status may affect the discrepancy in the frequency of exacerbations and chronic bronchitis between Japan and the other geographical regions. Another possible reason would be a selection bias in our cohort study, since all of the subjects were recruited and treated by respiratory specialists at a university hospital and its affiliated hospitals. Even though the exacerbation frequency was low in the present study, the recurrent nature of exacerbations was confirmed by showing that subjects who experienced exacerbations within the first year of follow-up experienced more frequent exacerbations after the first year of follow-up (Figure 3).

It was found that the number of exacerbation events was higher in the spring and autumn months, but not in the winter (Figure 2), which was an unexpected finding because COPD exacerbations were reported to be more frequent in the winter months [18, 19]. Our cohort study was performed in the north end of Japan, where the winter is very cold and accompanied by significant snowfall; therefore, patients with COPD may tend to stay inside their homes in the winter. Since the trigger for a large part of exacerbations is a respiratory virus infection [20], such patients may have a lower chance of getting a virus infection in the community in the winter. Whatever the reason, the present result indicates that the seasonality of COPD exacerbations can vary depending on where the patients live due to climate differences.

Another notable finding of the present study is that whether subjects experienced exacerbation events or not during the follow-up period did not affect the annual decline in FEV_1, regardless of its definition and the degree of airflow limitation (Figure 4). People may consider that this is an unexpected finding since it has been emphasized that COPD exacerbations accelerate the rate of decline in lung function. The GOLD guideline [1] cited two references for this statement [21, 22]. However, using the Lung Health Study data, Kanner et al. reported that lower respiratory tract illness promoted FEV_1 decline in current smokers with mild COPD, but not in ex-smokers [21]. Furthermore, Donaldson et al. just showed a faster annual decline in FEV_1 in patients with frequent exacerbations defined by symptom-based criteria (>2.92 events/person/year) when compared to patients with infrequent exacerbations (<2.92 events/person/year) [22]. In the present study, 85.1% of the subjects quit smoking during the follow-up period, and the exacerbation frequency was very low; thus, it is reasonable that the effect of exacerbation events on the annual decline in FEV_1 in the present study was small. Moreover, the relationship between exacerbation events and

a decline in FEV_1 does not seem to be simple, since the large-scale UPLIFT study failed to show an improvement in the FEV_1 decline, whereas it did show a significant reduction in the development of exacerbations by drug intervention [11]. On the other hand, there was also a tendency of rapid decline in FEV_1 in subjects who experienced more than one exacerbation defined by admission criteria per year in the present study (online supplement Figure 2). Therefore, the effect of exacerbations on respiratory function seems to be especially larger in patients who experience frequent and more severe exacerbations.

In the multivariate analysis, impaired health-related QOL was significantly associated with exacerbation frequency (Table 3), which is in line with previous studies [2, 4]. The present data extend this observation by showing that impaired health-related QOL was also strongly related to shorter exacerbation-free survival and the development of recurrent exacerbations defined as either prescription change or hospital admission (Table 3). Furthermore, the SGRQ Activity score, closely related to the dyspnea scale and the 6-minute walking distance [7], was the only domain that was significantly associated with all of exacerbation-free survival, the exacerbation frequency, and the development of recurrent exacerbations (online supplement Table 9). One explanation of the association between dyspnea and exacerbations may come from the fact that dyspnea is one of the major symptoms in the symptom definition. It is also possible that reduced activity and poor QOL are just confounders for other factors. However, there are several speculations regarding that reduced activity with dyspnea is a risk factor for exacerbations. First, mucus hypersecretion in subjects with dyspnea may contribute to increase the risk of pulmonary infection that is an important trigger of COPD exacerbation. Second, lung hyperinflation in subjects with dyspnea increases the imbalance of the ventilation/perfusion ratio and may be more susceptible to triggers of exacerbation [23]. It was also found that low BMI was independently associated with COPD exacerbation (Table 3). Poor nutritional status or low BMI has been shown to be associated with increased morbidity and mortality in the natural course of COPD and in patients hospitalized with COPD exacerbation [24, 25]. Therefore, it would be very important to identify patients who have limited physical activities due to dyspnea or weight loss and perform a therapeutic intervention for such patients by medication, rehabilitation, and supporting nutrition in order to reduce the morbidity and mortality from COPD exacerbations.

Although this study was a prospective, observational cohort study, it had several limitations. First, information about exacerbation history before study entry was not obtained. Since it was shown that the best predictor of exacerbations was a history of exacerbations [4], collecting exacerbation history would be important for the clinical management of patients with COPD. Regarding this point, the recurrent nature of exacerbations was confirmed using our prospective data (Figure 3). Second, most subjects were males, and there were no female patients in GOLD 3 and 4 categories. Therefore, the present findings may not simply be applied to female patients with COPD. Third, we were unable to collect accurate information on anxiety and depression that have been reported to be associated with COPD exacerbations [26, 27]. Lastly, the sample size in this study was not as large as previous large-scale clinical studies.

In summary, the clinical characteristics and determinants of COPD exacerbations were identified in the Hokkaido COPD cohort study. In the present population, the exacerbation frequency was very low, while exacerbations appeared to be recurrent. Exacerbation events did not affect the annual decline in FEV_1. Furthermore, poor health-related QOL and weight loss were strong predictors of the development of COPD exacerbations. Identification of patients at high risk for the development of exacerbations and appropriate intervention for such patients are crucial for the prevention of COPD exacerbations.

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SUPPORT STATEMENT

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Table 1. Characteristics of subjects classified by severity of airflow limitation

	All subjects (N = 268)	GOLD 1 (N = 69)	GOLD 2 (N = 121)	GOLD 3 (N = 65)	GOLD 4 (N = 13)
Age, yr	70 ± 8	67 ± 8	70 ± 8	72 ± 6	70 ± 8
Female sex, N (%)	15 (6)	9 (13)	6 (5)	0 (0)	0 (0)
Body mass index, kg/m^2	22 ± 3	23 ± 3	23 ± 3	21 ± 3	21 ± 4
Current smoker at entry, N (%)	74 (28)	20 (29)	39 (32)	10 (15)	5 (38)
Smoking index at entry, pack-years	62 ± 30	63 ± 34	62 ± 30	64 ± 25	55 ± 22
Post-bronchodilator					
FEV_1, L	1.75 ± 0.67	2.55 ± 0.43	1.76 ± 0.41	1.11 ± 0.19	0.70 ± 0.14
FEV_1, % predicted	65 ± 22	93 ± 11	65 ± 9	42 ± 5	26 ± 4
FVC, % predicted	101 ± 19	118 ± 13	100 ± 14	90 ± 14	70 ± 20
FEV_1/FVC	0.51 ± 0.13	0.64 ± 0.06	0.53 ± 0.08	0.38 ± 0.07	0.31 ± 0.07
Reversibility of FEV_1, %	12 ± 10	6 ± 5	12 ± 8	17 ± 13	14 ± 11
Reversibility of FEV_1, ml	146 ± 105	124 ± 88	162 ± 101	153 ± 127	86 ± 66
Chronic bronchitis, N (%)	29 (11)	2 (3)	15 (12)	11 (17)	1 (8)
MRC dyspnea score ≥2, N (%)	224 (84)	47 (68)	102 (84)	62 (95)	13 (100)
SGRQ total score	32 ± 18	23 ± 14	30 ± 17	41 ± 16	51 ± 14
Blood neutrophil count, $cells/mm^3$	3519 ± 1113	3597 ± 1220	3421 ± 1155	3580 ± 975	3713 ± 733
Blood eosinophil count, $cells/mm^3$	198 ± 134	185 ± 130	211 ± 137	184 ± 128	218 ± 152
Blood Hb, g/dl	14 ± 1	14 ± 1	14 ± 1	14 ± 1	14 ± 1
Serum IgE, IU/ml	213 ± 569	278 ± 764	251 ± 606	88 ± 106	140 ± 158
Any cardiovascular disease, N (%)	60 (22)	12 (17)	27 (22)	17 (26)	4 (31)
Ischemic heart disease, N (%)	19 (7)	5 (7)	9 (7)	5 (8)	0 (0)
Diabetes, N (%)	12 (4)	3 (4)	7 (6)	2 (3)	0 (0)

Data are shown as means ± SD or number (%).

Table 2. Exacerbation frequency classified by severity of airflow limitation

	All subjects (N = 268)	GOLD 1 (N = 69)	GOLD 2 (N = 121)	GOLD 3 (N = 65)	GOLD 4 (N = 13)
Exacerbation, events/person/yr					
Subjective complaint	0.78 ± 1.16	0.58 ± 0.79	0.63 ± 0.94	1.09 ± 1.51*†	1.80 ± 1.86*†
Symptom definition	0.24 ± 0.47	0.16 ± 0.29	0.16 ± 0.27	0.37 ± 0.57*†	0.81 ± 1.15*†
Prescription definition	0.20 ± 0.43	0.12 ± 0.26	0.14 ± 0.25	0.30 ± 0.49*†	0.77 ± 1.13*†‡
Antibiotics definition	0.13 ± 0.28	0.09 ± 0.23	0.09 ± 0.22	0.20 ± 0.35*†	0.37 ± 0.42*†‡
Admission definition	0.06 ± 0.19	0.01 ± 0.03	0.06 ± 0.19*	0.10 ± 0.27*†	0.09 ± 0.15*

Data are shown as means ± SD.

*p<0.05 vs. GOLD 1. †p<0.05 vs. GOLD 2. ‡p<0.05 vs. GOLD 3.

Table 3. Significant factors related to COPD exacerbation

A. Factors related to exacerbation-free survival

Multivariate model	Prescription definition		Admission definition	
Variables	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
BMI (1 kg/m^2 increase)	0.93 (0.87-0.99)	0.03	0.86 (0.76-0.96)	0.006
SGRQ total score (4 points increase)	1.12 (1.06-1.19)	<0.001	1.19 (1.08-1.30)	<0.001

(Cox proportional hazards model)

B. Factors related to exacerbation frequency

Multivariate model	Prescription definition		Admission definition	
Variables	Risk ratio (95% CI)	p value	Risk ratio (95% CI)	p value
BMI (1 kg/m^2 increase)	0.95 (0.90-0.99)	0.03	0.87 (0.79-0.95)	0.004
SGRQ total score (4 points increase)	1.09 (1.05-1.14)	<0.001	1.11 (1.03-1.20)	0.008
FEV_1 %predicted (10% increase)	0.89 (0.81-0.97)	0.008	-	-
Hb (1 g/dl increase)	0.84 (0.76-0.93)	0.001	-	-

(Poisson regression model)

C. Factors related to recurrent exacerbation

Multivariate model	Prescription definition		Admission definition	
Variables	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Age (10 years older)	-	-	1.57 (1.00-2.46)	0.049
BMI (1 kg/m^2 increase)	-	-	0.88 (0.80-0.98)	0.02
SGRQ total score (4 points increase)	1.07 (1.03-1.11)	<0.001	1.14 (1.04-1.24)	0.005
Hb (1 g/dl increase)	0.87 (0.78-0.97)	0.02	-	-

(PWP total time model)

Complete data tables including all variables and univariate analyses are shown in the online supplement.

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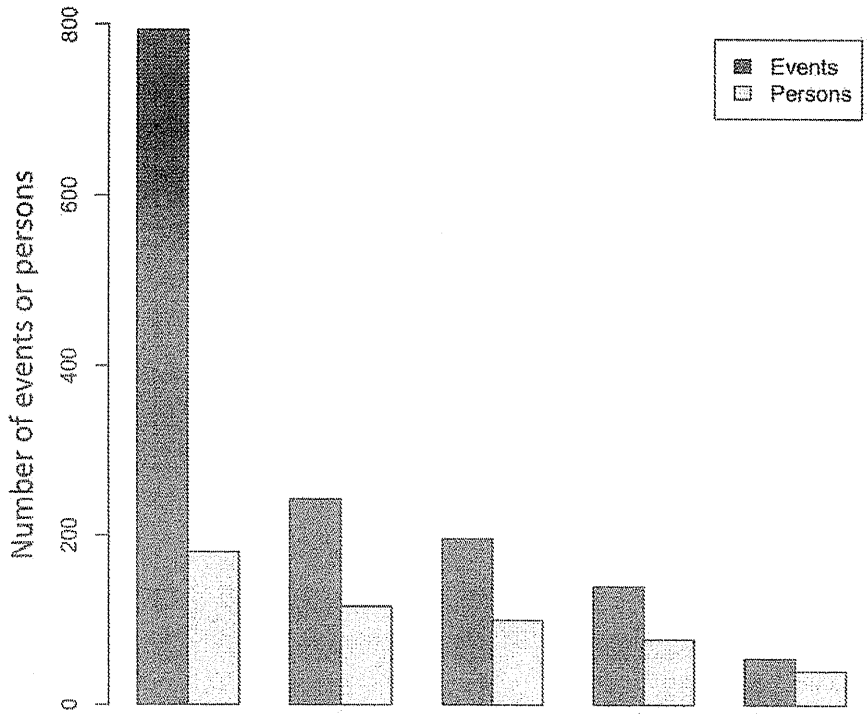
FIGURE LEGENDS

Figure 1. Bar plots of the number of exacerbation events or persons during the follow-up period

Exacerbation was defined by patient's subjective complaints, the symptom definition, the prescription definition, the antibiotic definition, and the admission definition.

Figure 1



	Complaint	Symptom	Prescription	Antibiotics	Admission
#Events	794	243	196	139	55
#Persons	190	116	100	77	40

Figure 2. Bar plots of the number of exacerbation events in each month during the follow-up period

Exacerbation was defined by the symptom definition, prescription definition, antibiotic definition, and admission definition.

Figure 2

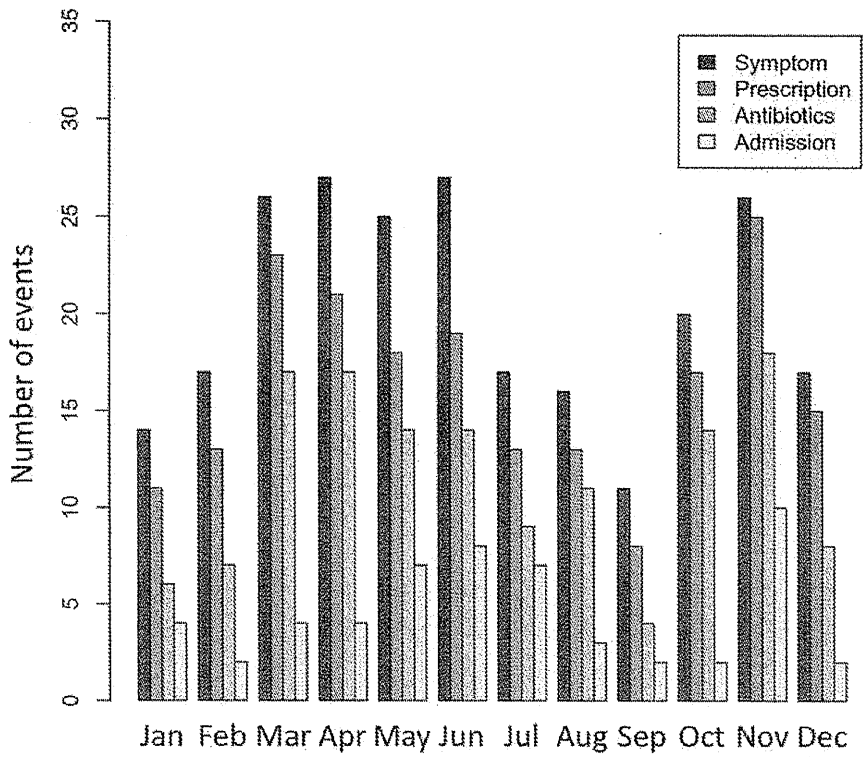

Number of events
0
5
10
15
20
25
30
35
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Symptom
Prescription
Antibiotics
Admission

Figure 3. Box plots of the exacerbation frequency after the first year of follow-up

Subjects were devided into two groups: subjects who did not experience exacerbations within the first year of follow-up (Event ≤1y (-)) and subjects who experienced exacerbations within the first year of follow-up (Event ≤1y (+)). Graphs show exacerbation defined by the symptom definition, the prescription definition, the antibiotic definition, and the admission definition, respectively.

Figure 3

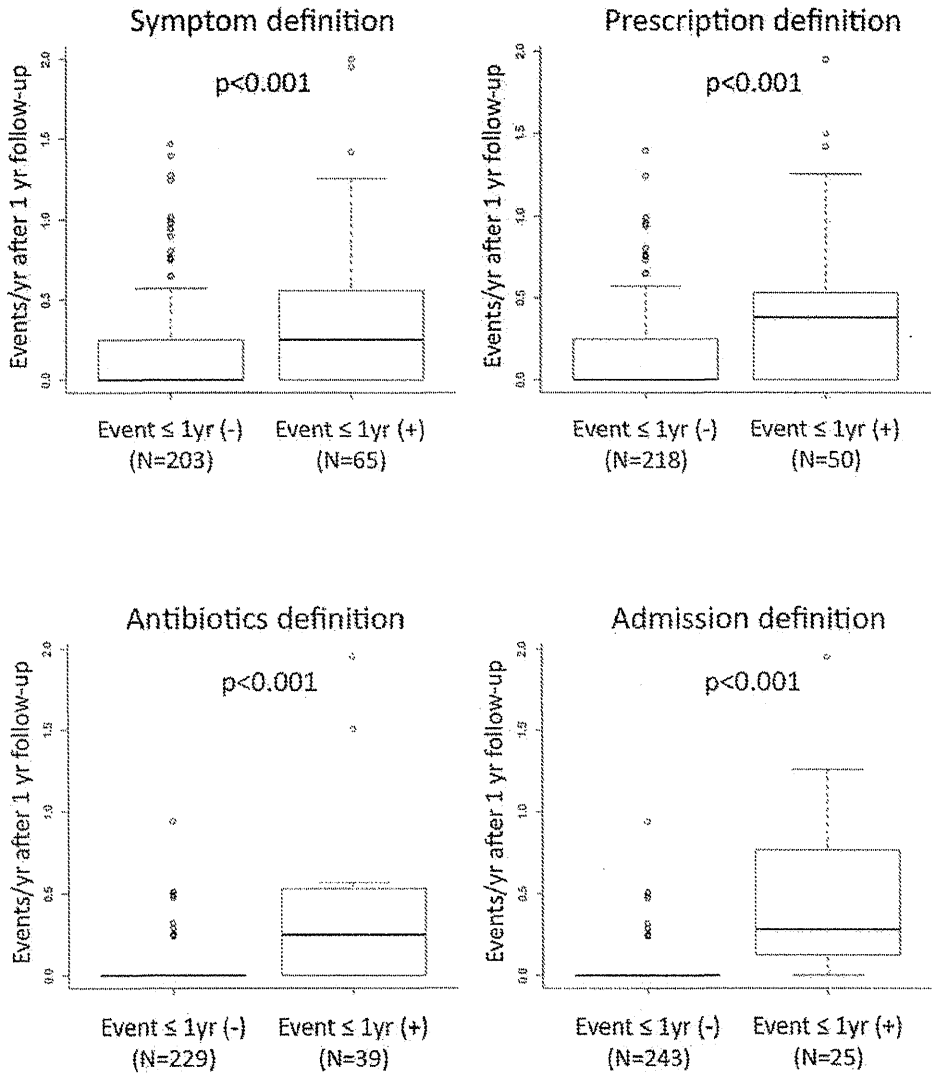
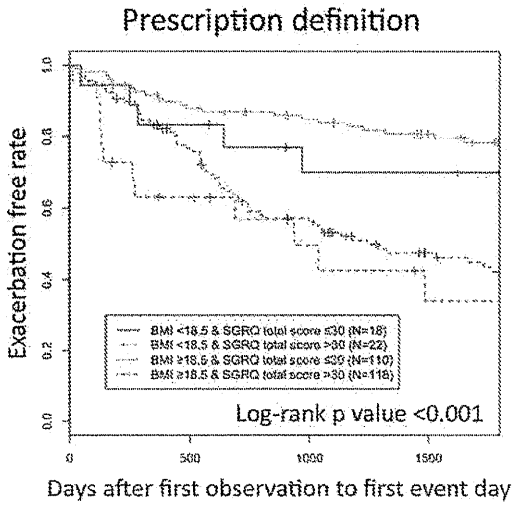
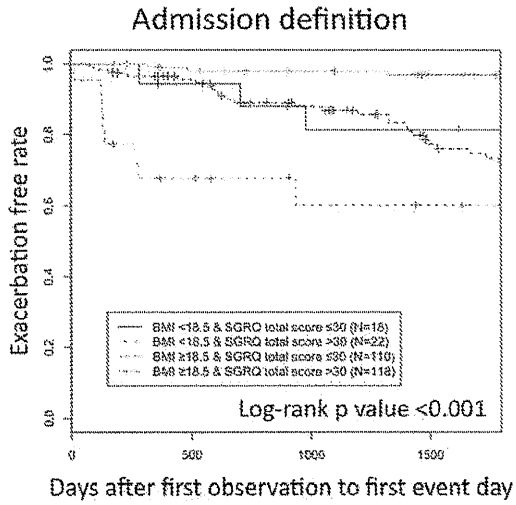

Symptom definition
p<0.001
Events/yr after 1 yr follow-up
Event ≤ 1yr (-)
(N=203)
Event ≤ 1yr (+)
(N=65)
Prescription definition
p<0.001
Events/yr after 1 yr follow-up
Event ≤ 1yr (-)
(N=218)
Event ≤ 1yr (+)
(N=50)
Antibiotics definition
p<0.001
Events/yr after 1 yr follow-up
Event ≤ 1yr (-)
(N=229)
Event ≤ 1yr (+)
(N=39)
Admission definition
p<0.001
Events/yr after 1 yr follow-up
Event ≤ 1yr (-)
(N=243)
Event ≤ 1yr (+)
(N=25)

Figure 4. Kaplan-meier curves for exacerbation-free survival

Subjects were devided into four groups according to SGRQ total score and BMI value. Graphs showing exacerbation defined by the prescription definition and the admission definition are shown.

Figure 4


Prescription definition
Exacerbation free rate
1.0
0.8
0.6
0.4
0.2
0.0
BMI <18.5 & SGRQ total score ≤30 (N=18)
BMI <18.5 & SGRQ total score >30 (N=22)
BMI ≥18.5 & SGRQ total score ≤30 (N=110)
BMI ≥18.5 & SGRQ total score >30 (N=118)
Log-rank p value <0.001
0
500
1000
1500
Days after first observation to first event day


Admission definition
Exacerbation free rate
1.0
0.8
0.6
0.4
0.2
0.0
BMI <18.5 & SGRQ total score ≤30 (N=18)
BMI <18.5 & SGRQ total score >30 (N=22)
BMI ≥18.5 & SGRQ total score ≤30 (N=110)
BMI ≥18.5 & SGRQ total score >30 (N=118)
Log-rank p value <0.001
0
500
1000
1500
Days after first observation to first event day

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PLOS | ONE

Paradoxical Interventricular Septal Motion as a Major Determinant of Late Gadolinium Enhancement in Ventricular Insertion Points in Pulmonary Hypertension

Takahiro Sato[1], Ichizo Tsujino[1]*, Hiroshi Ohira[1], Noriko Oyama-Manabe[2], Yoichi M. Ito[3], Teruo Noguchi[4], Asuka Yamada[1], Daisuke Ikeda[1], Taku Watanabe[1], Masaharu Nishimura[5]

1 First Department of Medicine, Hokkaido University Hospital, Sapporo, Hokkaido, Japan, **2** Department of Diagnostic and Interventional Radiology, Hokkaido University Hospital, Sapporo, Hokkaido, Japan, **3** Department of Biostatistics, Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan, **4** Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan, **5** First Department of Medicine, Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan

Abstract

Background: This study investigated the major clinical determinants of late gadolinium enhancement (LGE) at ventricular insertion points (VIPs) commonly seen in patients with pulmonary hypertension (PH).

Methods: Forty-six consecutive PH patients (mean pulmonary artery pressure ≥25 mmHg at rest) and 21 matched controls were examined. Right ventricular (RV) morphology, function and LGE mass volume at VIPs were assessed by cardiac magnetic resonance (CMR). Radial motion of the left ventricular (LV) wall and interventricular septum (IVS) was assessed by speckle-tracking echocardiography. Paradoxical IVS motion index was then calculated. Univariate and multivariate regression analysis were conducted to characterize the relationship between LGE volume at VIPs and PH-related clinical indices, including the paradoxical IVS motion index.

Results: Mean pulmonary arterial pressure (MPAP) of PH patients was 38±9 mmHg. LGE at VIPs was observed in 42 of 46 PH patients, and the LGE volume was 2.02 mL (0.47–2.99 mL). Significant correlations with LGE volume at VIPs were observed for MPAP ($r=0.50$) and CMR-derived parameters [RV mass index ($r=0.53$), RV end-diastolic volume index ($r=0.53$), RV ejection fraction ($r=-0.56$), and paradoxical IVS motion index ($r=0.77$)]. In multiple regression analysis, paradoxical IVS motion index alone significantly predicted LGE volume at VIPs ($p<0.001$).

Conclusions: LGE at VIPs seen in patients with PH appears to reflect altered IVS motion rather than elevated RV pressure or remodeling. Long-term studies would be of benefit to characterize the clinical relevance of LGE at VIPs.

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* E-mail: itsujino@med.hokudai.ac.jp

Introduction

Pulmonary hypertension (PH) is defined as mean pulmonary arterial pressure (PAP) ≥25 mmHg at rest. [1] If untreated, the vasculopathy often progresses and leads to right ventricular (RV) failure and premature death. Optimal assessment of RV morphology and function is thus critical in the management of PH.

Cardiac magnetic resonance (CMR) imaging is an established modality for the objective assessment of RV geometry and function. To date, CMR studies of PH have described increased size and impaired function of the right ventricle. [2] Recent CMR studies have also demonstrated late gadolinium enhancement (LGE) at ventricular insertion points (VIPs). [3–10] LGE is commonly seen in patients with coronary and myocardial diseases and is thought to emerge as a result of contrast leakage and pooling in fibrotic or severely damaged myocardium. [11,12] In PH, however, the underlying mechanisms of LGE at VIPs are insufficiently understood.

Regarding this, a possible explanation is that LGE at VIPs develops as a result of elevated RV pressure and resultant RV remodeling in PH. Indeed, previous studies have shown significant associations between LGE volume at VIPs and measurements of pulmonary hemodynamics and RV morphology. [4–6,10] Interestingly, however, we have recently experienced and reported a case in which paradoxical motion of the interventricular septum (IVS) alone caused LGE at VIPs without PH. [13] This paradoxical IVS movement has been described in PH[14–16] and, thus, it can be assumed that altered IVS motion might be the predominant mechanism of LGE at IVS rather than increased RV pressure and/or remodeling.

The present study investigated the underlying mechanisms of LGE at IVSs in PH by evaluating the association between LGE at VIPs and clinical parameters. Particular focus was made on the

possible contribution of paradoxical IVS motion assessed by speckle-tracking echocardiography to the development of LGE at IVSs.

Methods

In this single-center, case-control, prospective, observational study, subjects who met the entry criteria [mean PAP of ≥25 mmHg and pulmonary capillary wedge pressure (PCWP) of ≤15 mmHg at rest] were consecutively enrolled between April 2010 and December 2012. Exclusion criteria were the presence of comorbid disease that might affect cardiac morphology and function, an unstable PH condition requiring treatment modifications, and inability to obtain or analyze electrocardiogram-gated CMR images. Patients with atrial fibrillation/flutter were excluded based on the last criterion. Age- and gender-matched subjects who did not have cardiac and/or respiratory diseases were recruited from the (para)medical staff of our institution to serve as control subjects. Subjects with systemic hypertension were considered eligible in both groups when blood pressure was well controlled and when echocardiography exhibited no structural changes of the left ventricle and atrium.

Patients with PH underwentechocardiography, CMR and right heart catheterization (RHC) within a 1-week interval during which they were clinically stable. RHC was conducted according to the guidelines for the diagnosis and treatment of PH, [1] and PAP, PCWP, RV end-diastolic pressure (EDP), right atrial (RA) pressure, and cardiac output (CO) were measured. CO was measured by the thermodilution method, and the mean of at least three measurements was used as representative data.

All PH patients and control subjects gave informed written consent to participate, and the study protocol was approved by the ethics committee of the Hokkaido University Graduate School of Medicine.

CMR Study Protocol

CMR studies were performed using a 1.5-Tesla Philips Achieva magnetic resonance imaging system (Philips Medical Systems, Best, The Netherlands) equipped with Master gradients (maximum gradient amplitude, 33 mT/m; maximum slew rate, 100 mT/m/ms). Imaging was performed with 10–15 sec breath-holding during expiration, using a vector-cardiographic method for electrocardiogram gating. From coronal localizing images that demonstrated the gross cardiac anatomy, an orthogonal stack of axial slices was planned to cover the heart from a level just below the diaphragm to the bronchial bifurcation, covering the heart in diastole. Axial slices were acquired using a steady-state free precession pulse sequence (repetition time = 2.8 ms, echo time = 1.4 ms, flip angle = 60, acquisition matrix = 192×256, field of view = 380 mm, slice thickness = 10 mm, 0 mm inter-slice gap, and 20 phases/cardiac cycle). A slice thickness of 10 mm was used to minimize the number of image acquisitions, and to reduce the number and duration of the breath-holding.

Obtained images were evaluated using commercially available software (Extended MR Work Space: ver. 2.6.3, Philips Medical Systems, Amsterdam, The Netherlands). RV and left ventricular (LV) endocardial borders of contiguous axial slices were manually traced and the obtained time-volume curves allowed for calculation of RV and LV end-diastolic volume (EDV) and end-systolic volumes (ESV), and ejection fraction (EF). Epicardial ventricular borders were also manually contoured for quantification of the volume of RV and LV walls. The IVS was regarded as a part of LV wall. RV and LV masses were calculated by multiplying each wall volume by 1.05 g/cm^3. Ventricular volume and mass were indexed by body surface area.

In patients with PH, Gd-DTPA (0.1 mmol/kg, Magnevist; Berlex Laboratories, Wayne, NJ) was intravenously administered. Ten minutes after the injection, a breath-holding, inversion-recovery (IR)-prepared, three dimensional turbo field echo pulse sequence with electrocardiogram gating was performed to obtain a delayed-enhancement image with fat saturation of spectral presaturation with inversion recovery. The imaging parameters were as follows: slice thickness = 5 mm; FOV = 400 mm; matrix size = 157×256; TR/TE = 3.8 ms/1.2 ms; flip angle = 15°; and number of signal averages = 1. For each subject, the inversion time was adjusted to null the signal from the normal myocardium; the typical inversion time was 260 to 280 ms. Hyper-enhanced regions at the anterior and posterior VIPs were manually contoured on each short-axis slice using the same software, yielding total LGE volume. This procedure was conducted by an examiner who was not aware of the measurements of echocardiographic study.

Echocardiography

Echocardiograms were obtained using Vivid q (GE Healthcare, Milwaukee, WI). LV end-diastolic and end-systolic dimensions were assessed from the parasternal long-axis view. The eccentricity index, an index of IVS displacement toward left ventricle, was obtained using the parasternal short-axis view at both end-systole and end-diastole. [17]

For the objective assessment of the regional motion of the LV wall and IVS, established speckle-tracking analysis was conducted using commercially available software (EchoPAC, GE Vingmed, Horton, Norway). With this technique, LV free wall and IVS were automatically divided into six segments, and the radial motion of each segment was visualized by six lines in different colors. Figure 1A and 1B are representative images of a PH patient (patient 1) who showed no LGE at VIPs on a CMR image (A) and normal speckle tracking echocardiogram (B). Figure 2C is an image of another PH patient who showed LGE at VIPs on CMR. In the speckle tracking echocardiography of this patient, yellow and red lines are seen below the baseline in early systole (Figure 2D). Yellow and red lines represent the motion of the anterior and inferior IVS, respectively, indicating that the IVS moves paradoxically outward (toward right ventricle) in the early systolic phase in this case.

Figure 2 illustrates the manner of quantification of the paradoxical IVS motion. First, the paradoxical systolic motion of the anterior IVS (a1) and inferior IVS (b1) were added, and then the entire (inward and outward) motion of the anterior IVS (a1+ a2) and inferior IVS (b1+ b2) was calculated. Then, the summed paradoxical IVS motion (a1+ b1) was divided by the entire IVS motion [(a1+ a2)+(b1+ b2)], and the obtained quotient was used as the paradoxical IVS motion index.

Reproducibility and Reliability of the Measurement of LGE Volume and Paradoxical IVS Motion Index

Intraobserver agreement for the two measurements: IVS volume and paradoxical IVS motion index was assessed by comparing the measurements of repeated analysis in five randomly chosen control subjects and in 10 randomly chosen PH patients (T.S.). Interobserver agreement of the two measurements was assessed using the same patients (n = 15) by comparing the results measured by T.S. and those obtained by a second, experienced cardiologist (I.T.). The second cardiologist was not aware of the echocardiographic measurements by the first examiner or of the CMR measurements. Bland-Altman analysis and intraclass correlations (ICC) were used to assess reproducibility.

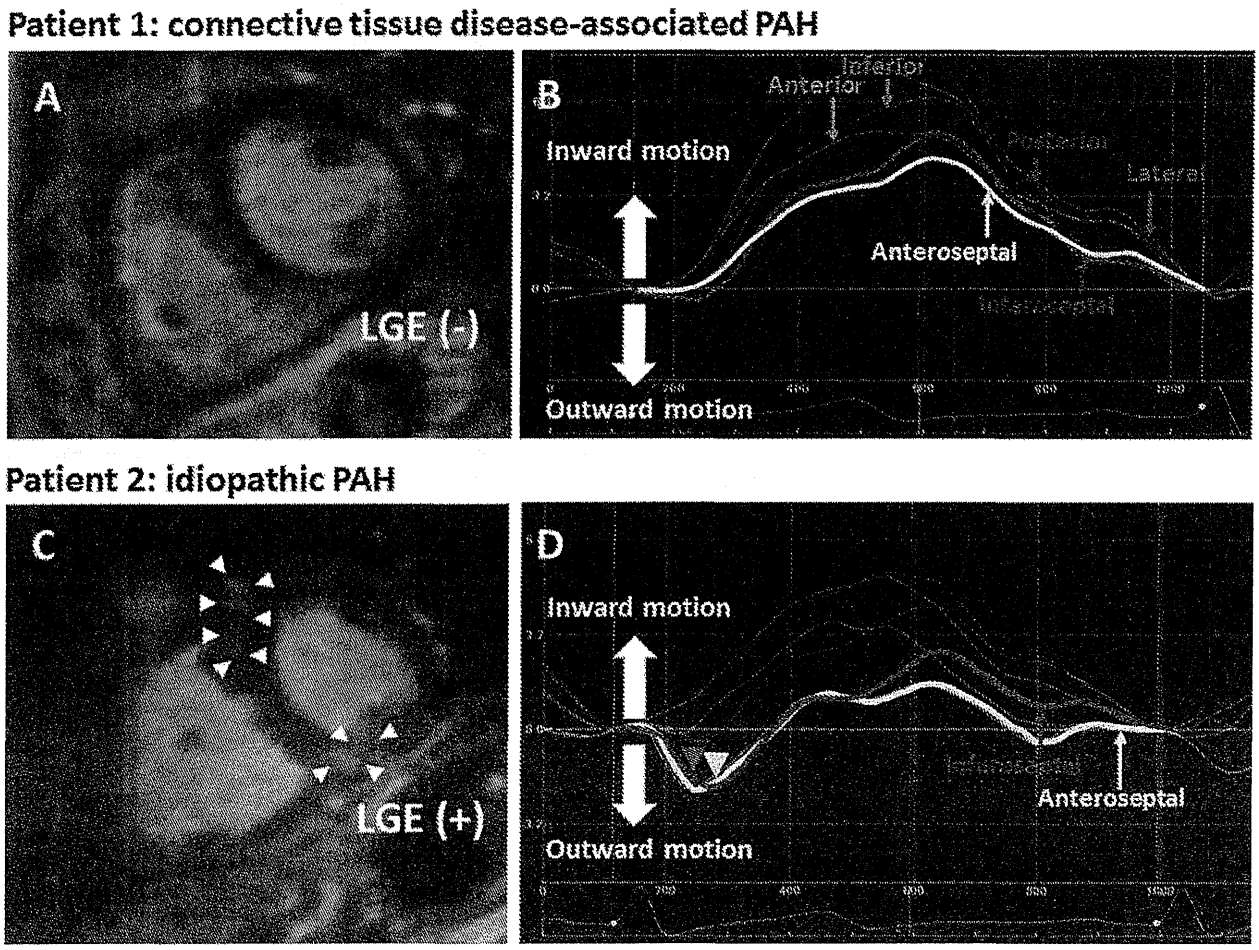

Figure 1. Representative images of cardiac magnetic resonance and speckle tracking echocardiography with or without late gadolinium enhancement and paradoxical motion of the interventricular septum. Patient 1 had connective tissue disease-associated PAH with a mean pulmonary artery pressure of 43 mmHg. CMR (A) shows no late gadolinium enhancement at ventricular insertion points. There is no paradoxical motion of the interventricular septum by speckle tracking echocardiography (B). Patient 2 had idiopathic PAH with a mean pulmonary artery pressure of 37 mmHg. Late gadolinium enhancement at ventricular insertion points is shown in a CMR image (arrow heads, C), and paradoxical motion of the interventricular septum at early systolic phase (arrow heads) is also noted on speckle tracking echocardiography (D). PAH, pulmonary artery hypertension; CMR, Cardiac magnetic resonance.
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Statistical Analysis

Continuous variables are expressed as mean ± standard deviation (SD) for those normally distributed or otherwise as medians and interquartile ranges (IQR). Departures from normality were detected with the Shapiro-Wilk statistic. Differences in measurements between the control and PH groups were assessed with the chi-square test, Student's *t* test, or the Wilcoxon test as appropriate. LGE volume in VIPs was compared between PH patients who were on vasodilation therapy and those who were not, and among PH patients treated with different regimens of vasodilators.

Correlations between LGE volume in VIPs and other clinical parameters were evaluated by Pearson's correlation coefficient. The statistical power of our study was greater than 0.8 with a significance level of 0.05, [18] given the estimation based on the previous study that the correlation coefficients between LGE mass in VIPs and morphological and hemodynamic parameters of PH were 0.4 or greater. [4]

Multiple regression analysis was also conducted to examine if any measurement predicted LGE volume at VIPs in an independent manner. In this analysis, six variables that were likely to be associated with LGE at VIPs (i.e., mean PAP, RV EDV index, RV mass index, RV EF, diastolic eccentricity index, and paradoxical IVS motion index) were chosen as explanatory variables.

All statistical analyses were performed using JMP® Version 9 (SAS Institute Inc., Cary, NC), and p values less than 0.05 were considered to represent statistical significance.

Results

A total of 51 Japanese patients met the entry criteria, but five patients were excluded based on pre-specified exclusion criteria. The mean duration between the initial recognition of any PH-related symptoms/signs and the diagnosis of PH was 43 months (range, 8–64). Twenty-one age- and gender-matched healthy controls were also enrolled. When comparing the 46 PH patients (male/female, 11/35; age, 50±15 years) and the 21 control subjects (male/female, 7/14; age 44±7 years), no significant demographic differences were apparent including in body mass