Pulmonary Artery Pressure as a Treatment Target to Improve the Prognosis of Idiopathic Pulmonary Arterial Hypertension
— Insight From a Cohort From Two Japanese Pulmonary Hypertension Centers —

Midori Ishiguro, MD; Kaori Takeuchi, MD; Hanako Kikuchi, MD;
Ayumi Goda, MD, PhD; Takumi Inami, MD, PhD; Yuichi Tamura, MD, PhD;
Masaharu Kataoka, MD, PhD; Keiichi Fukuda, MD, PhD; Toru Satoh, MD, PhD

Background: The prognosis of pulmonary arterial hypertension (PAH) has been improving since the introduction of epoprostenol (EPO). The 3-year survival of naïve idiopathic PAH (IPAH) and hereditary PAH (HPAH) was 96% in a recent prospective Japanese registry. This increase in survival in Japan may have been due to the reduction of pulmonary artery pressure (PAP) by a rapid and sufficient dosage of EPO. The aim of this retrospective study was therefore to analyze whether decreasing the PAP contributes to improving PAH prognosis.

Methods and Results: Sixty-four patients with IPAH/HPAH followed up at Keio and Kyorin University Hospitals between 1999 and 2011 were enrolled and divided into 2 groups: surviving or non-surviving. Of 14 variables, EPO use, most improved mean PAP (mPAP), brain natriuretic peptide level, cardiac output, 6-min walk distance, and sex were significantly different between the 2 groups. The former 3 variables were significantly related to death on multiple regression analysis. mPAP had the highest odds ratio of 1.44 and the largest area under the receiver operating characteristic curve. The value of mPAP with the optimal combination of sensitivity and specificity was 42 mmHg.

Conclusions: The best treatment target for the prognosis of IPAH/HPAH may be the reduction of mPAP; a similar large-scale study is anticipated.

Key Words: Pulmonary arterial hypertension; Pulmonary artery pressure; Retrospective study

Pulmonary hypertension (PH) has various causes and is classified into 5 categories according to the European Society of Cardiology (ESC) guidelines.[1] Pulmonary arterial hypertension (PAH) also has several etiologies, such as idiopathic, hereditary, connective tissue related, and congenital. The prognosis of idiopathic PAH (IPAH) and hereditary PAH (HPAH) was once very poor, and the mean survival was 2.8 years, with a 1-year survival of 68%, 3-year survival of 48%, and 5-year survival of 34%, as reported by the National Institute of Health.[2] However, with the advent of an ambulatory continuous drip infusion of the vasodilator epoprostenol, a prostacyclin derivative, in 1990, the prognosis of IPAH/HPAH dramatically improved. In a French registry from 2002 to 2003, Humbert et al reported that 354 IPAH patients had a 1-year survival of 89%, 3-year survival of 77%, and 5-year survival of 69%.[3] After the addition of other pulmonary vasodilators,

such as endothelin receptor antagonists (ERA) and phosphodiesterase type 5 inhibitors (PDE5I), the prognosis further improved. In the REVEAL registry from the USA published in 2010, the survival rates were 91% at 1 year, 74% at 3 years, and 59% at 5 years.[4]

One of the major problems in treating IPAH/HPAH has been the absence of a useful treatment target, although as many prognostic profiles as possible should be fulfilled to improve prognosis. Those targets include New York Heart Association (NYHA) functional class, exercise capacity, hemodynamics, brain natriuretic peptide (BNP) level, and echocardiography parameters.[1]

In Japan, the prognosis of IPAH/HPAH has been improving since the introduction of epoprostenol in 1999, and the 3-year survival of de novo IPAH and HPAH was 95.7% in a recent prospective registry of 108 patients from 2008 through 2013 in 8 Japanese specialized centers.[5] One

Table 1. Baseline IPAH/HPAH Patient Characteristics			
	Non-surviving	**Surviving**	**P-value**
n	24	40	
Age (years)	35±13	34±11	
Sex (F/M)	19/5	28/12	<0.05
Observation period (years)	3.4±2.1	6.3±3.6	<0.05
mPAP at diagnosis (mmHg)	59±12	60±14	
CO at diagnosis (L/min)	2.9±1.1	3.3±1.4	
6MWD at diagnosis (m)	330±109	362±124	
SvO$_2$ (%)	76±4	68±8	<0.05
BNP at diagnosis (pg/mL)	368±324	251±339	
Minimum mPAP (mmHg)	47±7	35±8	<0.05
Maximum CO (L/min)	3.9±1.2	5.3±1.4	<0.05
Maximum 6MWD (m)	316±173	487±104	<0.05
Minimum BNP (pg/mL)	141±238	15±20	<0.05
Epoprostenol use	22 (92)	24 (60)	<0.05
ERA use	22 (92)	32 (80)	
PDE5I use	19 (79)	35 (88)	

Data given as n (%) or mean±SD. 6MWD, 6-min walk distance; BNP, brain natriuretic peptide; CO, cardiac output; ERA, endothelin receptor antagonist; IPAH/HPAH, idiopathic/hereditary pulmonary arterial hypertension; mPAP, mean pulmonary artery pressure; PDE5I, phosphodiesterase type 5 inhibitors; SvO$_2$, mixed venous oxygen saturation.

factor in this advancement is the setting of the primary treatment target as the improvement of pulmonary artery pressure (PAP). In Japan, patients with IPAH/HPAH are now treated based on the Japanese Circulation Society guidelines,[6] with a few principles from the *Circulation/ Journal of the American College of Cardiology* guidelines as well as from the ESC/European Respiratory Society guidelines, emphasizing mean PAP (mPAP) as the prognostic target to be utilized the most, based on a Japanese study that analyzed patients treated with a rapid and sufficient dosage of epoprostenol.[7,8] Reduction of mPAP substantially contributed to improvement of the prognosis.[9]

In this retrospective study of a cohort from two Japanese local centers that was treated with a rapid and sufficient dosage of epoprostenol, we aimed to substantiate the usefulness of decreasing PAP for improving PAH prognosis by observing the yearly changes in prognostic factors, selecting and comparing the candidate factors, and determining the cut-off of a possible prognostic target to facilitate planning of the optimal therapeutic strategy.

Methods

Patients

This retrospective study targeted consecutive patients with IPAH/HPAH who visited Keio University Hospital and Kyorin University Hospital, two big PH centers in Tokyo, between 1999 and 2011. PH was defined as mPAP >25 mmHg on cardiac catheterization according to the ESC guidelines.[1] Those with group 2 etiology (left heart disease), group 3 (lung disease or hypoxic disease), group 4 (chronic thromboembolic PH), and group 5 (miscellaneous disease) were excluded after the appropriate examinations, and next, connective tissue disease, portopulmonary hypertension, congenital shunt disease, and other associated PAH types were ruled out according to the ESC guidelines.[1] The remaining 70 consecutive patients were screened, and finally, 64 patients were included because the 6-min walk test (6MWT) was not performed between 2004 and 2007

and hence some patients lacked these data. Age at the first hospital visit was used in the analysis. Patients were divided into 2 groups based on survival status in January 2013: 40 patients were living and 24 had died.

Treatment consisting of epoprostenol via an ambulatory continuous drip infusion was introduced in approximately 70% of the patients studied (46/64), with an NYHA functional class greater than III and many poor prognostic factors according to the ESC guidelines, or with right heart failure.

This study was conducted in accordance with the Declaration of Helsinki and approved by Kyorin University reviewing committee (approval number: 1261), and written approval to participate in the study was obtained from all of the patients.
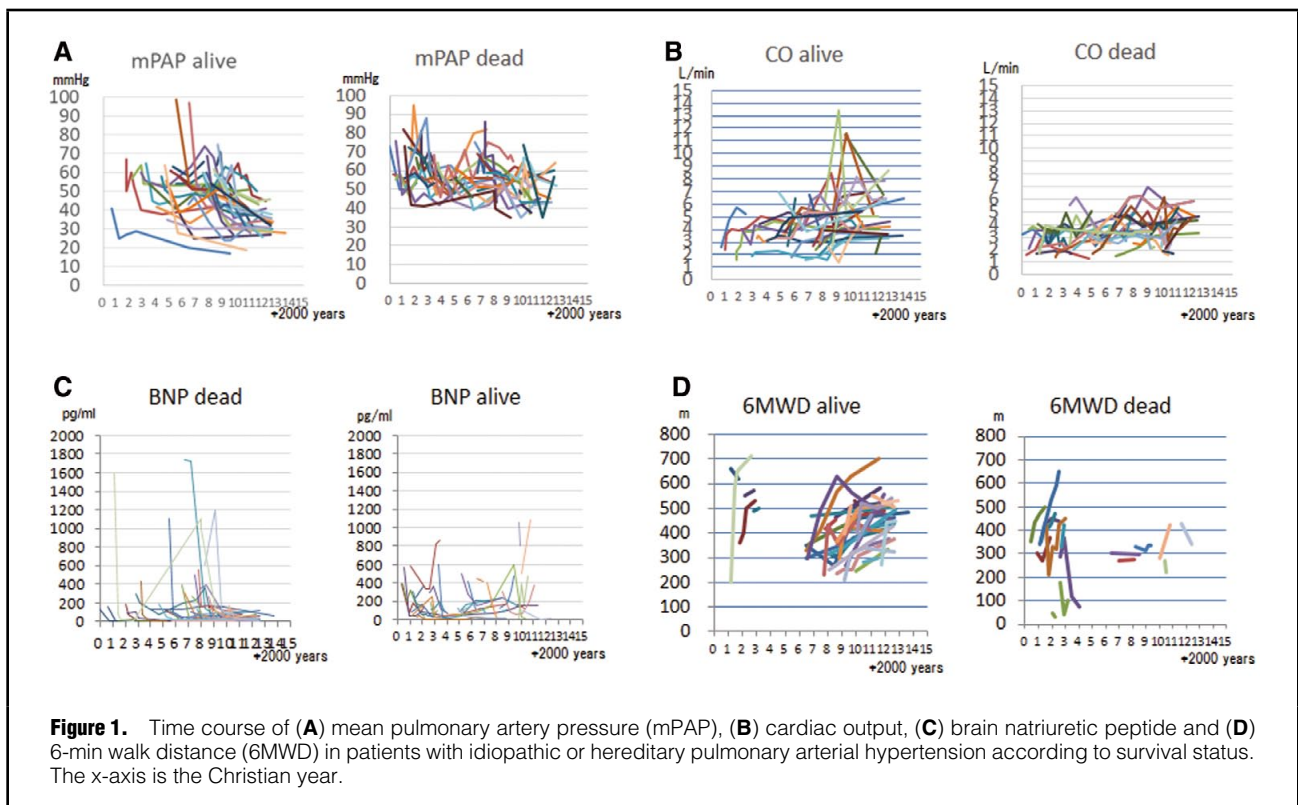
Prognostic Variables

The prognostic factors listed in the ESC guidelines,[1] that is, age, sex, and duration of symptoms, were used as baseline patient characteristics. In addition, use of drugs (i.e., epoprostenol, ERA, and PDE5I), mPAP, cardiac output (CO), mixed venous oxygen saturation (SvO$_2$) measured during right heart catheterization, BNP level, and 6-min walk distance (6MWD) at diagnosis and at the time of greatest improvement were evaluated. The data of diagnosis was defined as the time of right heart catheterization. Therefore, 14 variables (age, sex, duration of symptoms, use of the three drugs, and mPAP, CO, SvO$_2$, BNP, and 6MWD at diagnosis and at the time of greatest improvement) were analyzed.

Right heart catheterization was performed with a 6-Fr double-lumen, balloon-tipped, flow-directed catheter (Harmac Medical Products) via a transjugular approach. Measurements were obtained at the end of a normal expiration. Right atrial pressure, PAP, and pulmonary artery wedge pressure were recorded. CO was calculated using the Fick method.

Table 2. Multivariate Indicators of Death in IPAH/HPAH

	P-value	OR	95% CI
Sex	0.50	3.30	0.1–95
Minimum mPAP	0.005	1.44	1.1–1.9
Maximum CO	0.74	0.84	0.30–2.4
Maximum 6MWD	0.12	0.99	0.97–1.0
Minimum BNP	0.048	1.1	1.0–1.2
Epoprostenol use	0.03	0.1	0.0–0.7

CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

Figure 1. Time course of (**A**) mean pulmonary artery pressure (mPAP), (**B**) cardiac output, (**C**) brain natriuretic peptide and (**D**) 6-min walk distance (6MWD) in patients with idiopathic or hereditary pulmonary arterial hypertension according to survival status. The x-axis is the Christian year.

Statistical Analysis

Factors Related to Death Significant differences in the 14 prognostic variables between the survival and the non-survival groups were evaluated on univariate analysis using the Mann-Whitney U-test; when the continuous variables were not normally distributed (BNP and 6MWD), normal distribution was established using exponential transformation. Binary variables such as sex and use of certain drugs were compared between the 2 groups using the chi-squared test.

The variables that were significant on univariate analysis were then used in multivariate analysis with logistic regression to identify the variables most useful in differentiating the surviving from the non-surviving patients. In the logistic regression analysis, if the variables were not normally distributed (BNP and 6MWD), normal distribution was established using exponential transformation.
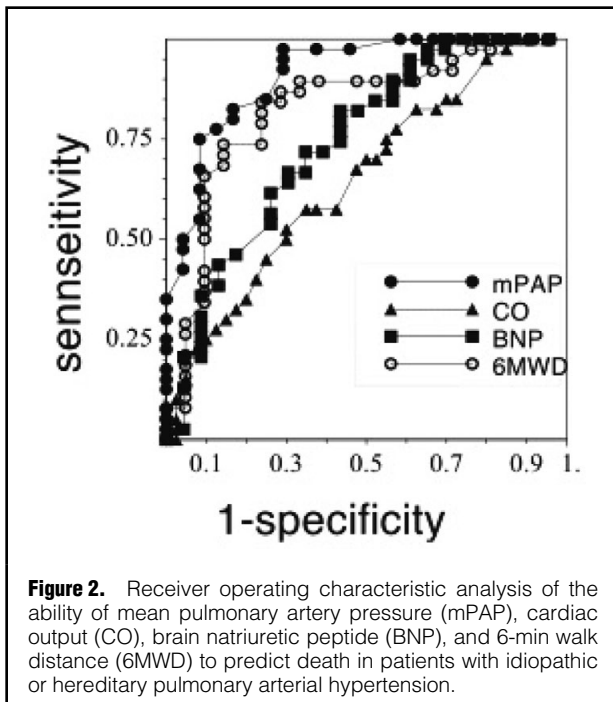
Time Course Changes Time-course changes in the variables identified as significantly different between the surviving and non-surviving patients on univariate analysis were evaluated.

Predictive Ability Area under the receiver operating characteristic (ROC) curve (AUC) was calculated for each significant prognostic variable selected on univariate analysis and was compared using Hanley's method, to identify the most effective prognostic variable.[10]

Identification of Optimal Cut-Off The prognostic variable identified as being the most effective according to AUC, was then analyzed to determine the optimal cut-off, using the sensitivity-specificity curve on ROC analysis. That prognostic variable was plotted on the x-axis, with the sensitivity and specificity both plotted on the y-axis, and the point at which the two curves intersected was identified as the optimal cut-off. The prognosis of 2 groups divided according to this cut-off was then compared on Kaplan-Meier analysis.

All statistical analyses were performed using Statflex (Artec, Osaka, Japan). P<0.05 was considered significant.

Figure 2. Receiver operating characteristic analysis of the ability of mean pulmonary artery pressure (mPAP), cardiac output (CO), brain natriuretic peptide (BNP), and 6-min walk distance (6MWD) to predict death in patients with idiopathic or hereditary pulmonary arterial hypertension.

Figure 3. Determination of the optimal cut-off of mean pulmonary artery pressure (mPAP; 42 mmHg) to differentiate between surviving and non-surviving patients with idiopathic or hereditary pulmonary arterial hypertension.

Results

Mean age of the 17 male patients was 32±11 years, and that of the 47 female patients was 36±11 years. The mean follow-up period was 5.2±3.4 years. Epoprostenol was used in 46 patients, ERA in 54 patients and PDE5I in 54 (**Table 1**).

Factors Related to Death

Survival Status The factors that differed significantly according to survival status were sex, minimum mPAP, maximum CO, maximum 6MWD, minimum BNP, and epoprostenol use during the entire clinical course (**Table 1**).

Differentiation of Survival On multiple regression analysis of the aforementioned 6 variables, minimum mPAP, minimum BNP and epoprostenol use were found to be significantly associated with death (**Table 2**), with mPAP having the largest OR of 1.44 of the 3 selected variables.

Time Course Changes

Very few of the non-surviving patients had a minimum mPAP <42 mmHg (**Figure 1**), but when the time courses of the other parameters were compared between the surviving and non-surviving groups, none of them differed significantly. mPAP, however, is useful, because it tells us that those non-surviving patients who had minimum mPAP <42 mmHg were unlikely to have died of PH.

Predictive Ability

The mPAP ROC curve plotted at the far left had the largest AUC of the 4 diagnostic variables on visual inspection. On comparison, the AUC of mPAP was significantly larger than that of CO and 6MWD, but not of that of BNP using Hanley's method.[10] The AUC of BNP, however, was not different from that of CO or 6MWD. Thus, mPAP was the best indicator for distinguishing fatality in patients with IPAH/HPAH (**Figure 2**). This corresponds to the results of
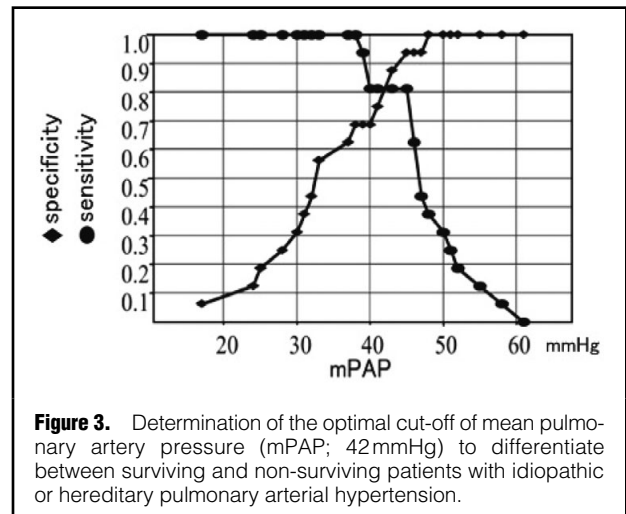
multiple regression analysis conducted to identify the factor most strongly associated with death.

Survival Analysis

The optimal value in the sensitivity-specificity curve of minimum mPAP during the clinical course was 42 mmHg (**Figure 3**). On Kaplan-Meier survival analysis of the 2 curves classified by mPAP of 42 mmHg, the survival of patients with mPAP ≤42 mmHg was significantly better and could reach as high as >80% up to 10 years (**Figure 4**).

Discussion

According to the present analysis, the treatment target most useful for improving the prognosis of IPAH/HPAH is mPAP, and the cut-off is less than approximately 40 mmHg. This principle was also adopted in the latest guideline for IPAH by the Japanese Circulation Society in 2017.[6]

The prognosis of IPAH/HPAH in Japan has improved greatly, and the 3-year survival in 108 de novo IPAH patients was approximately 96% according to a Japanese prospective registry from 2008 to 2013.[5] This was also recently demonstrated in a retrospective multicenter study in Japan.[11] The prognosis was excellent, probably because almost all Japanese PH specialists have been adopting an aggressive regimen of increasing epoprostenol following the experience in Okayama Medical Center in 2010.[7] In that report, the authors claimed that the survival rate of 46 IPAH/HPAH patients was 70% in the average follow-up period of approximately 6 years. Moreover, only the survivors had significantly reduced mPAP, and their 10-year survival was 100%.[7] In the present study, we investigated whether reducing mPAP was an effective strategy for improving prognosis in patients with IPAH/HPAH based on the rapid and sufficient increased dosage of epoprostenol used in a Japanese cohort,[8] and by using a uniform method of treatment and evaluation. We have been utilizing this aggressive epoprostenol strategy since 2005, and have treated approximately 70% of the patients enrolled in this study with epoprostenol. The difference between the Ogawa et al study[9] and the present one is that the Ogawa et al study lacked a comparison between the candidate diagnostic variables for the treatment target in IPAH, such
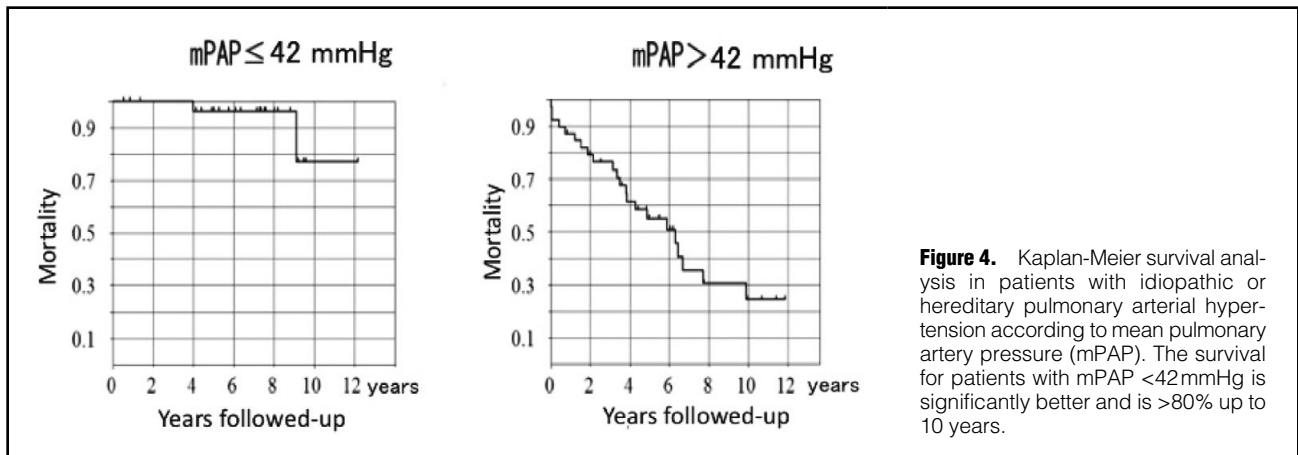
Figure 4. Kaplan-Meier survival analysis in patients with idiopathic or hereditary pulmonary arterial hypertension according to mean pulmonary artery pressure (mPAP). The survival for patients with mPAP <42mmHg is significantly better and is >80% up to 10 years.

as mPAP, 6MWD and so on. Their study principally referred to several diagnostic variables but did not explain why mPAP was selected after comparing these variables. We did, however, carry out such comparisons (**Figures 1,2**), and then we identified the critical value for good prognosis (**Figures 3,4**). The Ogawa et al work is represented in our **Figures 3,4**; their insight was extraordinary.

The value most improved was adopted in each prognostic variable to determine the best indicator of direct treatment for improving prognosis because in most patients who died, mPAP was ≥40mmHg during the clinical course (**Figure 1**). Thus, we observed that mPAP was less than approximately 40mmHg in most of the living patients. A small number of non-surviving patients whose mPAP was <40mmHg (4 patients) died of causes unrelated to PH. The only diagnostic variable that had this kind of critical value was mPAP. This was proven by the fact that prognosis differed significantly between the 2 groups when the patients were classified based on the critical mPAP cut-off, which was identified on ROC analysis and was the same as that reported at another center in Japan.[8]

The development of a risk stratification for IPAH/HPAH patients and of the resultant treatment strategy has been recommended using a multidimensional approach, including clinical, functional, exercise, biochemical, echocardiographic, and hemodynamic variables.[12] In the French Pulmonary Hypertension Network registry, functional class, BNP, 6MWD, mPAP, cardiac index, and SvO2 were reported to be significant in evaluating prognosis, but mPAP was not reported as the best variable for predicting outcome,[13] in contrast to the present report. This could be because only Japan has adopted an aggressive increase in the regimen of epoprostenol since 2005. Utilization of this strategy had increased its use substantially all over Japan by approximately 2010, and several centers in Japan have reported that a reduction of mPAP was found to be related to improved prognosis.[8,14] NYHA and echocardiography data, the reported important diagnostic markers, were not included in this paper. The purpose of this study was to determine the treatment target for improving IPAH, and not to identify the factors related to prognosis. NYHA is related to prognosis, but it is very difficult to use as a therapeutic target to improve prognosis in IPAH because downgrading of the NYHA functional class by one class is challenging to evaluate objectively. Echocardiography parameters were included in the 2018 Nice PH World Congress as one of the prognostic variables,[12] but it was not included in the French registry.[13] Sometimes echocardiography data cannot be obtained clearly because of difficulty in imaging, thereby causing problems with accuracy when they are compared to other diagnostic variables as treatment targets. Therefore, these parameters were not included in the present analysis.

Of the variables studied to identify a treatment target to improve prognosis, minimum BNP and epoprostenol use were found to be significant in addition to mPAP. BNP reflects improvement of PH, but no clear prognostic target can be seen in **Figure 1**, which shows BNP data during the entire IPAH patient clinical course. Epoprostenol has been used for patients who responded poorly to oral vasodilators. Therefore, extraction of epoprostenol as a significant prognostic marker resulted from the poor therapeutic response but did not contribute to the poor outcome. No previous study has reported that epoprostenol resulted in poor prognosis in patients with IPAH.

When we move, CO is increased, following which the pulmonary artery usually dilates to suppress the change in PAP so that it increases as little as possible. However, when the pulmonary artery wall is hypertrophied such as in PAH, a stiff pulmonary artery wall cannot suppress the increase in PAP sufficiently when we move to the same extent. Therefore, the slope of the PAP-CO curve in the pulmonary artery is usually gentle because compliance of the pulmonary artery is very high. In contrast, the slope is steep when the compliance of the pulmonary artery wall becomes low in PAH, and thus, PAP rises easily. Therefore, PAP could potentially play a key role in aggravating PAH from a physiological viewpoint. In this report, this important physiological factor, PAP, was clarified in clinical practice.

Study Limitations

A limitation of this study was the small number of patients analyzed. Several studies, however, have used local cohorts to correlate mPAP with significant prognostic factors in Japan.[15] A large-scale multicenter collaborative study on mPAP as the treatment target to improve prognosis in IPAH or PAH should be performed in Japan. Another limitation was a selection of prognostic variables in this study, indicating that other unrecognized confounding factors assumed the same role instead of mPAP. In the present study, however, the most important possible

therapeutic targets were included, and several significant prognostic factors that were considered difficult to use as treatment targets, such as the NYHA functional class, were not evaluated.

Conclusions

In treating patients with IPAH/HPAH, mPAP is the most useful treatment target, and mPAP should be decreased to less than approximately 40 mmHg in order to improve outcome. If this is accomplished, the 10-year survival may reach 80%. Future prospective research incorporating the current study design should be performed.

Data Availability

The authors confirm that the data supporting the present findings are available in the article.

The individual de-identified participant data such as the background information, hemodynamics, and other examination data will be shared after publication of this study for 6 months only, after identification of the researchers interested for future treatment of PAH. The data in the article, other documents on the study protocol and statistical analysis will also be available.

Disclosures

The authors declare no conflicts of interest.

IRB Information

This study was approved by the Kyorin University reviewing committee (approval number: 1261).

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