

Exercise-Induced Desaturation During a Six-Minute Walk Test in Patients with Pulmonary Arterial Hypertension : A Retrospective, Observational Study

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Research

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Abstract

Background: The study aimed to evaluate the practical implication of exercise-induced oxygen desaturation (EID) in pulmonary arterial hypertension (PAH) patients.

Methods: We conducted a single-center, retrospective, observational study from April 2016 to March 2018. Twenty patients diagnosed with PAH after right-sided heart catheterization (RHC) were assessed using trans-thoracic echocardiogram (TTE), pulmonary function test (PFT), 6-minute walking test (6MWT) with gas analysis, body composition test, and muscle power tests. The occurrence of adverse events was assessed.

Results: Ten patients showed EID during the 6MWT. Patients were divided into an EID group and a non-EID group. Epidemiological characteristics, TTE data, and RHC data did not differ between the two groups. Forced expiratory volume in the first second (FEV_1), 6-minute walking distance, and peak oxygen consumption were significantly lower in the EID group (all $p < 0.05$). The EID group showed higher risk of emergency room visits, readmission, lung transplantation surgery, and death (OR = 13.5, 95% CI 1.20–152.21). We developed a predictive scale for exercise-induced desaturation (PSEID) in PAH (AUC=0.91, 95% CI 0.75–1.00). A PSEID score of 4 or more predicted EID with 90% sensitivity and 90% specificity.

Conclusions: EID occurred in half of the PAH patients during the 6MWT, and this group showed poor prognosis with more events, such as emergency room visits, re-admission, lung transplantation, and death. Our PSEID using 6MWT and PFT can assist physicians in the early identification of patients at risk of adverse events.

Trial registration: CRIS KCT0005132 (retrospectively registered 16 Jun 2020, <https://cris.nih.go.kr/cris/index/index.do>)

Background

Pulmonary arterial hypertension (PAH) is a rare but potentially life-threatening condition characterized by elevated mean pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR).^{1–3} Different pathological features characterize the diverse clinical PAH groups, but in general, PAH affects the distal pulmonary arteries. Eventually PAH leads to right ventricle (RV) dilation, impaired function, RV failure, and premature death. Prognosis can differ according to the underlying etiology, but generally, patients experience worsening quality of life due to progressive worsening of symptoms, such as dyspnea, fatigue, and syncope.^{2, 4} Furthermore, PAH is associated with decreased exercise capacity. Current European guidelines recommend that patients be encouraged to engage in physical activity within their limits.⁵ During exercise, mild breathlessness is acceptable, but patients should avoid exertion that leads to severe breathlessness, exertional dizziness, or chest discomfort.

Patients with pulmonary diseases feel breathlessness due to deficient oxygenation during exercise. In chronic obstructive pulmonary disease (COPD), it is known that decreased baseline oxygen saturation

and the occurrence of exercise-induced desaturation (EID) are correlated with mortality.^{6,7} Some patients with PAH show EID; however, no previous studies have revealed a relationship between the severity of PAH and EID. The aim of this study was to evaluate the occurrence of EID and elucidate the contributing factors in patients with PAH.

Methods

Study design and population

This was a single-center, retrospective, observational study. The enrolled patients had been diagnosed with PAH using trans-thoracic echocardiogram (TTE) and right-sided heart catheterization (RHC) between April 2016 and March 2018. We categorized the types of PAH into four groups according to etiology: idiopathic PAH = group I, congenital heart disease = group II, connective tissue disease (CTD) = group III, and portopulmonary hypertension = group IV. We excluded patients with any uncorrected congenital heart disease, including patent foramen ovale. The patients who were in a decompensated state requiring advanced or intravenous medical therapy, patients who were not able to walk without oxygen support, and patients with other physical problems which interfered with exercise were excluded. Finally, 20 patients (male = 3, female = 17) were included with a mean age of 46 years (Table 1). The study protocol was approved by the institutional review board (approval number: H-1903-018-077) of Pusan National University Hospital, Busan, Korea. The study was conducted according to the principles of the Declaration of Helsinki, and the requirement for informed consent was waived due to the retrospective nature of the research.

Table 1
Epidemiological characteristics

	Level	Non-EID group (n = 10)	EID group (n = 10)	p-value
Age (median [IQR])		46.00 [39.00,56.00]	44.50 [34.00, 61.00]	1.000
Height (median [IQR])		59.30 [154.90, 163.00]	158.30 [151.00, 164.00]	0.910
Weight (median [IQR])		58.50 [53.00, 61.40]	61.50 [54.00, 65.20]	0.545
BMI (median [IQR])		22.85 [22.06, 24.41]	22.65 [20.08, 26.35]	1.000
BB (%)		3 (30.00)	0 (0.00)	0.211
DM (%)		1 (10.00)	1 (10.00)	1.000
HTN (%)		4 (40.00)	2 (20.00)	0.629
Angina pectoris (%)		0 (0.00)	0 (0.00)	-
Dyslipidemia (%)		0 (0.00)	0 (0.00)	-
COPD (%)		0 (0.00)	1 (10.00)	1.000
ILD (%)		0 (0.00)	4 (40.00)	0.087
LC (%)		2 (20.00)	3 (30.00)	1.000
Alcohol (%)		2 (20.00)	2 (20.00)	1.000
Smoking (%)		0 (0.00)	2 (20.00)	0.474
Aetiologic group (%)	1	3 (30.00)	4 (40.00)	0.081
	2	5 (50.00)	0 (0.00)	
	3	1 (10.00)	4 (40.00)	
	4	1 (10.00)	2 (20.00)	
WHO functional class (%)	1	1 (10.00)	0 (0.00)	0.459
	2	4 (40.00)	5 (50.00)	
	3	5 (50.00)	3 (30.00)	

EID, exercise-induced desaturation; IQR, interquartile range; BMI, body mass index; BB, beta-blocker; DM, diabetes mellitus; HTN, hypertension; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; LC, liver cirrhosis; WHO, World Health Organisation.

Aetiologic groups: idiopathic pulmonary arterial hypertension (PAH), group I; congenital heart disease, group II; connective tissue disease, group III; portopulmonary hypertension, group IV.

	Level	Non-EID group (n = 10)	EID group (n = 10)	p-value
	4	0 (0.00)	2 (20.00)	
Risk classification	Low	7 (70.00)	6 (60.00)	0.666
	Intermediate	2 (20.00)	1 (10.00)	
	High	1 (10.00)	3 (30.00)	
EID, exercise-induced desaturation; IQR, interquartile range; BMI, body mass index; BB, beta-blocker; DM, diabetes mellitus; HTN, hypertension; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; LC, liver cirrhosis; WHO, World Health Organisation.				
Aetiologic groups: idiopathic pulmonary arterial hypertension (PAH), group I; congenital heart disease, group II; connective tissue disease, group III; portopulmonary hypertension, group IV.				

Transthoracic echocardiogram

All images were obtained using a standard ultrasound machine (Vivid S70 and Vivid E9; GE Healthcare, Andover, MA, USA). Standard techniques were used to obtain 2-dimensional and Doppler measurements according to the American Society of Echocardiography guidelines. Global longitudinal strain (GLS) was assessed in the left ventricle (LV) and the RV. E(early diastolic transmitral velocity)/E'(early myocardial velocity) ratio was measured by tissue doppler. For deformation analysis, endocardial borders were traced on the end-systolic frame in three apical views (4-, 2-, and 3-chamber) and the RV free wall using Image-Arena® software (Tomtec GmbH, Munich, Germany). Peak longitudinal strain (PLS) was computed automatically, generating regional data from six segments and an average value for each view.

Right heart catheterization

RHC was performed using a Swan-Ganz catheter via the right internal jugular vein. The mean PAP, pulmonary capillary wedge pressure (PCWP), PVR, right atrial pressure (RAP), and cardiac index (CI) were evaluated. Pulmonary hypertension was diagnosed according to the 2015 European Society of Cardiology (ESC) and the European Respiratory Society (ERS) guidelines.⁵

Pulmonary function test (PFT)

A single, well-trained medical laboratory technologist administered the PFT using PONY Fx (Cosmed, Rome, Italy). All patients performed three repetitions, and the best result was accepted when the difference between each trial was within 0.150 L according to the 2017 American Thoracic Society (ATS) statement.⁸ Standard spirometric measurements such as forced vital capacity (FVC), forced expiratory volume in one second (FEV₁), and diffusing capacity of the lung for carbon monoxide (DLCO), were assessed.

Six-minute walk test with gas analysis

Exercise performance was evaluated using the 6-minute walk test (6MWT) with percutaneous oxygen saturation (SpO₂) monitoring and gas analysis. The exercise tests were performed when the patient was considered to be in a medically stable state just before discharge or at the outpatient clinic. 6MWT was performed on a 30-metre walking track according to the ATS guidelines and observed by one skilled physical therapist.⁹ SpO₂ was observed using the wrist Ox 3150 pulse oximeter (Nonin Medical Inc., Plymouth, MN, USA) during the 6MWT. Using the K4b2 system (Cosmed, Rome, Italy), peak oxygen consumption (VO_{2peak}) and the minute ventilation/carbon dioxide production (VE/VCO₂) slope were measured simultaneously.¹⁰

Muscle function test

Grip strength (GS) was tested using a hand-held dynamometer (Jamar® Hydraulic Hand Dynamometer; Sammons Preston Patterson Medical Products Inc., Bolingbrook, IL, USA).¹¹ In a seated position with elbow flexed at 90 degrees, patients were asked to grip the dynamometer as strongly as possible three times. Knee extensor strength (KES) was measured using a digital hand-held dynamometer (Jtech Medical, Salt Lake City, UT, USA).¹² Patients sat in a chair with folded arms and knees bent at a 35-degree angle. The head of the dynamometer and the leg were wrapped with a belt and KES was measured three times.

Definition of sarcopenia

Based on the consensus definition of the Asian Working Group for sarcopenia,¹³⁻¹⁵ we diagnosed sarcopenia if the following conditions were met: (1) a gait speed < 1.0 m/sec or a maximal gait speed < 28 kg for men or < 18 kg for women and (2) Appendicular skeletal muscle mass (ASM)/height² < 7.0 kg/m² for men or < 5.7 kg/m² for women. Bioimpedance analysis was used to measure the muscle mass (Inbody; Biospace, Seoul, Korea).

Definition of event

We defined an event as any of the following events that occurred during the first year after the exercise test: (1) emergency room (ER) visit, (2) re-admission due to cardiopulmonary problem, (3) lung transplantation surgery, and (4) death.

Statistical analysis

Data were analyzed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). We used the Wilcoxon rank-sum test for evaluating continuous data. Qualitative data were analyzed with the Fisher's exact test. To evaluate the relationship between EID and cardiac, pulmonary, and exercise function, a Pearson correlation analysis was used. Statistical significance was defined by a p-value of less than 0.05. The receiver operating characteristic (ROC) curve analysis was performed using SPSS for Windows version 21.0 (SPSS Inc., Chicago, IL, USA).

Results

Epidemiological characteristics

There were 10 patients in the EID group and 10 patients in the non-EID group. Age, height, weight, body mass index (BMI), and co-morbidities did not differ between the two groups. Patient activity level, as defined by World Health Organization (WHO) functional class, did not differ between the two groups (1/4/5/0 vs. 0/5/3/2, $p = 0.459$). Disease severity, as defined by the ESC/ERS guidelines,⁴ did not differ between the two groups (7/2/0 vs. 6/1/3, $p = 0.108$). Etiological classifications did not differ significantly between the two groups (3/5/1/1 vs. 4/0/4/2, $p = 0.081$) (Table 1).

Cardiac and pulmonary function

Using TTE, systolic function, evaluated with LV ejection fraction and LV GLS, and diastolic function, evaluated with the E/E' ratio, did not differ between the two groups. Mean PAP, PVR, PCWP, CI, and RV GLS were not significantly different. FEV₁ was significantly lower in the EID group (70% vs. 83%, $p = 0.037$). FVC and DLCO did not differ between the two groups (Tables 2 and 3).

Table 2
Transthoracic echocardiogram and cardiac catheterization data

	Non-EID group (n = 10)	EID group (n = 10)	p-value
Echocardiography			
LVEF	58.00 [55.00, 60.00]	60 [54.00, 60.00]	1.000
LV GLS	-21.1 [-22, -14.4]	-20.95 [-21, -18]	0.733
E/E'	8.05 [7.80, 12.80]	8.75 [7.40, 10.20]	0.733
Mean PAP	40.00 [34.00, 46.00]	41.00 [36.00, 45.00]	0.880
RVSP	68.50 [46.00, 92.00]	64.00 [54.00, 76.00]	0.940
RV GLS	-14.78 [-18.30, -9.70]	-12.37 [-19.40, -6.6]	0.503
RV_TAPSE	15.00 [14.00, 20.00]	16.00 [14.00, 18.00]	0.970
S	10.30 [8.80, 12.00]	11.00 [8.20, 12.00]	0.970
RAA	20.85 [17.40, 30.30]	19.45 [14.00, 32.90]	0.734
Cardiac catheterization			
PCWP	15.00 [13.00, 18.00]	14.50 [12.00, 15.00]	0.618
PVR	13.00 [9.98, 16.25]	10.31 [6.47, 13.34]	0.596
Mean PAP	43.00 [31.00, 66.00]	44.00 [39.00, 52.00]	0.775
RAP	15.00 [12.00, 17.00]	12.00 [10.00, 13.00]	0.121
Venous sat	69.20 [50.90, 74.40]	67.25 [61.40, 70.90]	0.967
CI	2330.00 [2059.00, 2748.00]	2975.00 [2306.00, 3134.00]	0.331
DPG	18.78 [3.50, 32.00]	15.67 [10.00, 24.50]	0.512
EID, exercise-induced desaturation; LVEF, left ventricular ejection fraction; LV GLS, left ventricular global longitudinal strain; E/E', early diastolic transmitral velocity (E) to early myocardial velocity ratio measured by tissue doppler (E'); PAP, pulmonary artery pressure; RVSP, right ventricular systolic pressure; RV GLS, right ventricular global longitudinal strain; RV TAPSE, right ventricular tricuspid annular plane systolic excursion; S, Mitral Annular Systolic Velocity; RAA, right atrial appendage; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; CI, cardiac index; DPG, diastolic pulmonary gradient.			
Data are expressed as median [IQR].			

Table 3
Pulmonary function test and exercise test data

	Non-EID group (n = 10)	EID group (n = 10)	p-value
FVC (%)	89.00 [81.00, 90.00]	74.50 [65.00, 84.00]	0.078
FEV₁ (%)	83.00 [81.00, 84.00]	70.00 [69.00, 80.00]	0.037*
DLCO (%)	73.00 [58.00, 86.00]	55.00 [32.00, 70.00]	0.086
6MWD (m)	503.00 [450.00, 520.00]	331.00 [252.00, 467.00]	0.021*
6MWD (%)	71.00 [65.10, 77.10]	48.65 [45.20, 64.30]	0.011*
VO_{2peak} (ml/min/kg)	15.73 [13.56, 20.12]	11.41 [10.48, 16.22]	0.021*
VO _{2peak} (%)	57.50 [52.00, 63.30]	48.00 [32.00, 57.20]	0.064
VE/VCO ₂ slope	37.85 [29.60, 39.10]	41.10 [32.80, 60.20]	0.241
Peak HR (%)	63.36 [57.40, 77.27]	63.96 [59.78, 72.20]	0.910
Sarcopenia (n (%))	1 (10%)	7 (70%)	0.020†
EID, exercise-induced desaturation; FVC, forced vital capacity; FEV ₁ , forced expiratory volume in the first second; DLCO, diffusing capacity for carbon monoxide; 6MWD, 6-minute walking distance; VO _{2peak} , peak oxygen consumption; VE, minute ventilation; VCO ₂ , carbon dioxide production; HR, heart rate.			
Data are presented as median [IQR].			
* p < 0.05 in Wilcoxon rank-sum test			
† p < 0.05 in Fisher's exact test			

Exercise capacity

Nadir SpO₂ during the 6MWT was 83.5% in the EID group and 93.9% in the non-EID group. In the EID group, the 6-minute walk distance (6MWD) was significantly shorter (331.00 m vs. 503.00 m, p = 0.021) and the percentage of normal predicted values was significantly lower (48.65% vs. 71.00%, p = 0.011). VO_{2peak} was significantly lower in the EID group (11.41 ml/min/kg vs. 15.73 ml/min/kg, p = 0.021). The VE/VCO₂ slope was elevated in both groups. HR was elevated during exercise in all patients, and there was no difference between groups (63.36% vs. 63.96% of predicted maximal, p = 0.91) (Table 3). Eight patients met the criteria for sarcopenia, and seven were in the EID group (p = 0.020, odds ratio (OR) = 21.00, 95% confidence interval (CI) = 1.780–248.10) (Table 1).

One-year prognosis

In the EIP group, six patients required an ER visit and readmission. Among these, one patient died, and one patient underwent lung transplantation surgery. In the non-EIP group, only one patient required an ER visit and readmission ($p = 0.057$, $OR = 13.50$, $95\% CI = 1.20-152.21$).

Correlation between occurrence of EID and physiologic factors

Using a Pearson's correlation test, EID correlated with 6MWD ($r = 0.57$, $p = 0.0092$), percentage of 6MWD ($r = 0.56$, $p = 0.0103$), DLCO ($r = 0.49$, $p = 0.034$), and FEV_1 ($r = 0.49$, $p = 0.035$). VO_{2peak} during the 6MWT was correlated with EID ($r = 0.47$, $p = 0.036$). There was no correlation between cardiac function evaluated with TTE or RHC and EID (Table 4).

Table 4
Correlation between occurrence of EID and physiologic factors

	Pearson's r	p-value
LVEF	0.18014	0.4473
GLS	-0.186	0.4324
E/E'	-0.1748	0.4611
RV TAPSE	0.29882	0.2006
RA pr	0.33482	0.1744
Mean PAP	-0.29435	0.2078
PCWP	0.11445	0.6408
PVR	0.04585	0.8566
RVSP	-0.03982	0.8676
Venous saturation	0.06855	0.7804
Cardiac index	-0.23838	0.3408
6MWD	0.56651	0.0092*
6MWD_%	0.55982	0.0103*
HRpeak	-0.15983	0.5009
HRpeak_%	-0.19071	0.4206
DLCO	0.44651	0.0553
DLCO_%	0.48808	0.034*
FVC	0.23752	0.3275
FVC_%	0.38337	0.1052
FEV ₁	0.3013	0.21

EID, exercise-induced desaturation; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; E/E', early diastolic transmitral velocity (E) to early myocardial velocity ratio measured by tissue doppler (E') ; RV TAPSE, right ventricular tricuspid annular plane systolic excursion; RA pr, right atrial pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RVSP, right ventricular systolic pressure; 6MWD, 6-minute walking distance; HR, heart rate; DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; FEV₁, forced expiratory volume in the first second; VO_{2peak}, peak oxygen consumption; VE, minute ventilation; VCO₂, carbon dioxide production.

* p < 0.05 in Pearson's correlation analysis.

	Pearson's r	p-value
FEV ₁ _%	0.48507	0.0353*
VO _{2peak}	0.47095	0.0361*
VE/VCO ₂ slope	-0.33081	0.1543
<p>EID, exercise-induced desaturation; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; E/E', early diastolic transmitral velocity (E) to early myocardial velocity ratio measured by tissue doppler (E') ; RV TAPSE, right ventricular tricuspid annular plane systolic excursion; RA pr, right atrial pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RVSP, right ventricular systolic pressure; 6MWD, 6-minute walking distance; HR, heart rate; DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; FEV₁, forced expiratory volume in the first second; VO_{2peak}, peak oxygen consumption; VE, minute ventilation; VCO₂, carbon dioxide production.</p>		
<p>* p < 0.05 in Pearson's correlation analysis.</p>		

Predictive scale for exercise-induced desaturation in pulmonary arterial hypertension (PSEID)

To predict the occurrence of EID, we selected several physiologic factors which were strongly correlated: the 6MWD, percentage of DLCO and FEV₁ for predicted value, VO_{2peak}, presence of ILD, and sarcopenia. The area under receiver operating characteristic (ROC) curve for PSEID was 0.91 (95% CI 0.75–1.00). When PSEID was same or above 4, the occurrence of EID was predicted with 90% sensitivity and 90% specificity (Table 5 and Fig. 1).

Table 5
 Predictive scale for exercise-induced desaturation in pulmonary arterial hypertension (PSEID)

	Score
6-minute walk distance (m)	
≥ 450	1
450 > and ≥ 300 m	2
< 300	3
Forced expiratory volume in the first second (% of predicted)	
≥ 80 of predicted value	0
80 > and ≥ 50	1
50 > and ≥ 30	2
< 30	3
Peak oxygen consumption (ml/min/kg)	
≥ 14	1
14 > and ≥ 10	2
> 10	3
Diffusion capacity for carbon monoxide (% of predicted)	
≥ 50	0
< 50	1
Interstitial lung disease	
Present	0
Absent	1
Sarcopenia	
Present	0
Absent	1

Discussion

PAH patients show clinical characteristics consistent with right-sided heart failure. Although the etiology and mechanisms behind the progress of PAH are unknown, the shortness of breath experienced by patients with PAH is similar to that experienced by patients with other pulmonary diseases. When exercise

intensity increases, oxygen consumption for energy metabolism should also increase. Furthermore, respiratory rate and minute ventilation elevate as needed. Because Manes et al.¹⁶ suggested that survival may be worse for patients who tend to desaturate at a greater extent during exercise and Morris et al.¹⁷ reported that patients with PAH desaturated during the 6MWT, we aimed to investigate the exercise-induced desaturation during exercise and the severe COPD that may explain this phenomenon.

In advanced COPD patients, ventilation capacity decreases for the following reasons: reduced elastic lung recoil, increased airway narrowing, increased airway resistance, expiratory limitation, and dynamic hyperinflation.¹⁸ Furthermore, decreased FEV₁, increased reserve volume, sputum accumulation, and large bullae disturb effective gas exchange. Breathlessness and desaturation eventuate from the imbalance between increased ventilatory demand and decreased ventilatory capacity.⁵ Severity of COPD, as classified by the Global Initiative for Obstructive Lung Disease (GOLD) criteria, correlates with prognosis.¹⁹ GOLD grade is determined according to airflow limitation and symptoms such as FEV₁, as well as a medical history of acute exacerbation and functional capacity, as evaluated with the modified Medical Research Council dyspnea scale and COPD assessment test. In the study by Golpe et al., patients with a 6MWT score below 395 m or resting SpO₂ below 86% showed poor survival probability (AUC = 0.80 and 0.80, respectively).²⁰ Among COPD patients without resting hypoxemia, EID would be considered as the other critical factor. Casanova et al. showed that COPD patients with EID without resting hypoxemia had a higher mortality rate (67% vs. 38% in non-EID patients) and a relative risk of 2.63.²¹ Shogo et al. revealed that EID was a predictive factor for the decline in the functional capacity of patients with COPD.²² However, there are some studies that reported the existence of EID in patients with PAH, while there were no studies on the relationship between EID and outcomes. Therefore, the risk assessments suggested by the 2015 ESC/ERS guidelines do not include the occurrence of EID.⁵

In this study, half of the PAH patients showed EID during the 6MWT, and they showed lower 6MWD and FEV₁. Interestingly, functional class—categorized by subjective symptoms—did not influence the occurrence of EID. There was no statistical difference in the distribution of WHO classifications in the EID and non-EID groups. Further, Manes et al. demonstrated that patients in different clinical subgroups showed hemodynamic and survival differences but no WHO functional class differences.¹⁶ Therefore, subjective symptoms during daily living or exercise are insufficient to evaluate PAH patients, and PFT and exercise testing with monitoring of oxygen saturation should be evaluated.

Andrianopoulos et al. reported that the sensitivity of a baseline SpO₂ ≤ 95% for the prediction of EID was 81.0%, specificity was 49.2%, and positive and negative predictive values were 50.8% and 80.0%, respectively.⁷ Additionally, they suggested that a DLCO < 50%, an FEV₁ < 45%, and a PaO₂ < 10 kPa could predict the occurrence of EID. In this study, 6MWD, percentage of predicted 6MWD, percentage of predicted DLCO, percentage of predicted FEV₁, and VO_{2peak} were correlated with EID. We suggest that a PSEID predictive scale include these factors, as well as the presence of ILD and sarcopenia. These tests are commonly used for PAH patients. Further, as mentioned in the above results, the predicted accuracy

of the PSEID was higher than expected, with 90% sensitivity and specificity. Thus, it would be applicable for clinical use. However, as there is a limit to conducting research on PAH patients in a single center, it is believed that such a “PSEID” needs to be extended to a multi-center study in order to be useful in clinical use.

There was no significant difference regarding the comorbidities in the two groups in this study. However, this could be a statistical error given the small sample size. Four of 10 patients in the EID group were diagnosed with interstitial lung disease (ILD) on chest CT scan. In contrast, none of the 10 non-EID patients had ILD. For the reasons mentioned above, we assume that PAH etiology would not be different between the two groups. PAH with connective tissue disease (CTD) was found in one of 10 patients in the non-EID group and four of 10 patients in the EID group. Four CTD patients showed ILD patterns on chest CT, and they also showed significantly lower DLCO. Considering the correlation between nadir SpO₂ and DLCO in the Pearson’s correlation analysis ($r = 0.49$, $p = 0.03$), the small sample size might have affected these results.

Casanova et al. demonstrated that the consequences of EID in COPD would suggest a poor prognosis.²¹ However, there is no consensus that the occurrence of EID in PAH patients would increase mortality. In this study, we defined ER visits, re-admission, heart or lung transplantation, and death as events. EID affected the occurrence of events with statistical significance (OR = 13.50, 95% CI 1.20–152.21). Serious events, such as death or lung transplantation surgery, were observed only in the EID group.

Exercise based pulmonary rehabilitation and breathing retraining are effective therapeutic interventions that improve physical performance, shortness of breath, and the quality of life in COPD patients.²³ However, the effect of rehabilitation on the improvement of desaturation or FEV₁ is still controversial because exercise could not restore the destroyed lung parenchyma and airways. In PAH, the safety and effectiveness of exercise training has now been well established. A meta-analysis of 16 trials found the overall risk of adverse events during exercise to be 4.7%.²⁴ Another meta-analysis found that exercise training led to improvements in the 6MWD, VO_{2peak}, and peak workload.²⁵ Conversely, there is limited evidence on the effect of exercise on pulmonary vascular resistance and right ventricular pump function, and there are currently no studies investigating the effect of exercise on disease progression and survival. Further studies are necessary to investigate the effect of exercise-based rehabilitation on the occurrence of EID and improvements in PFT, particularly FEV₁ and DLCO, and on the long-term prognosis.

This study had several limitations. First, we analyzed a small sample of patients. As mentioned, PAH is a very rare disease with a prevalence of 2.5–7.5 per 100,000 persons in Scotland and France.^{26,27} Although there is no cohort data regarding PAH in South Korea, it is estimated that there are only 5,000 patients.²⁸ This is considered a low prevalence; however, studies with longer durations including multiple centers are required. Second, this study was designed as a cross-sectional, observational study. Thus, long-term cohort studies are warranted to confirm the influence of EID on the prognosis in PAH patients.

Conclusion

EID occurred frequently during the 6MWT. It occurred in half of the PAH patients, and this group had a worse prognosis with more events, such as emergency room visits, re-admissions, lung transplantations, and deaths, in our study. We conclude that pulmonary function, exercise capacity, and functional status are more closely related to the occurrence of EID, rather than cardiac function. Our PSEID can assist physicians in the early identification of patients at risk of adverse events.

Abbreviations

EID: Exercise-induced oxygen desaturation; PAH: Pulmonary arterial hypertension; RHC: Right-sided heart catheterization; CTD: Connective tissue disease; TTE: Trans-thoracic echocardiogram; PFT: Pulmonary function test; 6MWT: 6-minute walking test; FEV1: Forced expiratory volume in the first second; PSEID: Predictive scale for exercise-induced desaturation; PAP: Pulmonary artery pressure; PVR: Pulmonary vascular resistance; RV: Right ventricle; COPD: Chronic obstructive pulmonary disease; GLS: Global longitudinal strain; E: Early diastolic transmitral velocity; E': Early myocardial velocity; LV: Left ventricle; PLS: Peak longitudinal strain; PCWP: Pulmonary capillary wedge pressure; RAP: Right atrial pressure; CI: Cardiac index ; ESC: European Society of Cardiology; ERS: European Respiratory Society; ATS: American Thoracic Society; FVC: Forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; SpO₂: percutaneous oxygen saturation; VO₂peak: peak oxygen consumption; VE/VCO₂: minute ventilation/carbon dioxide production; GS: Grip strength; KES: Knee extensor strength; ASM: Appendicular skeletal muscle mass; ER: Emergency room ; ROC: Receiver operating characteristic; BMI: Body mass index; WHO: World Health Organization; 6MWD: 6-minute walk distance; GOLD: Global Initiative for Obstructive Lung Disease; ILD: Interstitial lung disease

Declarations

Ethics approval and consent to participate

This study was retrospective study and approved by the ethics committee of Pusan National University Hospital, Busan, Korea (approval number: H-1903-018-077).

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

JHC has no relevant conflicts to disclose. M-JS has no relevant conflicts to disclose. B-JL has no relevant conflicts to disclose.

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Author Contributions

M-JS and JHC contributed to the conception and design of the work. B-JL, M-JS conducted the acquisition, analysis, and interpretation of data for the work. B-JL and JHC drafted the manuscript. JHC and M-JS critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work, ensuring integrity and accuracy.

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Figures

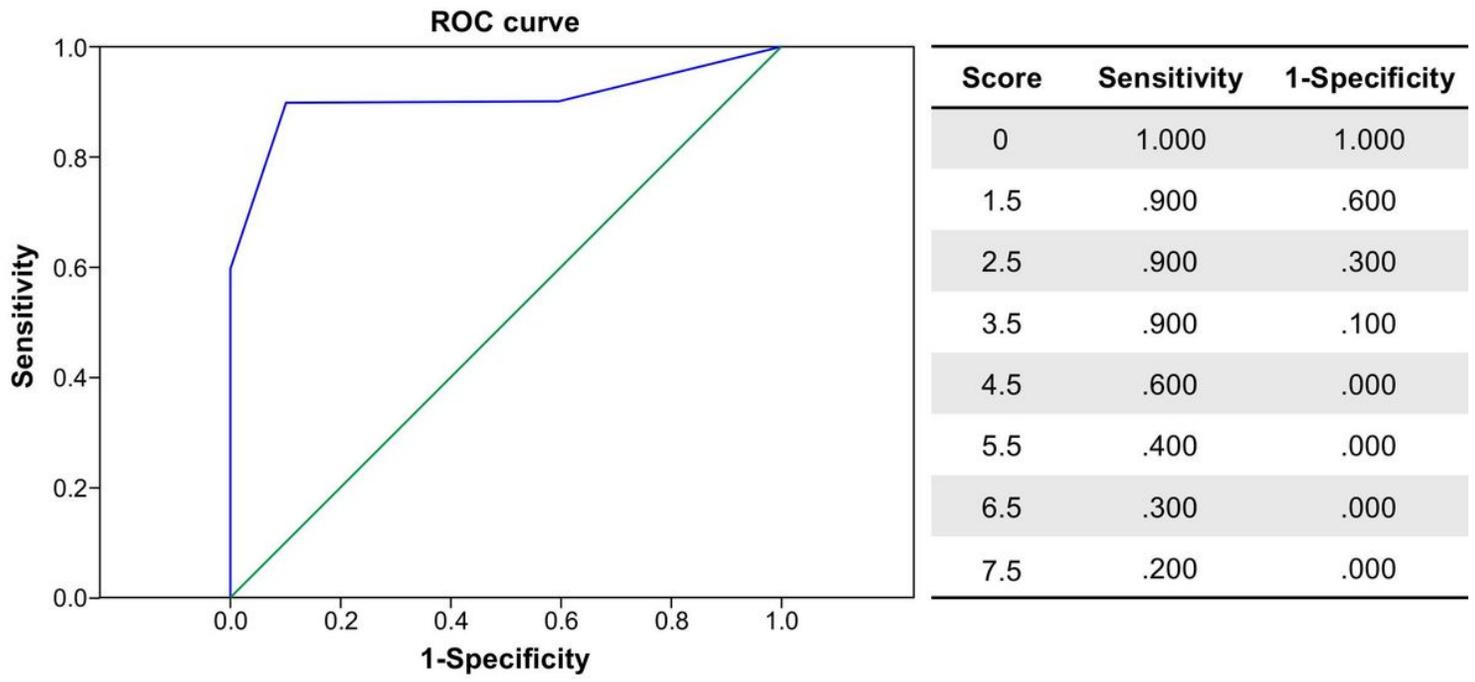


Figure 1

ROC curve of predictive scale for exercise-induced desaturation in pulmonary arterial hypertension (PSEID).