm，7 cm，5 cmに位置する．これは実際には体格，心拡大の有無など多くの因子で変わるため，本当に大雑把な目安と考えていただきたい．図4に示すように，45° 座位で胸骨角より

●右房圧の推定値は，胸骨角から内頸静脈が視診できる最高点までの垂直距離を測り，これに体位によって決まる右房までの距離を加えた値となる．

図3　右房の位置推定
図の三つの体位で観察し，おのおの胸骨角より右房までの距離を図の推定値とする．
（高久史麿ほか訳：ミシガン診察診断マニュアル，1999，メディカル・サイエンス・インダーナショナル，South Med J 100：1022，2007より改変引用）

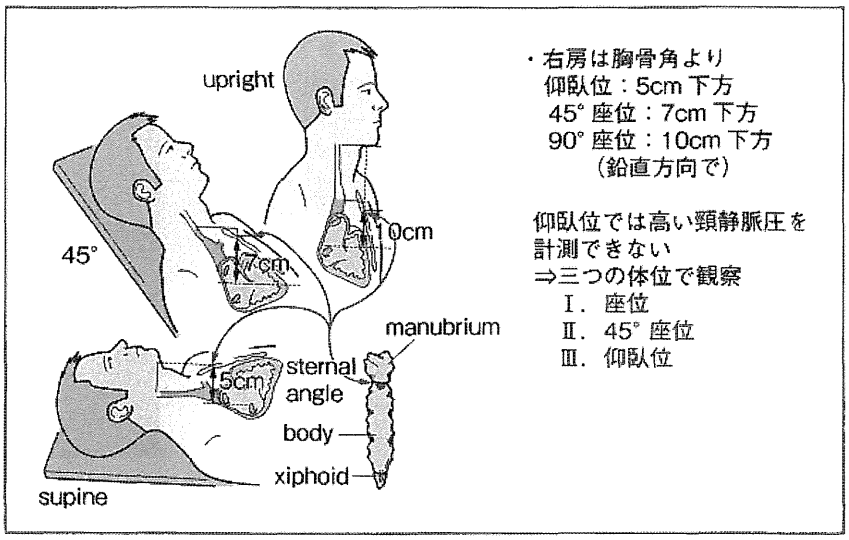
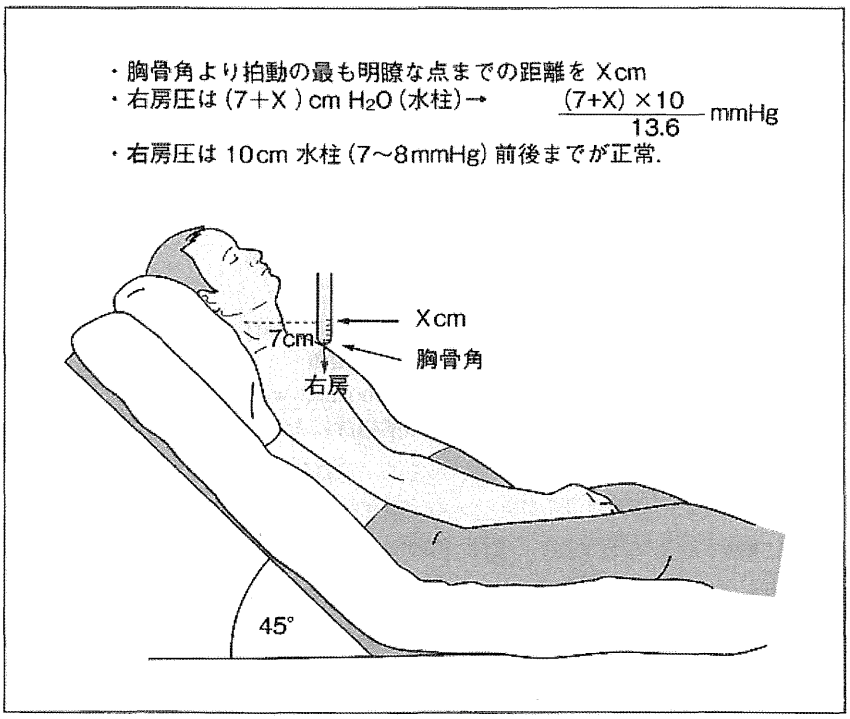


図4　右房圧の推定
45°座位で内頸静脈が胸骨角より垂直距離でXcm上に視診されたとすると，推定右房圧は(X＋7)cmとなる．これをmmHgに換算するには図中の式を用いる．
（Constant, J.：Bedside Cardiology. Lippincott Willams & Wilkins, 1999より改変引用）



垂直距離で1cm上に頸静脈が観察されたとすると，右房から頸静脈までの距離は8cmとなり，図4中の計算式から推定右房圧は6mmHgとなる．自験例の推定右房圧とカテーテル検査での右房圧との関係を**図5**に示す．一般には視診による推定右房圧は過小評価されることが多いとされる．

b.　肝腫大

肝うっ血により肝臓は腫大して肝臓を触知するようになるが，右房圧上昇の程度と持続期間により腫大の程度も増す．左葉が主に拡大するため正

●肝腫大では腫大した肝臓を触れ圧痛があることが多い.
●下腿浮腫は pitting edema を生じ圧迫によりなかなか解除されない.

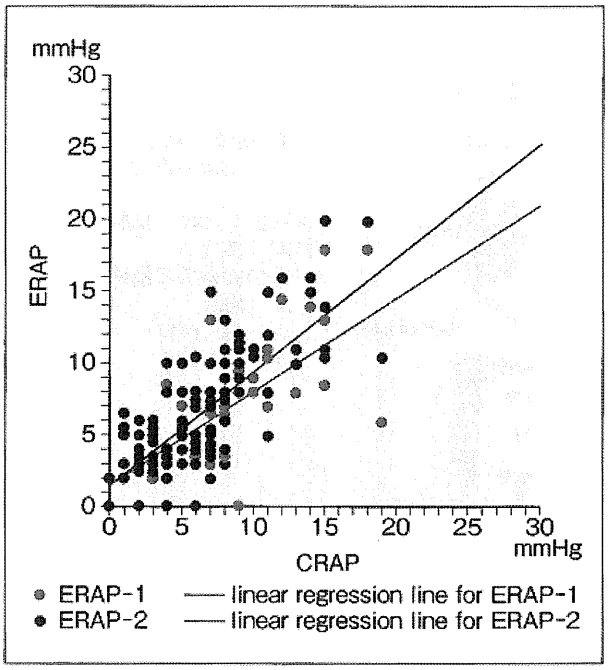


図5　平均右房圧の，カテーテル検査による実測値と頸静脈視診による推測値の比較
ERAP-1：頸静脈視診による右房圧推定値と実測値の回帰直線．ERAP-2：腹部圧迫を施行したときの，頸静脈視診による右房圧推定値と実測値の回帰直線．いずれも推測値と計測値には有意な正相関を認める．
CRAP：the right atrial pressure measured with right heart catheterization，カテーテル検査による実測平均右房値
ERAP：the estimated right atrial pressure obtained with inspection of the internal jugular vein，頸部視診による推測平均右房圧

中部に触れるようになる．急性例では柔らかく，そのつもりで注意して触診しないと見逃されやすい．また肝被膜が急激に伸長されるため圧痛を認めることが多い．慢性の右心不全では固く触れるようになり圧痛もはっきりしなくなる．

c.　下腿浮腫(図6)

静脈圧の上昇により静脈うっ血を生じるが，立って生活をしているため最も心臓からの距離が大きく静脈圧が高い下腿部にまず浮腫を認める．さらに静脈圧が上がって罹患期間が長くなると大

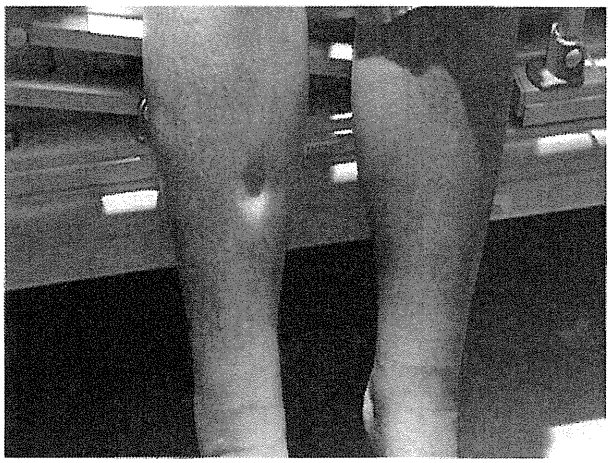


図6　右脚中央部の pitting edema
検者が指で5秒間圧迫し解除後．

腿部，陰嚢，大臀筋へと浮腫は広がってゆく．ベッド上安静を続けていると体内で最も低い位置にあたる背部に浮腫ができる．このような静水圧の上昇によって起こる心不全のむくみは指で強く押すと凹むため pitting edema と呼ばれる．10秒間圧迫して40秒間消失しないと心不全性，40秒以内に消失する浮腫は低アルブミン血症によるものとの報告もある．

d.　右心性 S_{III} (図7)

右心室は本来壁が薄くコンプライアントな心腔であるためは S_{III} は出現しがたい．S_{III} と思い心音図を記録すると S_{IV} であることもしばしば経験する．心不全では心拍数が速くなり S_{III} と S_{IV} が重なり summation gallop となることも多い．また急激に右心不全が悪化したときに一過性に出現することもよく経験する．

2.　右室負荷を示唆する診察所見

a.　右室拍動

図8に示すように左前胸部に手の平を当て，軽く圧迫して拍動を感じると右室の拍動であることが多い．上行大動脈，肺動脈の拍動を触れること

- 傍胸骨拍動の多くは右室の拍動によって生じ，右室負荷を示唆している．
- 右心負荷を生じると三尖弁閉鎖不全雑音を認めることがある．
  頸静脈の視診でも診断できる．

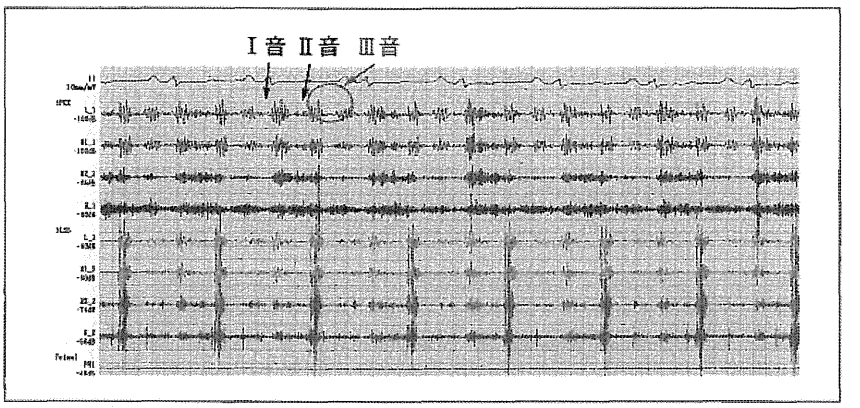


図7 心音図上のⅢ音
summation gallop に近いが心電図のP波より前に位置しているためⅢ音の成分は最低限含まれている．心尖部でも S_{IIp} が聴取され S_{IIp} の亢進を示唆しており肺高血圧症があることがわかる．

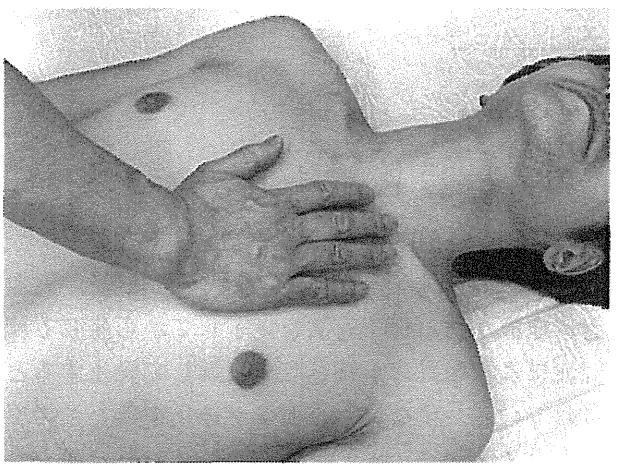


図8 傍胸骨拍動の触診
本文参照．

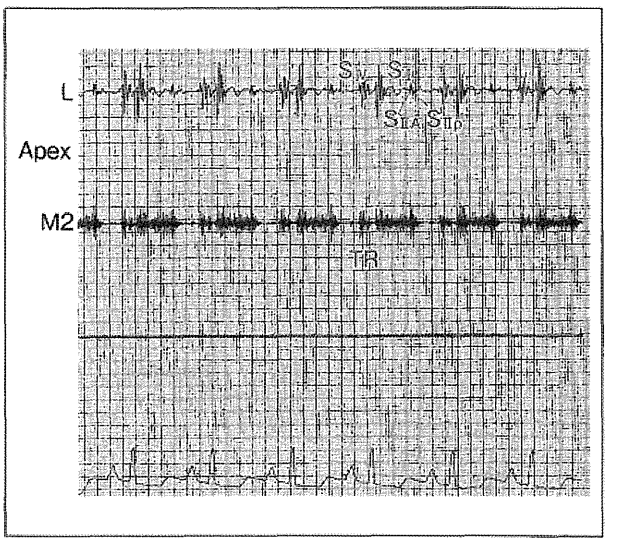


図9 三尖弁閉鎖不全雑音の心音図
S_{IV} も聴取し，心尖部でも S_{IIp} が聞こえる．高調な収縮期逆流性雑音が記録され，S_I よりはじまって S_{II} まで連続している．症例は27歳女性，特発性肺動脈性肺高血圧症．
PA 113/49 (71) mmHg,. PVR 16 unit, mRA 10 mmHg.

もある．ごく軽度のものは正常でも認めることがあるがはっきりした拍動は右室負荷により生じる．圧負荷では持続性拍動(収縮期全般にわたって触れる拍動)であるのに対し，量負荷(心房中隔欠損など)では非持続性拍動となる．右室圧負荷に対する右室拍動触知の感度は以前に約70例を集計したときには，70%ぐらいであった．右室拍動自体は右心不全のサインではないが，右心不全を起こす疾患の存在を示唆する所見となる．

b. 三尖弁閉鎖不全

これも右心不全を直接示す所見ではないが，右室負荷が増すと認められる．患者さんによっては右心不全出現時に雑音が聞かれるようになり改善とともに消失することがある．逆流性雑音であるためⅠ音よりはじまって急速に音量が大きくなり同じ大きさでⅡ音まで連続する(**図9**)．多くは肺高血圧症を伴うため高調で逆流量が大きくなると低音成分が混在するようになる．重症の三尖弁閉

◎右心負荷が強いとSⅣを聴取することがある.
◎肺高血圧症が原因となることが多くSⅡpが亢進する.

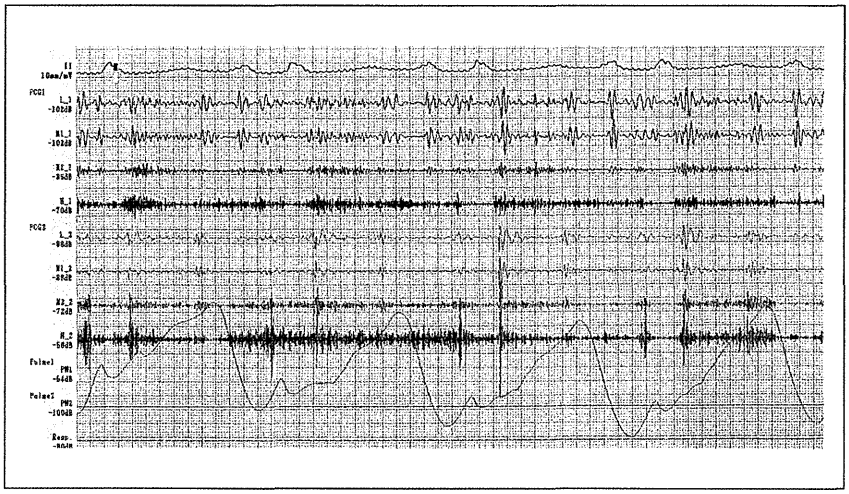


図10　三尖弁閉鎖不全(TR)の頸静脈図
本文参照.

鎖不全であることは頸静脈拍動を視診し，収縮期に陽性波を認めることからも診断できる．これの診かたは，橈骨動脈の拍動を触診しながら頸静脈を視診すると，正常では橈骨動脈の拍動を感じる収縮期に陰性波となるはずのところが陽性波を呈すると，心房細動でなければ，重症の三尖弁閉鎖不全である可能性が高い(**図10**)．

c.　右心性Ⅳ音

これもⅢ音と同様に，コンプライアンスの高い右室からはSⅣ音が聞かれることは少ない．右室の拡張障害によって生じ，右室のSⅢよりは聴取する頻度は多いがかなり右室負荷の強い症例でみられる．ベル型聴診器を本当にソフトに当てて聞く必要があり，膜型で聞くとはっきり聴取できなくなることでSⅣと確認できる．SⅣが聴取できる病態では右心室は拡大して通常の左室心尖部(乳頭付近)を占めるため，SⅣはこの辺りでも聞こえる．

3.　肺高血圧症の所見

a.　SⅡpの亢進(図7参照)

SⅡは心室圧が大血管圧より低下した後，大血管に血液がある程度充満を完了してから生じる反射波により半月弁が押されて閉鎖して発生するとされている．すなわち大血管が硬化するとこの反射が強くなりSⅡが亢進する．SⅡp亢進の聞きかたは胸骨左縁でSⅡAより大きいこととともに，乳頭付近より外側では正常ではSⅡpを聴取することはまずないことから，この位置より外側で聞こえればSⅡp亢進とされる．

b.　肺動脈弁閉鎖不全

肺動脈が拡張した症例で聞かれることが多いが，肺高血圧症が悪化し右心不全を呈したときに聞かれる症例もある．他の所見より発生頻度は低い．

特集
循環器疾患と呼吸器疾患

治す 13

肺高血圧症の最新の薬物療法

Contemporary drug treatment of pulmonary hypertension

佐藤 徹（杏林大学医学部循環器内科）

肺高血圧症は，表1に示すように5つに分類される。これは1998年の世界会議から採用された新しい分類で，解剖学的分類かつ機序による分類といえ，どこに属するかが診断できれば基本的治療（表2）も決まる。このなかで分類2（左心疾患に伴う肺高血圧症），分類3（肺疾患に伴う肺高血圧症）の治療は原病を治療することが原則となるが，“out of proportion”とよばれる，各原病で通常生じる以上の肺高血圧症の治療は分類1（肺動脈性肺高血圧症，pulmonary arterial hypertension；PAH）の治療法を適用することになる。分類4（慢性血栓塞栓性肺高血圧症）については，亜区域枝以上の肺動脈の内膜に生じた器質化血栓を機械的に除く治療が原則となるが，肺細動脈も二次的に障害することが知られておりそれに対してはPAH治療薬が使用される。分類5は原因が複合しているもの，全身疾患に伴うものが含まれ，分類1（PAH）の治療が主に使われる。以下，PAHの薬物治療について述べる。

ガイドラインに基づくPAHの治療

新しい血管拡張薬は，日本では2009年ごろよりプロスタグランジン系の内服薬ベラプロストが最初に使用され，次いで在宅持続静注薬のエポプロステノールが認可されて格段に予後は改善した。その後内服薬として，エンドセリン受容体拮抗薬のボセンタン，PDE V（phosphodiesterase V）阻害薬のシルデナフィル，PDE阻害薬のタダラフィル，エンドセリン受容体拮抗薬のアンブリセンタンが相次いで開発されて，治療の幅が広がっている。

1342-6591/12/¥400/論文/JCOPY