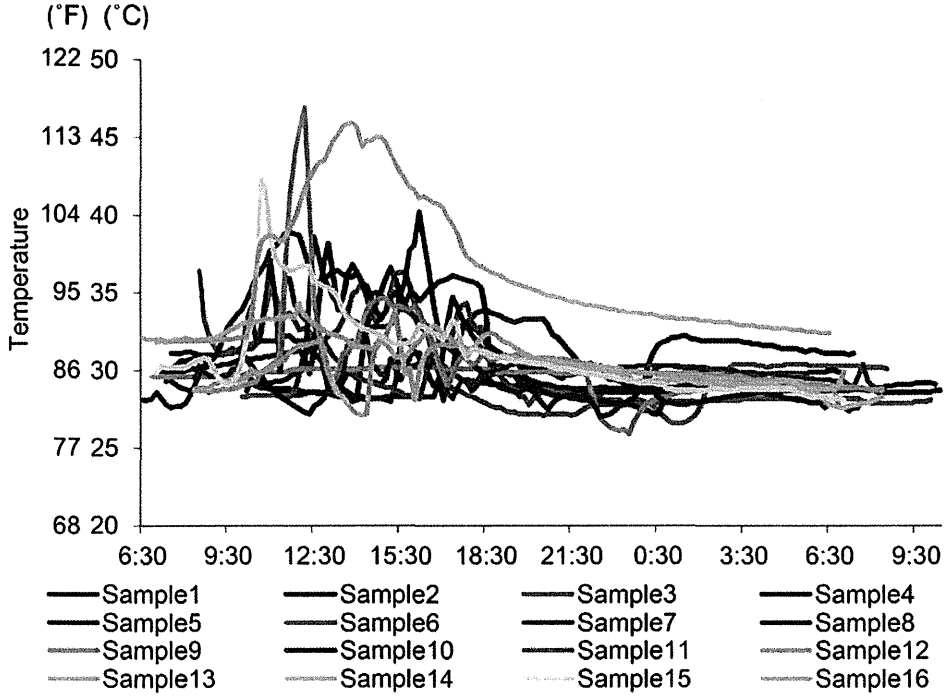

Figure 1. Temperature changes around the medication cassette.
doi:10.1371/journal.pone.0052216.g001

Materials and Methods

Study Design

The investigation was performed in cities located in Saitama, Yamanashi, Gifu, Shiga, and Osaka Prefectures from August 11, 2011, to August 25, 2011. Five healthy volunteers carried the CADD-Legacy Pump (Smiths Medical Inc.) in a bag during their daily living activities. The 100-mL medication cassette was filled with physiological saline instead of the usual epoprostenol solution and attached to the CADD-Legacy Pump. However, no interventions were performed on the volunteers, and no samples were gathered. This study does not fall under the category of a clinical trial according to the ethical guidelines for clinical studies of the Ministry of Health, Labour and Welfare, Japan; therefore, ethical committee approval was not required. Despite this, we obtained written informed consent from all volunteers.

Temperature and Weather Record Sampling

A temperature sensor with a recording function (Temp Tale4, Nihon Sensitech Corp.) was attached to the side of the cassette, and a second sensor was attached to the outside of the bag. Each temperature sensor recorded the temperature at 10-min intervals for 24 h from the start of the study. Five volunteers participated in the study for 24 h continuously on at least 3 occasions. On each occasion, the volunteer recorded the weather of the current day, type of bag containing the pump, activity undertaken every hour, and location (i.e., indoors or outdoors). As indoor conditions are likely to be controlled by air conditioning, to comprehensively assess temperatures, the subjects were required to spend time or undertake activities outdoors for at least 2 consecutive hours per day.

We also investigated the temperatures of the solution in the medication cassette, and their correlation with temperatures around the medication cassette. Three healthy volunteers carried a medication cassette containing saline and a thermometer to record for 24 h continuously on at least three occasions. Additionally, temperature changes outside the bag, around the cassette, and in the solution were compared between when the bag was left outdoors in the sunlight and in the shade.

The temperature sensors were retrieved after the investigation was completed, and the temperatures recorded therein were tabulated. Data for atmospheric temperature and sunshine duration on the days of the investigation were obtained from appropriate meteorological agencies.

Statistical Analysis

All statistical analyses were performed with SAS software version 9.1.3 (SAS Institute Japan Ltd., Tokyo, Japan). The correlations of temperatures within groups were analyzed using the correlation (CORR) procedure. Regression curves from plotted graphs were calculated using the general linear model (GLM) procedure.

Results

Correlation Among the Temperatures at each Site

A total of 16 assessments were performed. The environmental conditions on each occasion of the investigation are shown in Table S1. During the investigation periods, the mean, mean maximum, and mean minimum atmospheric temperatures were 29.6±1.5°C (85.3±2.7°F), 34.6±1.9°C (94.3±3.4°F), and 26.1±1.5°C (79.0±2.7°F), respectively (Table 1). The temperature around the medication cassette did not fall below 25°C (77°F) on any occasion during the investigational period; however, it exceeded 35°C (95°F) on some occasions (Figure 1). During the study period, the mean durations during which the temperature

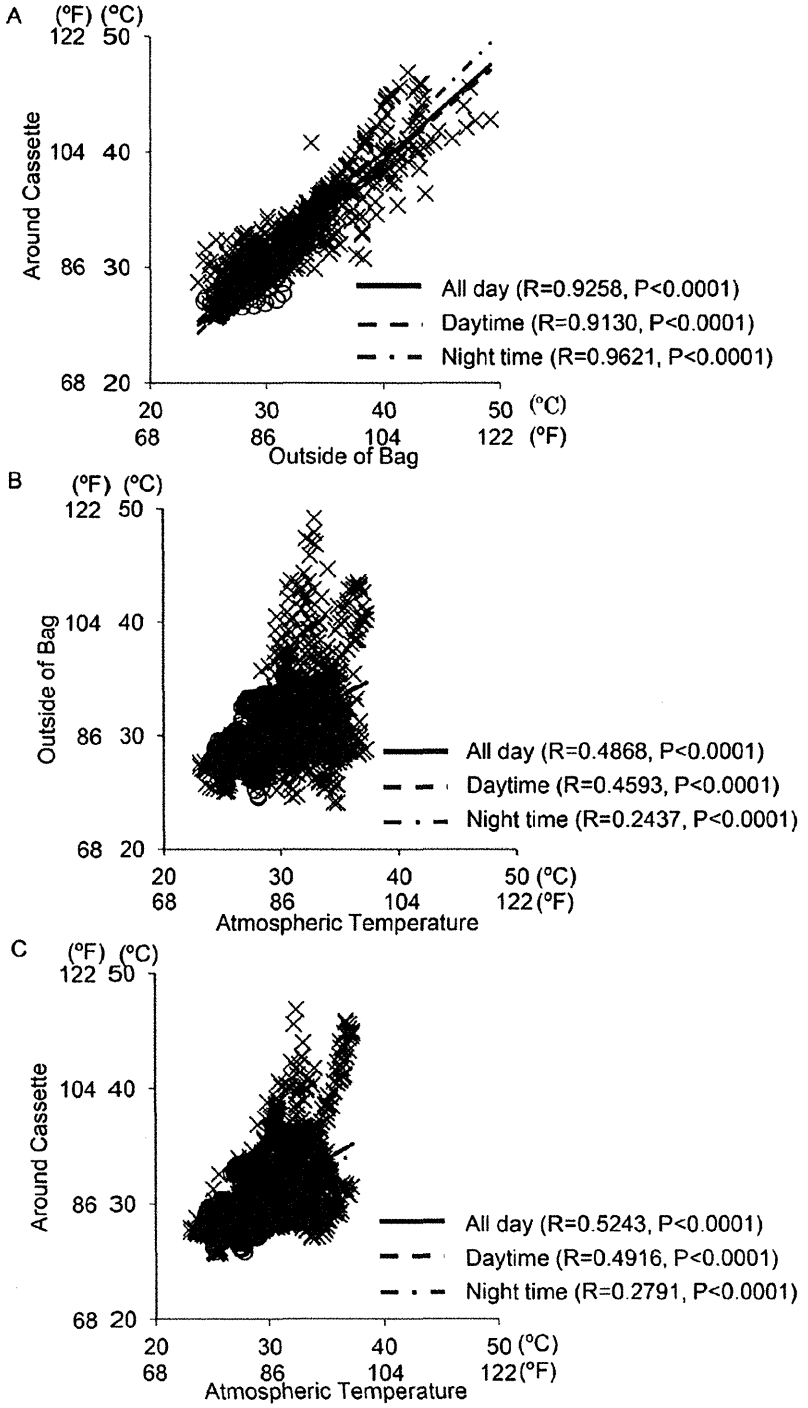

Figure 2. Temperature correlation among outside the bag, around cassette and atmosphere. Correlation between the (A) temperature outside the bag and around the cassette, (B) atmospheric temperature and temperature outside the bag, and (C) atmospheric temperature and temperature around the cassette in daytime (×) and nighttime (○). The relativity of temperatures within groups was analyzed using the CORR procedure. Regression curves from plotted graphs were calculated using the GLM procedure.
doi:10.1371/journal.pone.0052216.g002

around the cassette exceeded 35°C or 40°C were 96.9±156.4 min and 24.4±77.3 min, respectively. On 4 instances, the temperature around the medication cassette rose rapidly, i.e., the rise in temperature was more than 6°C (11°F) in 20 min. However, on the whole, the temperatures rose slowly, i.e., the temperature increased by 6°C in more than 60 min. Three different

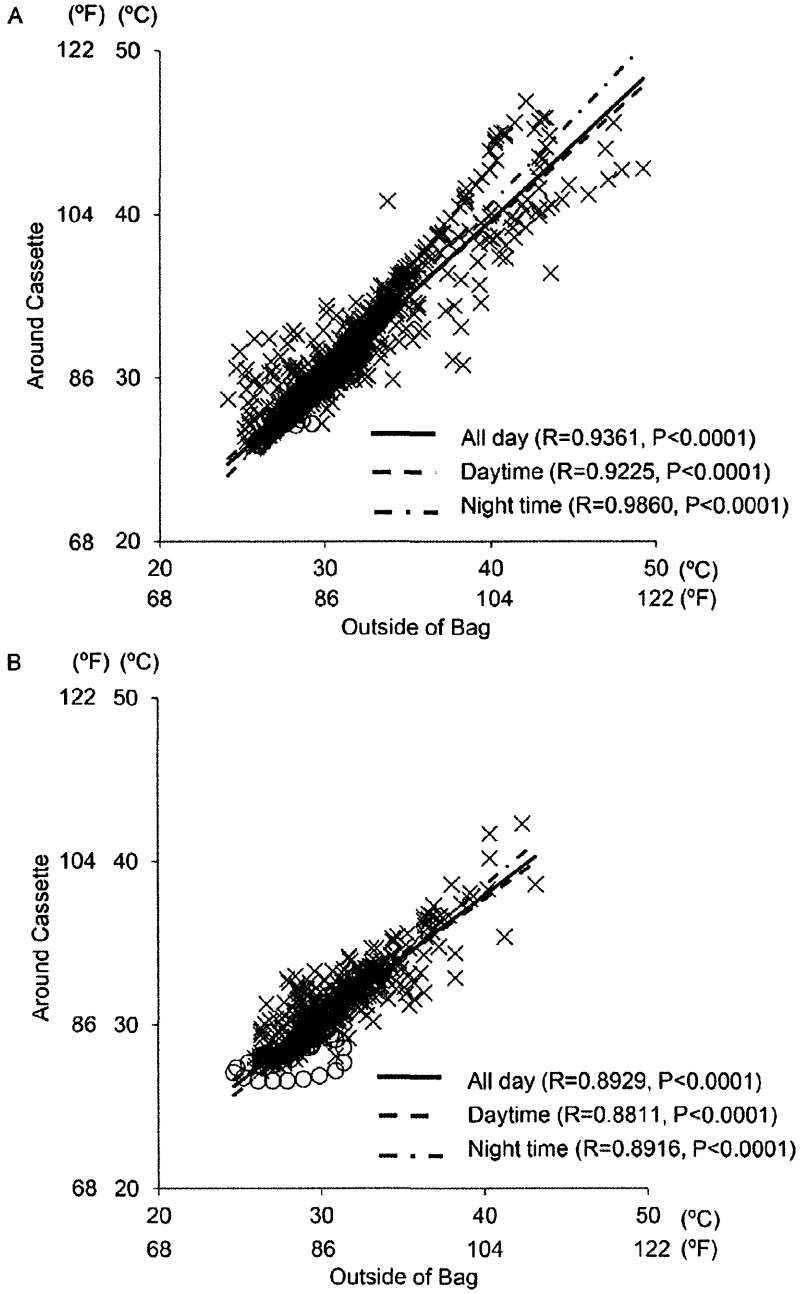

Figure 3. Difference in temperature correlation by material of the bag. Correlations between temperature outside the bag and temperature around the cassette in (A) cloth bags and (B) leather/synthetic leather bags in daytime (×) and nighttime (○). The relativity of temperatures within groups was analyzed using the CORR procedure. Regression curves from plotted graphs were calculated using the GLM procedure.
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temperature correlation analyses were conducted: (1) between the temperatures outside the bag and around the cassette, (2) between the temperature outside the bag and atmospheric temperature, and (3) between the temperature around the cassette and atmospheric temperature. The temperatures outside the bag and around the cassette were positively correlated ($r = 0.9258$, $P<0.0001$, Figure 2A). Meanwhile, weak correlations were observed between the atmospheric temperature and temperature outside the bag ($r = 0.4868$ for all days, $P<0.0001$, Figure 2B), and atmospheric temperature and temperature around the cassette ($r = 0.5243$ for all days, $P<0.0001$, Figure 2C). At one instance in which the temperatures outside the bag and around the cassette increased rapidly, there were no correlations between them, the atmospheric temperature, or the sunshine duration. The changes in the bag and cassette temperatures in shaded areas were similar to those in atmospheric temperature when the bag was left outdoors in the daytime (Figure S1A). When the bags were exposed to sunlight, continuously high temperatures persisted

Table 1. Atmospheric temperature and time durations when the temperature around the cassette exceeded 25°C, 35°C, and 40°C.

	Maximum	Minimum	Mean	S.D.
Mean atmospheric temperature (°C/°F)	31.7/89.1	27.0/80.6	29.6/85.3	1.5/2.7
Maximum atmospheric temperature (°C/°F)	37.3/99.1	31.1/88.0	34.6/94.3	1.9/3.4
Minimum atmospheric temperature (°C/°F)	28.7/83.7	23.1/73.6	26.1/79.0	1.5/2.7
Determination time (min)	1450	1450	1450	0
Cumulative time (min) during which the temperature around the cassette exceeded 25°C (77°F)	1450	1450	1450	0
Cumulative time (min) during which the temperature around the cassette exceeded 35°C (95°F)	0	600	96.9	156.4
Cumulative time (min) during which the temperature around the cassette exceeded 40°C (113°F)	0	310	24.4	77.3

doi:10.1371/journal.pone.0052216.t001

irrespective of the atmospheric temperature (Figure S1B). Additionally, the influence of the material of the bag on the temperature outside the bag and around cassette in daytime was analyzed. However, no differences were observed between synthetic leather, leather, and cloth bags (Figure 3). On one occasion, the temperature around the cassette increased at a greater rate than that outside the bag when left outdoors for more than 2 h. In addition, the temperature around the cassette decreased slower than the temperature outside the bag after returning indoors, although the temperatures around the cassette were very close to or lower than those outside the bag before going outdoors (data not shown).

Correlation between Temperatures Around the Cassette and in the Solution

Nine additional assessments were performed to compare temperatures around the cassette and in the solution. During the investigation period, the mean temperatures around the cassette and in the solution were 28.8±1.0°C (83.8±1.8°F) and 29.3±1.0°C (84.7±1.8°F), respectively. The temperature of solution did not fall below 25°C (77°F) on any occasion. Temperature around the cassette therefore correlated positively with those of the solution ($r = 0.8276$, $P<0.0001$; Figure S2).

The peak temperature of the solution was delayed compared to that outside the bag and around the cassette. Moreover, the temperature decline of the solution was also delayed compared to decreases in temperature around the cassette (Figure S1 A and B). To evaluate how sensitive the temperature was to change at each site, we compared temperature changes every 10 minutes in each segment within the nine additional assessments. The mean change in solution temperature (0.15±0.19°C/0.27±0.34°F) tended to be less than that outside the bag (0.77±1.25°C/1.35±2.25°F, Figure S3).

Discussion

In this study, the changes in temperature around the cassette and carrying bag during routine daily activities in the hottest period of summer were investigated. Summers in Japan are hot and humid, and the atmospheric temperature exceeds 30°C regularly. In this study, the change in temperature around the cassette was strongly correlated with the temperature outside the bag. There was a high correlation between the temperatures of the solution and around the cassette ($r = 0.8276$: Figure S2). These results suggested that measurement of temperature around the cassette provided a good representation of the solution temperature inside the cassette bag. In contrast, the cassette temperature and temperature outside the bag were weakly correlated with the atmospheric temperature. Furthermore, when the bag was left outdoors in shaded areas all day long, the temperatures outside the bag and around the cassette tended to follow changes in the atmospheric temperature, although the baseline temperatures were different. However, when the bag was exposed to direct sunlight, temperature of the cassette and temperature outside the bag were considerably higher than the atmospheric temperature; the atmospheric temperature was weakly correlated with the temperatures outside the bag and around the cassette. Moreover, the temperature inside cars can increase significantly in sunlight even in winter [7]. Although, it is possible that patients with PAH with significant functional impairment are likely to spend most of their time indoors where temperatures are controlled by air conditioning, the present findings demonstrate that exposure to sunlight can significantly increase the temperatures of the cassette very quickly. Therefore, additional care should be taken to protect the bag and cassette/pump system from sunlight exposure. Other studies report that the thickness of the cloth of a bag may influence the temperature under radiant light [8]. However, the present results indicate that the bag material does not affect changes in cassette temperature; in this study, there were no significant differences with respect to temperature changes between bags made of cloth, leather, or synthetic leather.

Moreover, mean temperature changes every 10 minutes were smaller for the solution compared to the other three measurement sites. These results suggested that temperature of the medication solution is less influenced by rapidly rising temperatures around the cassette and outside the bag, but also that once the temperature of solution rises with long-term exposure to a high temperature such as that induced by sunlight exposure, the increased temperature is maintained for a prolonged time. This highlights the need to avoid exposure to direct sunlight or minimize any unavoidable exposure to raised atmospheric temperature.

This study was performed in the summer to evaluate the temperatures during the hottest time of the year. However, a similar study in the winter may also be useful since patients may spend most of their time in warm environments and inadvertently come into close contact with various heating sources–the impacts of which were not assessed in the present study.

Conclusion

The results of this study demonstrate that the cassette temperature and temperature outside the bag are closely

correlated and are likely to be higher than the atmospheric temperature in conditions of both shade and direct sunlight. In addition, in Japan during summer, the temperatures of the cassette and carrying bag on the study days remained consistently above 25°C (77°F) and at times, up to 35°C (95°F) or higher. These results suggest that exposure to direct sunlight should be avoided to minimize the risk of medication cassette temperatures exceeding the temperature specifications for intravenous medications that are used for continuous infusion.

Supporting Information

Figure S1 Temperature changes in (A) shaded and (B) sunny regions. Temperature changes outside the bag, around the cassette and in the solution. They were recorded when the bag was left outdoors in the shade (A) and in the sunny (B) areas.
(TIF)

Figure S2 Temperature correlation between the solution and around the cassette. Correlations between daytime (×) and night (○) temperatures around the cassette and in the solution. The relativity of temperatures within groups was analyzed using the CORR procedure. Regression curves from plotted graphs were calculated using the GLM procedure.
(TIF)

Figure S3 Mean temperature changes over time. Temperature changes every 10 minutes were analyzed in the solution, around the cassette, outside the bag, and in the atmosphere (0.15±0.19(SD)°C/0.27±0.34°F, 0.37±0.66°C/0.67±1.2°F, 0.77±1.25°C/1.38±2.26°F and 0.32±0.30°C/0.58±0.54°F, respectively).
(TIF)

Table S1 Atmospheric temperature and duration of time in which the temperature was higher than 25, 35 or 40°C around cassette on determination of each sample.
(DOC)

Author Contributions

Conceived and designed the experiments: YT KF. Performed the experiments: TY MT TO. Analyzed the data: YT YN. Contributed reagents/materials/analysis tools: YN YO. Wrote the paper: YT YN.

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Human Pentraxin 3 (PTX3) as a Novel Biomarker for the Diagnosis of Pulmonary Arterial Hypertension

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Abstract

Background: Although inflammation is an important feature of pulmonary arterial hypertension (PAH), the usefulness of local inflammatory markers as biomarkers for PAH is unknown. In this study, we tested whether plasma concentrations of human pentraxin 3 (PTX3), a local inflammatory marker, would be a useful biomarker for detecting PAH.

Methods: Plasma PTX3 concentrations were evaluated in 50 PAH patients (27 with idiopathic PAH, 17 with PAH associated with connective tissue disease (CTD-PAH), and six with congenital heart disease), 100 age and sex-matched healthy controls, and 34 disease-matched CTD patients without PAH. Plasma concentrations of B-type natriuretic peptide (BNP) and C-reactive protein (CRP) were also determined.

Results: Mean PTX3 levels were significantly higher in all PAH patients than in the healthy controls (4.40±0.37 vs. 1.94±0.09 ng/mL, respectively; $P<0.001$). Using a threshold level of 2.84 ng/mL, PTX3 yielded a sensitivity of 74.0% and a specificity of 84.0% for the detection of PAH. In CTD-PAH patients, mean PTX3 concentrations were significantly higher than in CTD patients without PAH (5.02±0.69 vs. 2.40±0.14 ng/mL, respectively; $P<0.001$). There was no significant correlation between plasma levels of PTX3 and BNP or CRP. Receiver operating characteristic (ROC) curves for screening PAH in patients with CTD revealed that PTX3 (area under the ROC curve 0.866) is superior to BNP. Using a PTX3 threshold of 2.85 ng/mL maximized true-positive and false-negative results (sensitivity 94.1%, specificity 73.5%).

Conclusion: Plasma concentrations of PTX3 may be a better biomarker of PAH than BNP, especially in patients with CTD.

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Introduction

Despite the development of drugs that can bring about improvements in hemodynamics, exercise capacity, and quality of life, pulmonary arterial hypertension (PAH) remains a life-threatening disease with a poor prognosis. Recent guidelines [1], [2] encourage the use of screening examinations, such as an echocardiogram (UCG), in high-risk populations for the early detection of PAH [3].

To detect PAH in patients with connective tissue disease (CTD), the obvious screening tests are an UCG [4] and spirometry, including assessment of the diffusing capacity of the lung for carbon monoxide (DLCO) [5], [6]. Previous studies have suggested that B-type natriuretic peptide (BNP) and its N-terminal prohormone (NT-proBNP) are potential biomarkers for PAH [7], [8]. However, neither BNP nor NT-pro BNP are specific biomarkers of the degeneration of the pulmonary artery; rather, they are biomarkers of cardiac burden resulting from right heart failure.

In the present study, we demonstrate that human pentraxin 3 (PTX3) is a specific biomarker for PAH, reflecting pulmonary vascular degeneration, especially in patients with CTD. This is the first study in which the usefulness of PTX3 as a biomarker for PAH has been demonstrated.

Pentraxins are a family of evolutionarily conserved proteins [9]. They are divided into short and long pentraxins on the basis of their primary structure. C-Reactive protein (CRP) and serum amyloid P are the classic short pentraxins that are produced in the liver in response to systemic inflammatory cytokines. In contrast, PTX3 is one of the long pentraxins. It is synthesized by local vascular cells, such as smooth muscle cells, endothelial cells and fibroblasts, as well as innate immunity cells at sites of inflammation [10]. PTX3 plays a key role in the regulation of cell proliferation and angiogenesis [11]. In the field of cardiovascular diseases, increased serum PTX3 levels have been reported in patients with

acute coronary syndromes. For example, increased plasma PTX3 levels have been reported in patients with acute myocardial injury in the 24 h after admission to hospital, with levels returning to normal after 3 days [12]. Similarly, PTX3 levels are higher in patients with unstable angina pectoris [13], with the changes in PTX3 levels found to be independent of other coronary risk factors, such as obesity and diabetes mellitus [13]. Finally, high serum PTX3 levels have been reported in patents with vasculitis, such as small-vessel vasculitis [14] and Takayasu aortitis [15], [16]. Thus, on the basis of these observations, we chose to investigate PTX3 as a potential biomarker for PAH.

Methods

Study Population

This study was approved by local ethical committee in Keio University Hospital (KEIO UNIVERSITY SCHOOL OF MEDICINE AN ETHICAL COMMITTEE, Tokyo, Japan), and all patients and controls who were enrolled in the study provided written informed consent. All patients with PAH and CTD in the present study were cared for at Keio University Hospital (Tokyo, Japan). Fifty consecutive PAH patients (27 with idiopathic or heritable PAH, 17 with CTD-associated PAH (CTD-PAH), and six with congenital heart disease-associated PAH) attending Keio University Hospital between January 2011 and July 2011 were eligible for inclusion in the study. As suggested by the Dana Point Classification system, diagnoses of PAH were made by performing right heart catheterization. The diagnostic criteria for PAH were based on the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines [1]. Extensive diagnostic evaluations were also performed to exclude other types of pulmonary hypertension (Class 2–5 of the Dana Point Classification system 2008). Two different populations were recruited to the study as control groups. The first comprised 100 healthy blood donors from a published cohort [17], matched for sex and age (within 10 years) with the PAH patients. There were twice as many donors as PAH patients, and the donors served as the control group for PTX3 measurements. The second control group consisted of 34 disease matched CTD patients without PAH (ruled out on the basis of UCG or right heart catheterization results). CTD patients with or without PAH were classified as having either scleroderma (SSc) or non-SSc CTD and disease matched. The plasma analysis performed in the present study was approved by the institutional review board of Keio University Hospital.

Assays

Serum markers (PTX3, CRP, BNP) were evaluated in all PAH patients during a single visit. Plasma concentrations of PTX3 were determined using a well-established, commercially available, highly sensitive and specific plasma ELISA using monoclonal antibodies (Perseus Proteomic, Tokyo, Japan) [13]. Plasma PTX3 concentrations were determined in healthy subjects using the same assay. No cross-reactions were observed with other pentraxins, including CRP. There were no missing data for PTX3, CRP, or BNP.

Patient Assessments

Disease duration (months) in the present study was calculated from the time of the initial diagnosis of PAH. Hemodynamic parameters were also evaluated by right heart catheterization within 1 month of the collection of blood samples. Furthermore, mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance (PVR) were determined in all patients with PAH. Patients with PAH were classified into two groups: (i) those undergoing active treatment with phosphodiesterase 5 inhibitors, endothelin receptor antagonists, and/or intravenous prostacyclin; and (ii) "treatment-naïve" patients (i.e. those not undergoing any active treatment regimen). Finally, patients with diabetes mellitus, obesity, and coronary artery diseases were analyzed separately because the inflammatory responses associated with these conditions may affect PTX3 levels.

Statistical Analysis

Plasma concentrations of PTX3, BNP, and CRP are given as the mean±SE. Statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Parametric tests, such as analysis of variance (ANOVA), were used after log transformation of the data, because PTX3 values did not exhibit normal distribution, but approximated a log-normal distribution [16]. Plasma concentrations of PTX3 were compared between the patient groups and healthy controls by Student's *t*-test. Differences in plasma PTX3 concentrations between patients with and without active treatment, as well as between SSc patients with and without PAH, were evaluated the same manner. Two-tailed $P<0.01$ was considered significant. Pearson's product–moment correlation coefficient was used to describe correlations between PTX3 and CRP or BNP after log transformation of the original data. Correlations between PTX3 and mPAP, PVR or disease duration were assessed by Spearman's rank correlation coefficient. Receiver operating characteristic (ROC) curves were constructed to determine optimal threshold values for plasma PTX3. Areas under ROC curves (AUC_{ROC}) and 95% confidence intervals (CI) were calculated to compare the effectiveness of PTX3 and BNP as markers of PAH.

Results

Patient Characteristics

In all, 184 subjects (50 PAH patients, 100 healthy controls, and 34 control CTD patients) were evaluated in the present study. In the group of PAH patients and healthy controls combined, there were 30 men and 120 women, with a mean (±SE) age at study entry of 52.6±1.2 years. As indicated in Table 1, the two groups were age and sex matched. Other patient characteristics are also given in Table 1. All PAH patients met the diagnostic criteria for PAH as specified in recent guidelines (1), and the presence of PAH was confirmed by right heart catheterization.

Plasma Concentrations of PTX3 and Other Biomarkers

Mean plasma PTX3 concentrations in PAH patients were 4.40±0.37 ng/mL (range 1.18–14.11 ng/mL, median 3.83 ng/mL), compared with 1.94±0.09 ng/mL (range 0.39–4.60 ng/mL, median 1.78 ng/mL) in healthy subjects (Figure 1A). The log-transformed values of original plasma PTX3 concentrations approximated a symmetrical distribution in both healthy control group and patients with PAH group (Figure 1B). After log transformation, PTX3 concentrations in the PAH patients and healthy controls were 1.34±0.07 and 0.55±0.05 log ng/mL, respectively, revealing a significant increase in PTX3 concentrations in PAH patients compared with controls ($P<0.001$). In addition, BNP and CRP concentrations, hemodynamic parameters (mPAP and PVR), and disease duration were determined in patients with PAH. There were no significant correlations between PTX3 concentrations and either CRP ($r=0.21$, $P=0.14$) or BNP ($r=0.33$, $P=0.02$). Similarly, there were no significant correlations between PTX3 concentrations and mPAP ($r=0.13$, $P=0.38$), PVR ($r=0.15$, $P=0.42$), or disease duration ($r=0.17$, $P=0.24$).

Table 1. Clinical characteristics of patients with pulmonary arterial hypertension and healthy controls.

	PAH patients (n=50)	Healthy controls (n=100)	P-value
Age (years)	51.0±2.4	53.3±1.4	0.377
No. women (%)	40 (80)	80 (80)	NS
No. with heart failure (%)	2 (4)	0	–
No. taking active treatment for PAH (%)	41 (82)	0	–
No. patients with diabetes mellitus (%)	0	0	NS
No. patients with obesity (%)	2	0	NS
No. patients with CAD (%)	0	0	NS
Pulmonary artery pressure (mmHg)	37.4±1.6	–	–
Pulmonary artery resistance (dyne.sec.cm^{-5})	691.0±64.6	–	–
Disease duration period (months)	33.3±4.4	–	–
Serum CRP (mg/dL)	0.14±0.04	–	–
Serum BNP (pg/mL)	113.2±28.6	–	–

Unless indicated otherwise, data are given as the mean ± SE.
PAH, pulmonary arterial hypertension; CAD, coronary artery diseases; CRP, C-reactive protein; BNP, B-type natriuretic peptide; NS, not significant.
doi:10.1371/journal.pone.0045834.t001

Conversely, significantly higher PTX3 concentrations were found in treatment-naïve patients (6.47±1.03 ng/mL, median 5.70 ng/mL) compared with patients undergoing active treatment (3.95±0.04 ng/mL, median 3.38 ng/mL; P<0.01; Figure 1C). The ROC curves indicated that PTX3 (AUC_{ROC} 0.866; 95% CI 0.805–0.928) is a potent biomarker for PAH (Figure 2). Using a threshold of 2.84 ng/mL, PTX3 maximized true-positive and false-negative results (sensitivity 74.0%, specificity 84.0%).

Plasma PTX3 as a Screening Biomarker for PAH Associated with CTD

From the PAH patient cohort, 17 patients with CTD were chosen for comparison with 34 disease-matched control patients who had CTD (SSc or non-SSc) but not PAH. The two groups were matched for age, gender, and the type of CTD (see Table 2). As noted in the Methods section, PAH was ruled out on the basis of right heart catheterization and/or UCG results.

Mean plasma PTX3 concentrations in the CTD-PAH and CTD patients were 5.02±0.69 ng/mL (range 1.82–12.94 ng/mL) and 2.40±0.14 ng/mL (range 0.70–4.29 ng/mL), respectively (Table 2). Log transformation of the data revealed significantly higher PTX3 levels in CTD-PAH than in CTD patients (1.49±0.12 vs. 0.82±0.06 log ng/mL, respectively; P<0.001). Conversely, there were no significant differences in CRP levels between the two groups, and BNP levels in CTD-PAH patients were tend to higher than those in CTD patients but not significant (Table 2). In addition, we evaluated the correlation between PTX3 levels and levels of BNP and/or CRP in patients with CTD; however, we failed to find any significant correlations (P=0.15 and 0.94, respectively; data not shown).

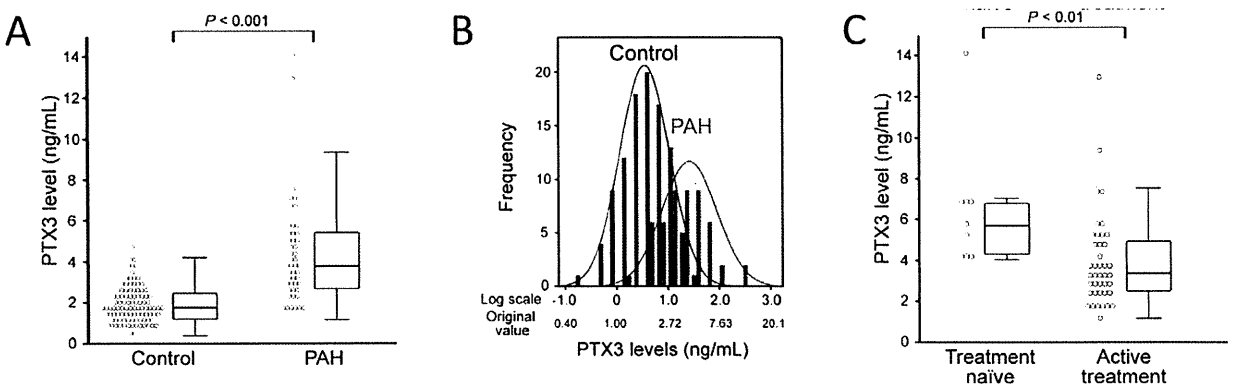

Figure 1. Serum pentraxin 3 (PTX3) concentrations in 50 patients with pulmonary arterial hypertension (PAH) and 100 healthy controls, and their correlation with serum concentrations of other biomarkers. A: Comparison of PTX3 concentrations in PAH patients and healthy controls. Mean plasma PTX3 concentrations were 4.40±0.37 and 1.94±0.09 ng/mL in the controls and PAH patients, respectively. B: Distribution of log-transformed PTX3 concentrations in PAH patients and healthy controls. C: Log-transformed PTX3 concentrations were significantly higher in patients with PAH than in healthy controls (1.34±0.07 vs. 0.55±0.05 log ng/mL, respectively; P<0.001). D, E: There was no correlation between plasma concentrations of PTX3 and either B-type natriuretic peptide (BNP; r=0.33, P=0.02) or C-reactive protein (CRP; r=0.21, P=0.14) in PAH patients.
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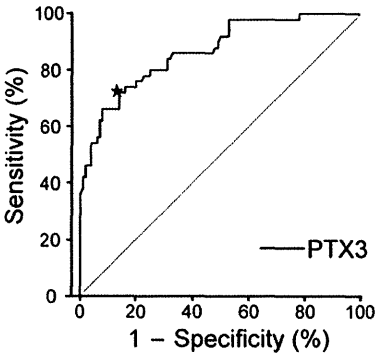

Figure 2. Receiver operating characteristic (ROC) curves for pentraxin 3 (PTX3). The area under the ROC curve was 0.866 (95% confidence interval 0.805–0.928). The star indicates the threshold concentration of 2.84 ng/mL PTX3 that maximized true-positive and false-negative results (sensitivity 74.0%, specificity 84.0%).
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The ROC curves revealed that PTX3 (AUC_{ROC} 0.866; 95% CI 0.757–0.974) was a more accurate marker of the presence of PAH than either CRP (AUC_{ROC} 0.518; 95% CI 0.333–0.704) or BNP (AUC_{ROC} 0.670; 95% CI 0.497–0.842; Figure 3). A threshold concentration of 2.85 ng/mL PTX3 maximized true-positive and false-negative results (sensitivity 94.1%, specificity 73.5%).

Discussion

The present study is the first report regarding the usefulness of PTX3, a local vascular inflammatory marker, as a screening tool for PAH. We found significantly higher levels of PTX3 in PAH patients compared with controls. There was no correlation between PTX3 levels and those of the classic systemic inflammatory marker CRP, which is of no value in screening for PAH. Moreover, in patients with CTD, comparisons of AUC_{ROC} revealed that PTX3 is a more sensitive biomarker for PAH than BNP. In addition, the AUC_{ROC} for PTX3 determined in the present study was superior to that reported previously for BNP [7].

Elevated PTX3 levels have been reported in many types of cardiovascular disease, including acute coronary syndrome [12], [13], congestive heart failure [18], and heart failure with normal ejection fraction [19]. In addition, recent reports have demonstrated the usefulness of PTX3 as a vascular inflammatory marker for distinguishing the activity of Takayasu aortitis [15], [16].

Local inflammatory activation in the pulmonary vasculature has already been shown to play an important role in the establishment of PAH [20], particularly PAH associated with CTD [21]. Recent studies have investigated whether PTX3 has a role in vascular disease and angiogenesis. PTX3 is produced at sites of vascular inflammation not only by smooth muscle and endothelial cells, but also by macrophages infiltrating the lesion [11], [22], [23], [24], [25], [26]. Interestingly, it has been reported that activated monocytes/macrophages contribute to the establishment of PAH under hypoxic conditions, as well as in patients with SSc [27], [28]. Moreover, some studies investigating gene expression in peripheral blood mononuclear cells from patients with SSc have reported upregulated *PTX3* gene expression in addition to that of VEGF and other inflammatory compounds [29], [30]. These findings provide strong support for our contention that PTX3 may be a potent biomarker for the detection of PAH, especially in patients with CTD.

Table 2. Clinical characteristics and biomarkers in patients with connective tissue disease, with or without pulmonary arterial hypertension.

	CTD-PAH ($n=17$)	CTD alone ($n=34$)	*P*-value
Age (years)	56.3±4.6	56.3±2.7	0.990
No. women (%)	15 (88)	31 (91)	0.745
No. with SSc (%)	10 (59)	20 (59)	1
No. with heart failure (%)	1 (6)	0	–
No. being treated for PAH (%)	17 (100)	0	–
Serum PTX3 (mg/dL)	5.02±0.69	2.40±0.14	<0.001
Serum CRP (mg/dL)	0.24±0.09	0.22±0.04	0.936
Serum BNP (pg/mL)	189.3±74.4	49.3±12.1	0.014

Unless indicated otherwise, data are given as the mean ± SE.
CTD, connective tissue disease; PAH, pulmonary arterial hypertension; SSc, scleroderma; CRP, C-reactive protein; BNP, B-type natriuretic peptide; PTX3, pentraxin 3.
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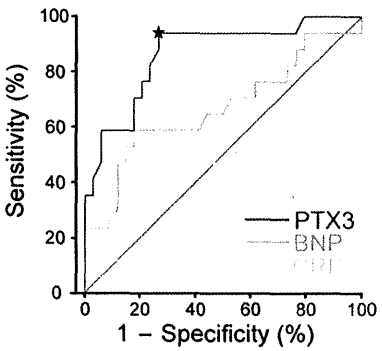

Figure 3. Receiver operating characteristic (ROC) curves for pentraxin 3 (PTX3) and other biomarkers in patients with connective tissue disease (CTD). The areas under the ROC curve (AUC_{ROC}) for PTX3 was 0.866 (95% confidence interval (CI) 0.757–0.974). The star indicates the threshold concentration of 2.85 ng/mL PTX3 that maximized true-positive and false-negative results (sensitivity 94.1%, specificity 73.5%). The AUC_{ROC} for C-reactive protein (CRP) was 0.518 (95% CI 0.333–0.704), whereas that for B-type natriuretic peptide (BNP) was 0.670 (95% CI 0.497–0.842).
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In the present study, we investigated whether PTX3, the regulation of which is independent of that of the systemic inflammatory marker CRP, was a useful biomarker for diagnosing PAH. We found that PTX3 may be a more sensitive biomarker for PAH than BNP, which is, to date, the most established biomarker for PAH, especially in patients with CTD-PAH. Our findings suggest that PTX3 does not reflect the cardiac burden due to the pulmonary hypertension, but rather the activity of pulmonary vascular degeneration because PTX3 levels were significantly decreased after active treatment specifically for PAH.

In conclusion, we found that determining PTX3 concentrations may be more useful than BNP measurements for the detection of PAH, especially among patients with CTD. A limitation of the present study is that it is a single center and cross-sectional case control study and, as such, does not confirm the causal relationship

between PTX3 and PAH. Further multicenter prospective studies to confirm the findings of the present study in a broader spectrum of patients with PAH and to evaluate the relationship between the disease activities of PAH and increases in PTX3 are needed before PTX3 can be used routinely as a screening biomarker. Furthermore, the role of PTX3 in lung tissue remains to be determined.

Author Contributions

Conceived and designed the experiments: YT TO KI. Performed the experiments: M. Kuwana MT TY M. Kataoka. Analyzed the data: KK MS TK JF. Contributed reagents/materials/analysis tools: KI HD TS KF. Wrote the paper: YT KF.

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Favorable Effect of Sorafenib in a Patient with Neurofibromatosis-associated Pulmonary Hypertension

To the Editor:

Neurofibromatosis type 1 (NF1) is an autosomal dominant disease that is caused by mutations in Nf-1. Nf-1 works as a tumor suppressor gene that regulates a proto-oncogene, Ras. Some patients with NF1 suffer from pulmonary arterial hypertension (PAH); the current classification for PAH (Dana Point classification) categorizes NF1-associated PAH as pulmonary hypertension with unclear multifactorial mechanisms (1). In recent years, some tyrosine kinase inhibitors, especially imatinib mesylate (2), have been regarded as promising drugs for severe PAH. Sorafenib is one of these tyrosine kinase inhibitors, and a small pilot study has already reported its tolerability and potency in treating PAH (3). In addition, sorafenib is expected to act simultaneously as a specific therapy against NF1-induced peripheral nerve sheath tumors by suppressing the mitogen-activated protein kinase (MAPK) cascade (4). A recent report indicated that the degenerated pulmonary vasculature in NF1-associated PAH is affected by NF1 vasculopathy (5). Studies also revealed that the regulation of Ras by Nf1 plays a critical role in vascular smooth muscle proliferation (6). Sorafenib is an oral inhibitor of multiple kinases, including Raf-1: the downstream target of Ras in the MAPK cascade. We hypothesized that sorafenib would have novel therapeutic potential in NF1-associated PAH by suppressing MAPK cascade activities.

We evaluated the safety and efficacy of sorafenib in a patient with refractory NF1-associated PAH. The patient was a 36-year-old female who was diagnosed with NF1 when she was 23 years old. She had typical café-au-lait spots and neurofibromas, but lacked bone lesions or schwannomas. She was diagnosed with PAH when she was 30 years old due to progressing dyspnea on effort and leg edema. She initially received prostacyclin infusion therapy to treat the severe PAH, but she was compelled to stop because of frequent catheter-related infections. Phosphodiesterase 5 inhibitor and endothelin receptor antagonist therapy were initiated following the failure of prostacyclin infusion therapy. However, her PAH became refractory and difficult to manage. During the previous 12 months, the pulmonary vascular resistance increased from 754 dyn·sec·cm^{-5} with 39 mm Hg of mean pulmonary artery pressure to 1,447 dyn·sec·cm^{-5} with 55 mm Hg of mean pulmonary artery pressure. Her 6-minute walking distance also declined from 355 m to 257 m, and the New York Heart Association functional class worsened from II to III. In this distressed situation, we decided to administer sorafenib at a dose of 100 mg once per day increasing to 200 mg after 4 weeks following a domestic ethical committee approval in Keio University.

Following 3 months of sorafenib administration without severe adverse events, reexamination of right heart catheterization revealed novel improvement of pulmonary arterial pressure (55 to 39 mm Hg) and pulmonary vascular resistance (1,447 to 1,063 dyn·sec·cm^{-5}) (Figure 1), despite the small decrease in cardiac index (2.2 to 2.0 L/min/m^2), which was not correlated with the decrease in left ventricular ejection fraction. Furthermore, the patient's symptoms and exercise tolerance showed great improvement with respect to New York Heart Association classification (class III to I) and 6-minute walking distance (257 m to 330 m). No adverse effect other than mild nausea was observed during the administration.

As we had expected, sorafenib was effective as a novel therapy for refractory NF1-associated PAH. We achieved pulmonary hemodynamic and functional improvements despite the small decrease in cardiac index, which was not correlated with the decrease in left ventricular ejection fraction. As previously reported (3), the decrease in cardiac index was related to blood volume shifts caused by concurrent vasodilating therapy that induced distribution of blood to the skin vasculature.

In conclusion, this case indicates that sorafenib is a favorable and well-tolerated therapy for refractory NF1-associated PAH. It is the first tailor-made PAH treatment directed at the signal transduction mechanism of proliferation.

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

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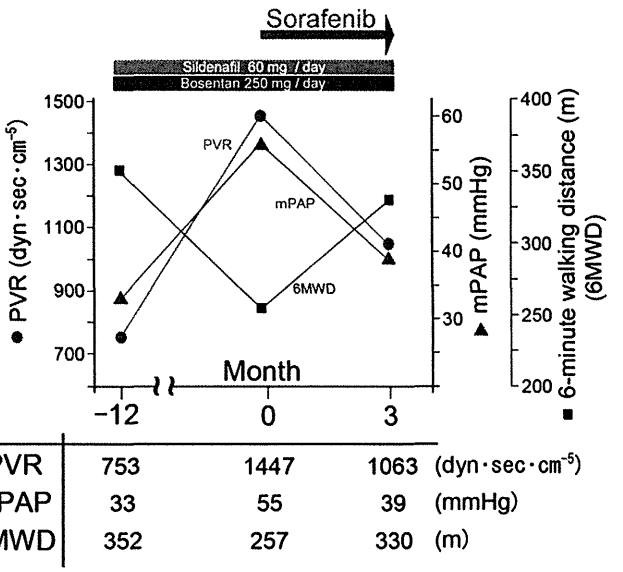

Figure 1. Time course of hemodynamic and exercise capacity before and after the administration of sorafenib. Pulmonary vascular resistance (PVR) and mean pulmonary arterial pressure (mPAP) attained by right heart catheterization and 6-minute walking distance (6MWD) are shown. The *horizontal arrow* above the graph indicates the administration period of sorafenib.

Author Contributions: This manuscript has been read and approved by all the authors. Y.T.: study manager; T.O.: gathered clinical data; M.K.: gathered clinical data; M.S.: gathered clinical data; T.S.: medical advisor; K.F.: physician in charge.

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Pseudobronchiectasis after Pertussis and Mycoplasma Infection

To the Editor:

Current understanding of the pathogenesis of bronchiectasis is one of defective airway remodeling from a vicious cycle of inflammation and recurrent infections resulting in irreversible airway dilatation (1). Very few cases of postinfective "reversal of bronchiectasis" have been previously reported, although clinicians may have encountered this poorly understood phenomenon (2, 3). The more appropriate term "pseudobronchiectasis" is used to describe such a radiological phenomenon, because the airway dilatation is temporary with improvement being noted over time, with or without treatment (3). However, it remains unclear if pseudobronchiectasis represents an early reversible stage in the pathogenesis of bronchiectasis, or if it is a separate clinical entity, or indeed a misinterpretation of available radiology.

Here, we report a case of a previously healthy 19-year-old man, a professional basketball player with no antecedent history of smoking or lung disease, who was misdiagnosed with widespread bronchiectasis following pertussis and mycoplasma infections. However, his clinical and radiological condition completely resolved within 2 years following targeted therapy, making the diagnostic label of pseudobronchiectasis more likely.

Our patient was first referred with a 6-month history of respiratory symptoms. Initially, he had nonproductive repetitive cough for 1 month and was diagnosed with pertussis infection on positive serology. Later, his cough became productive with purulent sputum. At this stage, he also had exertional wheezing, significant weight loss, fever, sweats, and decline in exercise tolerance. Prior to presentation to our pulmonology clinic, he had received multiple courses of antibiotics, including macrolides, for presumed recurrent bronchopneumonia with minimal response. Initial investigations showed mild anemia (hemoglobin 102 g/L), normal eosinophil count, elevated inflammatory markers, and increasing *Mycoplasma pneumoniae* serology titers (1:40 to 1:160). Serology and sputum samples for other respiratory pathogens were negative. Immunoglobulin levels (including total IgE), allergen-specific IgE levels, *Aspergillus* precipitins, allergen skin tests, autoimmune markers, and T-cell phenotypes were all normal. Detailed respiratory function tests showed air trapping, hyperinflation, and mild airway obstruction (Table 1). High-resolution computed tomography confirmed widespread bilateral airway dilations (Figures 1A–1D).

Diagnosis of postinfective bronchiectasis was made and the patient was treated with low-dose oral prednisolone for 4 weeks, budesonide–eformoterol, and sodium cromoglycate inhalers. He also received regular pulmonary physiotherapy with attention to sputum clearance techniques. He adhered to treatment and significant improvement in symptoms was noted over 6 months. At a review 2 years later, he had complete resolution of symptoms and further improvement in spirometry values (Table 1), and repeat high-resolution computed tomography (Figures 1E–1H) showed no evidence of previously noted dilated airways.

Our patient's initial clinical and radiological features were highly suggestive of bronchiectasis. Associations between bronchiectasis and pertussis and mycoplasma infections are also well documented, and sequential infective insults play an important role in its pathogenesis (4, 5). We were convinced that he did not have alternative diagnoses such as allergic bronchopulmonary aspergillosis, ongoing infective causes, or asthma. It was anticipated that our patient's "bronchiectasis" would be permanent. However, he stabilized quickly with a broad range of medical and physical therapies, and the subsequent reversal of his condition was totally unexpected, thus making the diagnosis more consistent with pseudobronchiectasis.

Pseudobronchiectasis may represent an early stage in the pathogenesis of bronchiectasis in which effective therapies and lack of repeated insults help gain better control over the initial inflammatory phase, thereby arresting the subsequent development of maladaptive irreversible airway remodeling (2). However, this hypothesis remains to be proven. Previous studies also suggested that inhaled corticosteroids have some benefit in controlling airways inflammation (6). In contrast, others proposed that pseudobronchiectasis may be an overreading of radiological findings, and features of advanced bronchiectasis such as beaded varicose dilations or cystic clusters are usually absent (3). Regardless, the definition and pathophysiology of pseudobronchiectasis remain poorly understood. In our patient, radiological overinterpretation alone is less likely given the clinical severity, extent of radiological change, and widespread nature of his condition. We believe that early aggressive therapy with antimicrobials, antiinflammatories, and bronchial hygiene may have played a significant role in promoting the resolution, although the process could have been spontaneous.

TABLE 1. RESPIRATORY FUNCTION TESTS RESULTS ON PRESENTATION AND AT TWO-YEAR REVIEW

	On Presentation (*% Predicted*)	2-yr Review (*% Predicted*)
FEV_1, L	3.51 (67%)	5.80 (108%)
FVC, L	4.95 (78%)	6.57 (101%)
FEV_1/FVC	70.9%	88.3%
Total lung capacity, L	8.07 (100%)	8.22 (100%)
Residual volume, L	3.54 (175%)	1.47 (80%)
D_{LCO}/V_A, ml/min/mm Hg/L	4.66 (89%)	6.09 (118%)

D_{LCO} = diffusion capacity of carbon monoxide; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; V_A = volume of alveoli.

Author Contributions: A.K.A.: conception of manuscript, acquisition and interpretation of data, preparation of manuscript, and provision of final approval; B.M.T.: acquisition and interpretation of data, critical revision of manuscript, and provision of final approval; C.M.: acquisition of data, critical revision of manuscript, and provision of final approval; P.J.T.: conception of manuscript, acquisition and interpretation of data, critical revision of manuscript, and provision of final approval.

CARDIOLOGY

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Unfavourable Effect of Pulmonary Arterial Dilatation in Pulmonary Hypertension

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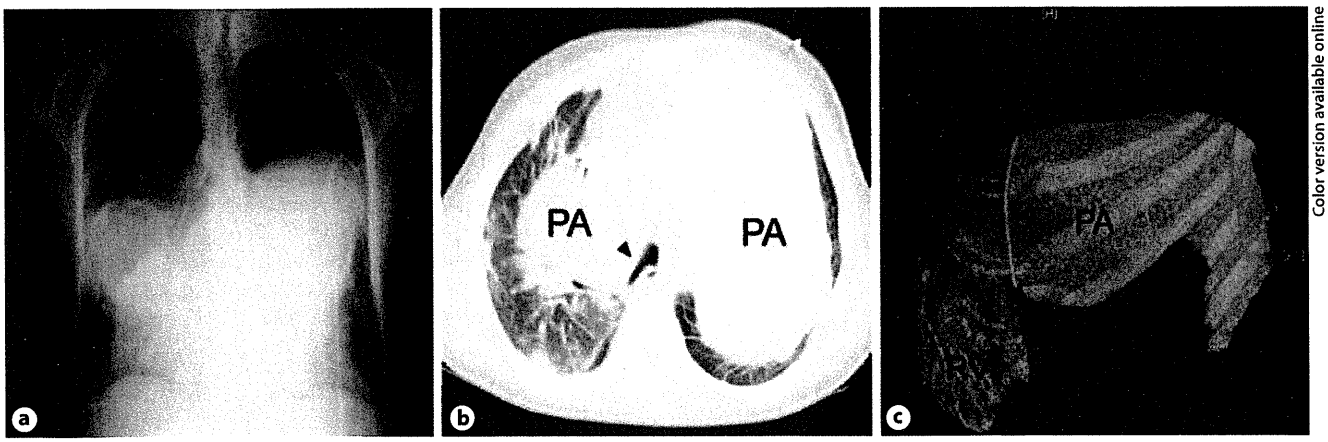
With regard to the paper by Badagliacca et al. [1] about the prevalence and prognostic relevance of pulmonary arterial dilatation in pulmonary hypertension, we have the following comments.

The authors discuss the risk of pulmonary artery (PA) dissection in patients with massive PA dilatation (>40 mm). However, it should be noted that the dilated PA itself causes unfavourable effects in some cases. Extrinsic compression of the left main coronary artery by a markedly dilated PA can bring about significant myocardial ischemia [2], and such compression may occur when the main PA diameter exceeds 40 mm [3]. These types of events can be diagnosed using 64-slice multidetector computed tomography (CT) coronary angiography [4]. Furthermore, we experienced a case in which an enlarged PA compressed the respiratory tract of a 21-year-old man who had been diagnosed with idiopathic pulmonary arterial hypertension 9 years previously. He presented with dilated PAs, and, despite continuous prostacyclin infusion therapy, the PA aneurysms continued to dilate progressively and the patient was admitted to our hospital with dyspnoea. At the time of admission, the patient's PA diameter was 90 mm. Figure 1a represents a chest X-ray showing the enlarged PA, while CT imaging represented in figure 1b further reveals



Color version available online

Fig. 1. a Chest X-ray showing enlarged PAs. **b** Chest CT showing PA aneurysms compressing the trachea (arrowhead) and lungs. **c** Three-dimensional CT showing the PA aneurysms occupying the intrathoracic space (left anterior oblique view). The descending white line indicates a Hickman® catheter. RV = Right ventricle.

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compression of the patient's trachea (arrowhead) and lungs. Three-dimensional volume-rendered CT imaging also showed the PA aneurysms occupying the intrathoracic space (the left anterior oblique view, fig. 1c). The patient thus experienced right heart failure due not only to the pulmonary hypertension, but also to deoxygenation caused by the dilated PA. Mechanical ventilation support and inotropic agents were required for recovery. Although rare, a massively dilated PA aneurysm in patients with pulmonary hypertension can cause hypoxia, as well as PA dissection and myocardial ischemia. We recommend performing multi-slice CT angiography to check for similar unfavourable complications in patients with dilated PA.

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Inducible Intrapulmonary Arteriovenous Shunt in a Patient with Beriberi Heart

To the Editor:

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

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

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

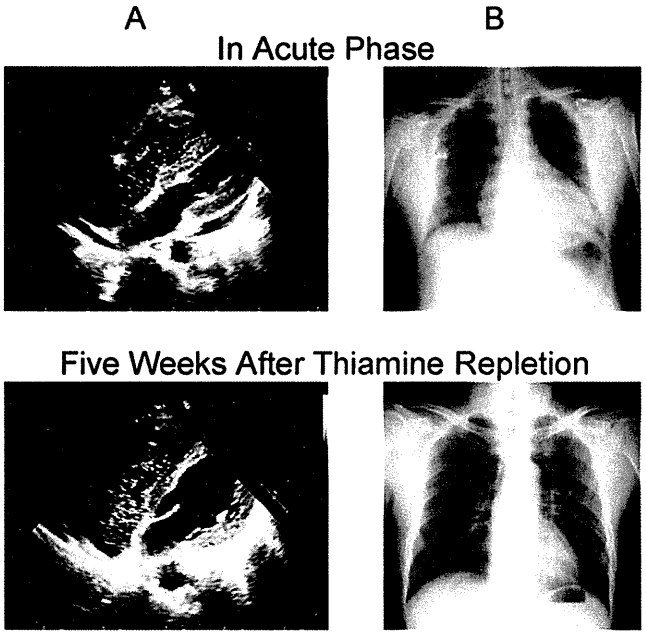

Figure 1. (*A*) Contrast-enhanced echocardiography and (*B*) chest X-rays in the acute phase and 5 weeks after the thiamine repletion. In the acute phase, microbubbles opacified the left atrium seven cardiac cycles after the initiation of right-atrial opacification (*A, upper panel*), whereas 5 weeks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

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

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

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

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

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

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

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

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Erratum: Evolving Epidemiology of Pulmonary Arterial Hypertension

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

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Erratum: Dieulafoy's Disease of the Bronchus

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

Reference

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Hepatology Research

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Letter to the Editor

Pulmonary embolism and deep venous thrombosis in hospitalized patients with liver cirrhosis

Bleeding complications are common in patients with liver cirrhosis and are frequently thought to be "auto-anticoagulated"; as such, they present little or no risk of venous thrombotic events (VTE) including pulmonary embolism and deep venous thrombosis. However, the true incidence of thromboembolism in liver cirrhosis patients is difficult to ascertain because of the paucity of data.

Here, we present liver cirrhosis patients who suffered critical VTE and describe the incidence of cirrhotic VTE at our institute. A 63-year-old woman with a history of alcoholism and cirrhosis (Child–Pugh class B) was admitted for a right ankle fracture that required surgical repair. Before her operation, two 5-mg doses of vitamin K were given orally to reverse the hypocoagulability (prothrombin time [PT], 21.1 s and international normalized ratio [INR], 2.4). On the second hospital day, while in the preoperative evaluation unit, the patient had a sudden onset of shortness of breath and went into cardiopulmonary arrest. After the patient was resuscitated, pulmonary embolism was diagnosed in both lungs using spiral computed tomography. An inferior vena cava filter was placed immediately after the diagnosis was made, but the patient died on the fourth hospital day.

We reviewed the medical records of 719 patients who were admitted with a diagnosis of liver cirrhosis. Ten patients (1.4%) had documented VTE (six pulmonary embolisms and six deep venous thromboses; two patients had both) during their hospital stay. Patient demographics and laboratory data are shown in Table 1. The average patient age was 58.9 years and 70.0% were female. Notably, these patients had a relatively low number of VTE risk factors (average, 1.6) and the majority of patients were graded B or C modified Child–Pugh score (average, 8.6). The overall incidence of VTE was 2100 per 10 000 person-years. All patients with VTE had elevated PT/INR values (mean PT, 13.9 s and mean INR, 1.66). Only three patients were on VTE prophylaxis before the event.

These findings suggest that, despite their elevated PT/INR values, patients with liver cirrhosis are at significant risk of thromboembolism. The balance between prothrombotic factors (e.g. decreased antithrombin III and proteins C and S) and coagulopathic factors (e.g. decreased levels of coagulation factors and platelets) is extremely precarious in patients with

Table 1 Patient demographics and laboratory data

Average age (years)	58.9
Male gender (%)	30.0
Ethnicity	
African-American (%)	60.0
Caucasian (%)	30.0
Asian-American (%)	10.0
Cause of cirrhosis	
Alcoholism (%)	70.0
Viral hepatitis (%)	20.0
Others (%)	10.0
Average number of VTE risk factors†	1.6
Average modified Child–Pugh score	8.6
Complete blood count	
White blood cells (10-3/u, average ± SD)	8.9 ± 7.9
Hematocrit (10-6/u, average ± SD)	34.1 ± 9.2
Platelets (10-3/u, average ± SD)	120.0 ± 45.1
Hepatic function panel	
Albumin (g/dL, average ± SD)	2.4 ± 0.5
Total bilirubin (mg/dL, average ± SD)	1.5 ± 1.0
Asparate aminotransferase (U/L, average ± SD)	51.0 ± 33.9
Alanine aminotransferase (U/L, average ± SD)	54.0 ± 78.6
Coagulation studies	
Prothrombin time (s, average ± SD)	13.9 ± 2.6
Partial thrombin time (s, average ± SD)	37.0 ± 16.8
International normalized ratio (average ± SD)	1.7 ± 0.4

†Risk factors for venous thrombotic events (VTE) include: immobility; prior pulmonary embolism or deep venous thrombosis events; obesity (body mass index >25); hypercoagulopathy; recent surgery; and history of stroke, cancer, or congestive heart failure.
SD, standard deviation.

cirrhosis; thus, elevated PT/INR values may not necessarily reflect the actual coagulative status of these patients.[1,2]

All hospitalized cirrhosis patients should be assessed for VTE risk and, when appropriate, an individualized course of a prophylaxis anticoagulant should be initiated. Evaluation for portal or hepatic vein thrombosis might provide additional insight. The ankle fracture might have been involved in VTE development in the present patient since it is a well-known risk factor for DVT.[3] In such patients, even under prolonged PT status, the local venous system has sufficient procoagulant activity to develop thrombosis. Decisions about whether to withhold prophylactic heparin should not be based on any assumption of "auto-anticoagulation." Furthermore, administration of procoagulants can unmask these patients' precarious hemostatic balance. Bleeding is generally a serious complication, especially in the present patient who has bone fractures and a highly prolonged PT; thus, vitamin K administration is considered reasonable. However, in using vitamin K to correct hypocoagulable status, clinicians might need to be aware of the patient's hemostatic balance shifting to a hypercoagulable status.

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ORIGINAL ARTICLE
Pulmonary Circulation

Prognostic Value of Cardiac Magnetic Resonance Imaging for Idiopathic Pulmonary Arterial Hypertension Before Initiating Intravenous Prostacyclin Therapy

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Background: Because few have reported the prognostic significance of cardiac magnetic resonance imaging (CMR) for idiopathic pulmonary arterial hypertension (IPAH), in this study we evaluated the value of CMR measurements as a prognostic predictor of IPAH before starting intravenous prostacyclin therapy.

Methods and Results: A total of 121 consecutive CMR studies for evaluating right ventricular (RV) function were reviewed. Forty-one patients were diagnosed with IPAH and served as the study group. Factors, such as age, sex, New York Heart Association functional class (NYHAFC), 6-min walk test, plasma brain natriuretic peptide level, serum uric acid level and CMR measurements were analyzed as predictors of first hospitalization and death. The mean follow-up period was 1,350±769 days. Nine patients were hospitalized because of heart failure, and 4 patients died from cardiopulmonary causes. The univariate analyses suggested that the left ventricular (LV) mass index, the left and right ventricular end-diastolic volume indices (LVEDVI, RVEDVI), the LV and RV end-systolic volume indices (LVESVI, RVESVI) and NYHAFC predicted the risk for hospitalization and that RVEDVI, RVESVI and NYHAFC predicted mortality. The multivariate analyses suggested that RVEDVI and NYHAFC are independent predictors of both hospitalization and mortality. The effects of RVEDVI and NYHAFC on hospitalization were not substantially affected by the concomitant medication.

Conclusions: In IPAH patients, the RVEDVI predicts both hospitalization for right heart failure and mortality before initiating intravenous prostacyclin therapy. (*Circ J* 2012; **76:** 1737–1743)

Key Words: Clinical outcome; Idiopathic pulmonary arterial hypertension; Magnetic resonance imaging

Idiopathic pulmonary arterial hypertension (IPAH) is a life-threatening chronic disorder that affects the pulmonary circulation and has an unknown etiology. Elevated pressure and resistance in the pulmonary vessels lead to progressive right heart failure, which results in functional limitations and ultimately the death of most patients.[1–3] The prognosis is poor; without specific treatment, the 1-, 3- and 5- year survival rates are 68, 48 and 34%, respectively.[4] Thus, monitoring right ventricular (RV) function is of great importance. Cardiac magnetic resonance imaging (CMR) is a noninvasive, 3-dimensional tomographic technique that enables visualization of the detailed morphology of the heart and accurate measurement of the RV volume, myocardial mass and transvalvular flow.[5–8] It can also determine whether impaired RV diastolic function results from pulmonary hypertension. However, few studies have reported the prognostic significance of CMR measurements.[9,10] Furthermore, to the best of our knowledge, the association between hospitalization for heart failure because of IPAH and CMR results has not been discussed in the literature. The purpose of this historical cohort study was to evaluate the value of CMR measurements as a prognostic predictor of IPAH before starting intravenous prostacyclin therapy.

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Methods

Patients

Our hospital is a pulmonary hypertension referral center in Japan. We performed a retrospective review of CMR results

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Table 1. Patients' Characteristics

Characteristic	Value
Demographic variables	
Total number	41
Age (years)	39±14
F/M	29 (71%)/12 (29%)
CMR measurements	
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	2.3±0.8
SVI (ml/m^2)	37±14
RVMI (g/m^2)	39±18
LVMI (g/m^2)	50±15
RVEF (%)	32±12
LVEF (%)	56±9
RVEDVI (ml/m^2)	123±43
RVESVI (ml/m^2)	86±39
LVEDVI (ml/m^2)	61±30
LVESVI (ml/m^2)	30±15
Functional status	
NYHAFC II, III, IV	20 (49%), 18 (44%), 3 (7%)
6MWT (m) (n=28)*	358±98
Biochemical markers	
Plasma BNP (pg/ml)	236±331
Serum uric acid (mg/dl)	6.9±2.4
Medication use	All follow-up duration/before CMR
Intravenous prostacyclin	14 (34%)/0 (0%)
Endothelin-receptor antagonists	22 (54%)/9 (22%)
Sildenafil	36 (88%)/18 (44%)
Calcium antagonists	9 (22%)/9 (22%)

*Of all the eligible patients, only 28 had a 6MWT within 1 week of the CMR examination without changing therapy.
CMR, cardiac magnetic resonance imaging; SVI, stroke volume index; RVMI, right ventricular (RV) mass index; LVMI, left ventricular (LV) mass index; RVEF, RV ejection fraction; LVEF, LV ejection fraction; RVEDVI, RV end-diastolic volume index; RVESVI, RV end-systolic volume index; LVEDVI, LV end-diastolic volume index; LVESVI, LV end-systolic volume index; NYHAFC, New York Heart Association functional class; 6MWT, 6-min walk test; BNP, brain natriuretic peptide.

Table 2. Right Heart Catheterization Measurements

Characteristic	Value
Mean PAP (mmHg)	51±14
Systolic PAP (mmHg)	80±22
Diastolic PAP (mmHg)	31±11
Mean right atrial pressure (mmHg)	6.8±4.0
PVR index (dyne $s \cdot cm^{-5} \cdot m^{-2}$)	737±504
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	2.2±0.7
SVI (ml/m^2)	33±12
Heart rate (beats/min)	72±13
Mixed venous O_2 saturation (%)	64±8

PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; SVI, stroke volume index.

from 122 consecutive examinations of patients who were either suspected of having pulmonary arterial hypertension (PAH) or who had been diagnosed with PAH between September 2003 and September 2010 at our institute. Of the 122 examinations, 41 patients were diagnosed with IPAH and served as the study group. The diagnosis of IPAH was based on a mean pulmonary arterial pressure (PAP) >25 mmHg at rest, pulmonary capillary wedge pressure (PCWP) <15 mmHg, and an elevated pulmonary vascular resistance (PVR) in a patient with no identifiable underlying causes (such as familial PAH, drug- or toxin-induced PAH, connective tissue disease, HIV infection, portal hypertension, congenital heart disease, schistosomiasis, chronic hemolytic anemia, pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis, pulmonary hypertension owing to lung disease/hypoxia, chronic thromboembolic pulmonary hypertension or pulmonary hypertension with unclear multifactorial mechanisms).[11,12]

To prevent the potential risk of damaging the intravenous prostacyclin equipment in the magnetic resonance imaging (MRI) scanner rooms, CMR was not performed for patients who had started prostacyclin treatment. Accordingly, all of the IPAH patients in this study were examined before starting intravenous prostacyclin therapy. Each patient's status was scored according to their New York Heart Association functional class (NYHAFC) at the time of the CMR examination. According to clinical guidelines, patients with a positive acute vasodilator challenge during right heart catheterization were treated with calcium antagonists;[13] 9 patients (22%) had been treated with an endothelin-receptor antagonist, 18 (54%) had been treated with sildenafil, and 9 (22%) had been treated with calcium antagonists before the CMR assessment. The study protocol was approved by the institutional review board.

Endpoint Determination

The follow-up data were retrospectively collected from medical charts, and the end of data collection was March 31, 2011. The following endpoints were used in this historical cohort study: (1) the date of the first hospitalization for right heart failure; (2) the date of the last clinical visit; (3) death; and (4) March 31, 2011. Clinical follow-up visits were performed at regular intervals (1–3 months) at the outpatient clinic.

CMR Imaging

The CMR scans were obtained using a 1.5-Tesla clinical scanner (Signa TwinSpeed, GE Healthcare, Milwaukee, WI, USA). For the RV volume measurements, contiguous transverse images were acquired through the entire RV using a 2D cine, steady-state, free-precession technique with prospective ECG gating. Each cross-sectional image was obtained while the patient held a single breath. Each cross-sectional image used the following parameters: repetition time=3.2 ms, echo time=1.6 ms, flip angle=45°, bandwidth=125 kHz, field of view=350×350 mm^2, matrix size=224×192, slice thickness=10 mm without a gap and 20 phases during 1 cardiac cycle. The in-plane spatial resolution was 1.6×1.8 mm^2. The CMR examination time was approximately 30 min and included short-axis images of the left ventricle (LV) to evaluate LV function after obtaining transverse images of the RV. The CMR functional parameters were calculated on a workstation (Advantage Workstation, GE Healthcare). The endocardial borders of all of the images at end-diastole and end-systole were manually traced by a radiologist with 10 years of experience with CMR. The end-diastolic volume, end-systolic volume, and ejection fraction (EF) were automatically calculated using Simpson's rule with commercially available analysis software (Mass Analysis Plus version 4.0, Medis, Leiden, the Netherlands). The incorporation of the trabeculae carneae into the RV volume followed the rules that are generally used in ultrasound methods. Fewer than 15 min were required for the RV volume measurement. The cardiac output was determined by multiplying the stroke volume by the heart rate. The measures were indexed by