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ORIGINAL ARTICLE

Predictors of exercise-induced pulmonary hypertension in patients with connective tissue disease

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Abstract
Screening and early detection of pulmonary arterial hypertension (PAH) in connective tissue disease (CTD) are currently recommended for early treatment. Exercise-induced pulmonary hypertension (EIPH) is thought to be a potential risk of developing resting pulmonary hypertension. However, accurate diagnosis of EIPH is needed hemodynamics by right heart catheterization during exercise. Therefore, we compared various parameters of EIPH group with non-EIPH group in patients with CTD. This study aimed to investigate noninvasive predictors of EIPH. A total of 162 consecutive patients with CTD who received screening of PAH was studied. Thirty-four patients with suspected PAH received right heart catheterization (RHC) at rest. Twenty-four patients without PAH underwent RHC during exercise, and they were divided into the EIPH group ($n=7$) and the non-EIPH group ($n=17$). Exercise tolerance such as 6-min walk distance and peak VO_2/kg in the EIPH group was lower than that in the non-EIPH group. For hemodynamics, pulmonary artery pressure, right atrial pressure, and vascular resistance in the EIPH group were significantly higher than those in the non-EIPH group. In echocardiography, RV Tei index in the EIPH group was significantly higher than that in the non-EIPH group (EIPH vs non-EIPH = 0.42 [0.41, 0.47] vs 0.25 [0.20, 0.32], $P=0.007$). The receiver operating characteristics curve showed a cutoff value of RV Tei index (0.41) with a sensitivity of 0.857 and specificity of 0.882. In conclusion, RV Tei index might be a feasible predictor of EIPH in patients with CTD.

Keywords Exercise-induced pulmonary hypertension · Connective tissue disease · Echocardiography · Right ventricular Tei index

Introduction

Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure (mean PAP) ≥ 25 mmHg and measured by right heart catheterization (RHC). Pulmonary artery hypertension (PAH) is found in a subpopulation of patients with PH. PAH is characterized hemodynamically by the presence of pre-capillary PH, including mean PAP ≥ 25 mmHg, an end-expiratory pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg, and a pulmonary vascular resistance (PVR) > 3 Wood units (WU) [1]. Currently, survival of idiopathic/heritable PAH shows improvement supported by pulmonary hypertension-targeted therapy [2]. However, PAH associated with connective tissue disease (CTD) has historically had a poor prognosis. Previously, the 1- and 3-year survival rates of patients with PAH and systemic sclerosis (SSc-PAH) were reported as 78% and 47%, respectively [3]. Humbert et al. observed a better prognosis in patients who were identified with PAH in an active screening program compared with those identified in the course of routine practice. They suggested the potential benefit of intervention earlier in the course of PAH [4].

EIPH is thought to be an abnormal response of the pulmonary circulation for increased cardiac output (CO) by exercise, and it has a potential risk of developing resting PH [5]. EIPH is assessed by several exercise protocols, methods, positions, and many cutoff values [6]. Herve et al. [7] proposed new diagnostic criteria of EIPH using RHC with a combined maximum mean PAP > 30 mmHg and total

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pulmonary vascular resistance (TPR) > 3 WU during exercise. RHC during exercise is necessary for accurately diagnosing EIPH, but it is invasive and complicated. Therefore, a noninvasive diagnostic method of EIPH is required in clinical practice. Consequently, we compared various parameters of EIPH group with non-EIPH group in patients with CTD. This study aimed to investigate noninvasive predictors of EIPH using the new criteria. We analyzed the associations between EIPH and indices of echocardiography, the pulmonary function test (PFT), the cardiopulmonary exercise test (CPET), hemodynamics, and laboratory data in patients with CTD.

Materials and methods

A total of 162 consecutive patients with CTD underwent screening of PAH in Kagoshima University Hospital from December 2013 to April 2017. Echocardiography was performed in all of the patients, and 38 patients had tricuspid valve regurgitation peak flow velocity (TR PFV) ≥ 2.8 m/s. In 38 patients, 34 with symptoms suggesting PAH, including dyspnea on effort, general fatigue, edema, and/or an abnormal PFT (e.g., forced vital capacity %predicted [%FVC]/diffusing capacity of the lung for carbon monoxide %predicted [%DLCO] ≥ 1.6 or %DLCO < 60%), received RHC. All of the patients underwent echocardiography, the 6-min walk test, and a blood test, including plasma brain natriuretic peptide (BNP) levels and hemoglobin on admission. Ventilation-perfusion scintigraphy and a high-resolution chest computed tomography scan were performed before RHC. The patients did not show chronic thromboembolic disease and severe lung disease. PAH was diagnosed from hemodynamics by RHC at rest (mean PAP ≥ 25 mmHg, PAWP ≤ 15 mmHg, and PVR > 3 WU). One patient had left heart disease (PAWP > 15 mmHg) and 9 patients had PAH. Among 34 patients, 24 did not show PAH and they underwent RHC during exercise at the supine position. Finally, they were divided into the EIPH group ($n = 7$) and non-EIPH group ($n = 17$). EIPH was diagnosed with a mean PAP > 30 mmHg and TPR > 3 WU by hemodynamics at exercise (Fig. 1). Furthermore, we compared various parameters of EIPH group with non-EIPH group in patients with CTD. This study was approved by the clinical research ethics board of Kagoshima University Hospital and informed consent was obtained from all of the patients.

Echocardiography

In echocardiography, left ventricular end-diastolic dimension (LVDd) and left atrial dimension (LAD) were measured from the parasternal view. The left ventricular ejection fraction (LVEF) was calculated using the modified Simpson method. Right ventricular end-diastolic dimension (RVDd) of the basal and mid-right ventricle was measured from apical 4-chamber view. Using the pulsed Doppler method, early diastolic mitral inflow velocity (E) was measured at the tips of the mitral valve leaflets, and early diastolic mitral annular velocity (e′) was measured at the septal annulus. The E/e′ ratio was then calculated from these measurements. TR PFV was measured for estimating RV systolic pressure. The tricuspid annular plane systolic excursion (TAPSE) by M-mode and tissue Doppler-derived tricuspid lateral annular systolic velocity (TDI S') were measured as parameters of RV systolic function. Tricuspid inflow by pulsed-wave Doppler was measured at end-expiratory during quiet breathing. Among them, a tricuspid E/A ratio and deceleration time were obtained as parameters of RV diastolic function. The LV and RV Tei indices by pulsed-wave Doppler, which comprehensively indicate systolic and diastolic function of the ventricles, respectively, were commonly calculated using the isovolumic relaxation time (IRT), isovolumic contraction time (ICT), and ejection time (ET) according to the following formula: Tei index = (ICT + IRT)/ET. Practically, the Tei index was calculated by measuring 2 intervals (Tei index = ([$a - b$]/b), where a is the interval between cessation and onset of mitral/tricuspid inflow and b is the ET of LV/RV). Additionally, 3 consecutive beats were measured and averaged for each measurement. All echocardiographic measurements were stored and analyzed by a single experienced cardiologist who was blinded to the other clinical and demographic data. For reproducibility of measurements, 2 independent observers repeated 10 measurements of the Tei index. Differences in the measurements by the 2 observers were obtained to estimate interobserver variability. The same observer repeated the 10 measurements, and intraobserver variability was calculated.

Right heart catheterization

RHC was performed at the supine position. A balloon-tipped, triple-lumen, fluid-filled 6 Fr Swan Ganz catheter (Edwards/Biosensors) was introduced from the internal jugular vein. A 4 Fr sheath was introduced from the radial or brachial artery for continuous monitoring of arterial pressure and blood gas analysis. Transducers were set at the mid-axillary line and zeroed to atmospheric pressure. PAWP, PAP, right ventricular pressure, and right atrial pressure (RAP) were measured. Diastolic pulmonary vascular pressure gradient (DPG) was calculated as diastolic PAP–PAWP to examine the influence of left heart disease. Additionally, mixed venous oxygen saturation (SvO_2) and arterial oxygen saturation (SaO_2) were measured by 2-mL samples of pulmonary and systemic artery blood. Cardiac output (CO) was calculated by the Fick principle and CO/body surface area yielded the cardiac index (CI). PVR was

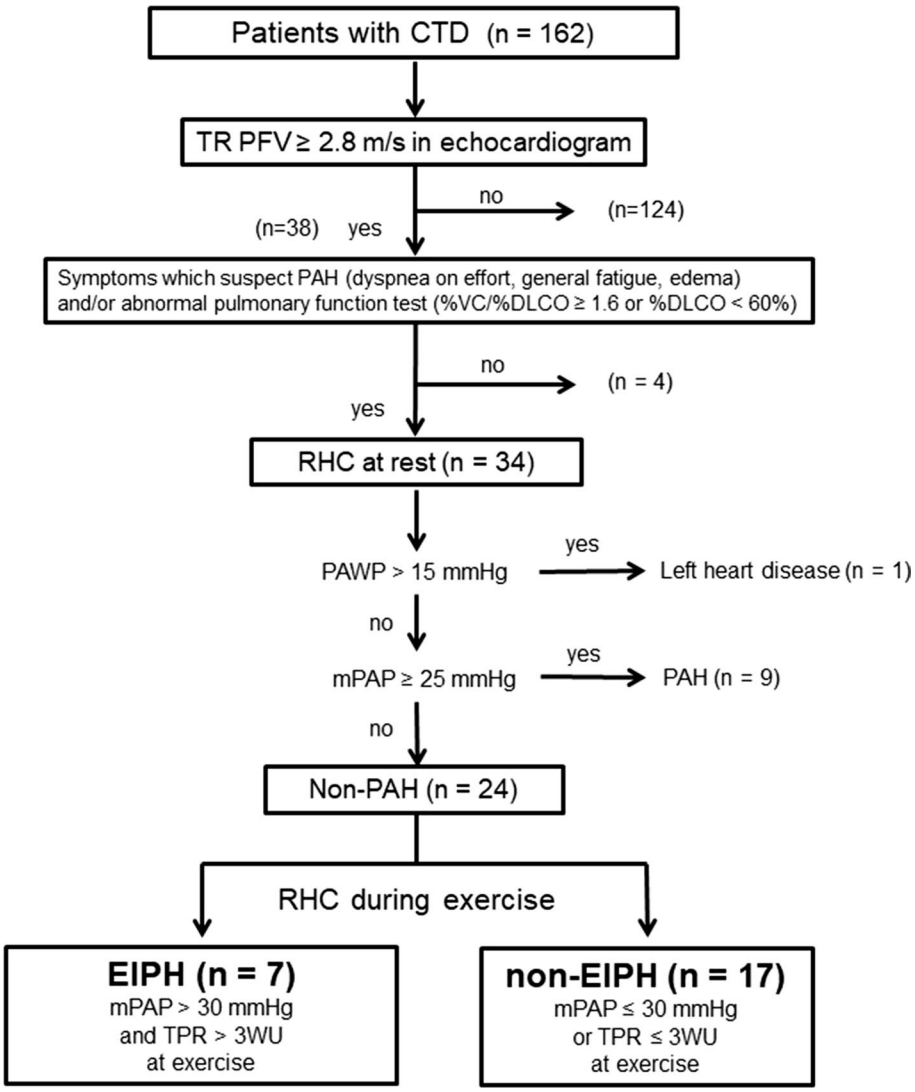

Fig. 1 Screening criteria of CTD-PAH and an algorithm for classification of EIPH and non-EIPH. A total of 162 patients with connective tissue disease (CTD) had screening for pulmonary artery hypertension (PAH). Thirty-four patients who matched the following screening criteria of PAH had right heart catheterization (RHC) performed at rest. One patient had left heart disease and nine patients had PAH. The remaining 24 patients without PAH received RHC during exercise. These 24 patients were divided into the exercise-induced pulmonary hypertension (EIPH) group ($n=7$) and the non-EIPH group ($n=17$). *%VC* forced vital capacity (% predicted), *%DLCO* diffusing capacity of the lung for carbon monoxide (% predicted), *mPAP* mean pulmonary artery pressure, *PAWP* pulmonary artery wedge pressure, *TPR* total pulmonary resistance, *TR PFV* tricuspid regurgitation peak flow velocity, *WU* Wood units

calculated as mean PAP–PAWP/CO and TPR was calculated as mean PAP–RAP/CO. An electrocardiogram and arterial oxygen saturation, which were measured by pulse oximetry, were continuously monitored.

The patients which did not show PAH at rest underwent RHC during exercise at the supine position. RHC and the cardiopulmonary exercise test (CPET) were simultaneously performed to observe hemodynamics and respiratory changes during exercise. The exercise protocol by a supine incremental cycle ergometer (Lode BV, Groningen, Netherlands) is shown in Fig. 2. Four minutes of rest were followed by 3 min of warming up in unloaded cycling. Subsequently, work was continuously increased by the Ramp method 10 W/min, and exercise was performed according to a symptom-limited stress test. Hemodynamics (PAP, systemic artery pressure, PAWP, and RAP), and blood gas analysis (radial artery and pulmonary artery blood) were measured before exercise, every 2 min during exercise, at the peak point, and every 2 min after termination of exercise. O_2 consumption (VO_2) for calculation of CO was obtained from CPET data. This examination was finished 6 min after termination of exercise and we confirmed that hemodynamics was restored at rest.

Statistical analysis

Results are expressed as median [25th, 75th percentiles] values when the distribution was not parametric. Comparisons of baseline clinical characteristics between the EIPH and non-EIPH groups were performed using the Wilcoxon test for nonparametric data. Pearson's Chi-square test was performed to compare sex and World Health Organization (WHO) function classification between the EIPH and non-EIPH groups. The correlations between two variables were examined by simple linear regression analysis. Statistical significance was accepted at $P<0.05$. Statistical analysis

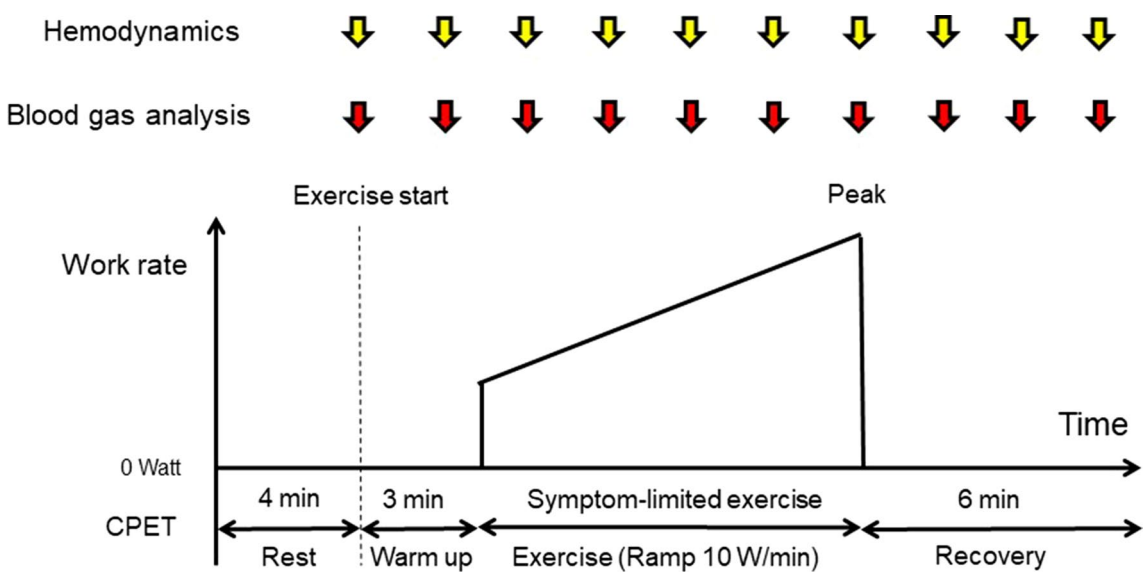

Fig. 2 Study protocol of the RHC during exercise. RHC during exercise and CPET were performed simultaneously to observe hemodynamics and respiratory change during exercise. Exercise was performed according to a symptom-limited stress test. Hemodynamics, blood gas analysis and echocardiography were measured before exercise, every 2 min during exercise, at the peak point, and every 2 min after termination of exercise. *RHC* right heart catheterization, *CPET* cardiopulmonary exercise test, *W* watts

was performed using JMP Statistical Discovery Software, version pro11 (SAS, Cary, NC, USA).

Results

Characteristics of patients and clinical data are shown in Table 1. There were no significant differences in age, height, body weight, BSA, WHO functional class, hemoglobin, and BNP levels between the EIPH and non-EIPH groups. Among 24 patients, 2 patients with SSc were orally administered a prostacyclin analog (Beraprost sodium 60 μg) and endothelin receptor antagonist (Bosentan 125 mg) for Raynaud's symptoms. No patients were administered diuretics. More than half of the patients with CTD had SSc, with no significant difference in type of CTD between the EIPH and non-EIPH groups. In the pulmonary function test, there were no significant differences between the EIPH and non-EIPH groups. In the CPET, peak VO_2/kg in the EIPH group was significantly lower than that in the non-EIPH group (EIPH vs non-EIPH = 11.2 mL/min/kg [10.4, 11.9] vs 14.1 mL/min/kg [12.3, 16.4], $P = 0.004$). The 6-min walk distance (6MWD) in the EIPH group was significantly shorter compared with that in the non-EIPH group (EIPH vs non-EIPH = 430 m [403, 510] vs 523 m [298, 593], $P = 0.041$).

We compared hemodynamics at rest and at exercise between the EIPH and non-EIPH groups (Table 2). In hemodynamics at rest, systolic PAP, mean PAP, RAP, PVR, and TPR in the EIPH group were significantly higher than those in the non-EIPH group (systolic PAP: EIPH vs non-EIPH = 29.0 mmHg [29.0, 31.0] vs 25.0 mmHg [21.5, 27.5], $P = 0.003$; mean PAP: 19.0 mmHg [18.0, 21.0] vs 15.0 mmHg [13.0, 17.0], $P = 0.006$; RAP: 7.0 mmHg [6.0, 7.0] vs 5.0 mmHg [3.5, 6.0], $P = 0.010$; PVR: 2.5 WU [2.3, 3.4] vs 1.8 WU [1.4, 2.2], $P = 0.006$; TPR: 3.4 WU [3.1, 4.0] vs 2.3 WU [2.2, 3.3], $P = 0.013$). SvO_2 and the CI in the EIPH group were significantly lower than those in the non-EIPH group (SvO_2: EIPH vs non-EIPH = 68.1% [65.3, 69.1] vs 72.5% [70.2, 75.0], $P = 0.011$; CI: 2.2 L/min/m^2 [1.9, 2.5] vs 2.7 L/min/m^2 [2.4, 3.1], $P = 0.031$). In hemodynamics at exercise, systolic PAP, diastolic PAP, mean PAP, PAWP, RAP, PVR, and TPR in the EIPH group were significantly higher than those in the non-EIPH group (systolic PAP: EIPH vs non-EIPH = 70.0 mmHg [58.0, 73.0] vs 45.0 mmHg [31.0, 47.5], $P < 0.001$; diastolic PAP: 27.0 mmHg [20.0, 32.0] vs 18.0 mmHg [14.0, 22.0], $P = 0.017$; mean PAP: 44.0 mmHg [40.0, 51.0] vs 29.0 mmHg [24.0, 36.0], $P < 0.001$; PAWP: 17.0 mmHg [14.0, 21.0] vs 11.0 mmHg [7.5, 15.5], $P = 0.013$; RAP: 10.0 mmHg [8.0, 14.0] vs 6.0 mmHg [4.0, 8.5], $P = 0.001$; PVR: 3.4 WU [2.6, 3.7] vs 1.4 WU [1.1, 2.0], $P < 0.001$; TPR: 3.9 WU [3.5, 4.1] vs 2.0 WU [1.7, 2.4], $P < 0.001$). Similar to at rest, the CI at exercise was significantly lower in the EIPH group compared with the non-EIPH group (CI: EIPH vs non-EIPH = 5.4 L/min/m^2 [4.9, 6.3] vs 7.2 L/min/m^2 [6.3, 8.2], $P = 0.007$). The Δmean PAP/ΔCO as an index of the pressure–flow relationship was significantly higher in the EIPH group than in the non-EIPH group (Δmean PAP/ΔCO: EIPH vs non-EIPH = 4.8 mmHg/L/min [4.4, 5.5] vs 1.6 mmHg/L/min [1.2, 2.4], $P < 0.001$).

Table 1 Patients characteristics in EIPH and non-EIPH groups

	EIPH ($n=7$)	Non-EIPH ($n=17$)	P value
Age, years	71.0 [52.0, 78.0]	53.0 [44.0, 67.5]	0.152
Women, *n* (%)	7 (100)	17 (100)	–
Height, cm	157.9 [144.7, 160.3]	156.3 [153.1, 160.0]	0.949
Weight, kg	59.0 [46.8, 68.8]	61.7 [48.6, 69.1]	0.800
Body surface area, m^2	1.60 [1.47, 1.79]	1.65 [1.45, 1.72]	0.727
WHO functional class (I/II/III/IV)	0/6/1/0	2/14/1/0	0.535
Diuretics, *n* (%)	0 (0)	0 (0)	–
PAH-targeted therapy, *n* (%)	1 (14.3)	1 (5.9)	0.237
Oral prostacyclin analog, *n* (%)	1 (14.3)	1 (5.9)	0.237
Endothelin receptor antagonist, *n* (%)	1 (14.3)	1 (5.9)	0.237
Phosphodiesterase type 5 inhibitor, *n* (%)	0 (0)	0 (0)	–
Type of connective tissue disease			
Systemic sclerosis, *n* (%)	4 (58)	9 (53)	0.851
Systemic lupus erythematosus, *n* (%)	1 (14)	4 (24)	0.612
Mixed connective tissue disease, *n* (%)	2 (28)	2 (12)	0.315
Sjogren syndrome, *n* (%)	0 (0)	2 (12)	0.343
Hemoglobin, g/dl	11.8 [10.9, 12.5]	11.7 [11.0, 12.8]	0.567
Brain natriuretic peptide, pg/mL	46.0 [27.9, 93.6]	30.0 [15.2, 49.4]	0.112
Pulmonary function test			
%FVC, %	71.6 [69.4, 102.5]	91.1 [82.8, 99.8]	0.112
%FEV1.0, %	74.9 [72.9, 83.6]	78.0 [72.8, 83.5]	0.546
%DLCO, %	64.4 [54.0, 68.1]	68.6 [66.5, 78.0]	0.075
%FVC/%DLCO	1.2 [1.0, 1.5]	1.3 [1.1, 1.5]	0.657
Peak VO_2/kg, mL/kg/min	11.2 [10.4, 11.9]	14.1 [12.3, 16.4]	0.004
Six-minute walk distance, m	430 [403, 510]	523 [298, 593]	0.041

Values are median [25th, 75th percentiles] when appropriate

%DLCO diffusing capacity of the lung for carbon monoxide %predicted, EIPH exercise-induced pulmonary hypertension, %FVC forced vital capacity %predicted, %FEV1.0 forced expiratory volume in 1 s %predicted, VO_2 oxygen consumption, WHO world health organization

Echocardiographic data in the EIPH and non-EIPH groups are shown in Table 3. All of the patients were in sinus rhythm during echocardiography. LVDd, LAD, LVEF, mitral E/e′, RVDd, TR PFV, TAPSE, TDI S', tricuspid E/A ratio and deceleration time were not significantly different between the EIPH and non-EIPH groups. The RV Tei index in the EIPH group was significantly higher than that in the non-EIPH group (0.42 [0.41, 0.47] vs 0.25 [0.20, 0.32], $P=0.007$) (Fig. 3). The mean differences of interobserver and intraobserver variability for the measurement of the RV Tei index were measured (Tei index: 0.02 ± 0.02 or $5.5\pm5.5\%$ and 0.01 ± 0.01 or $2.9\pm2.9\%$, respectively).

The RV Tei index significantly and positively correlated with systolic PAP ($R=0.655$, $P=0.001$) and mean PAP during exercise ($R=0.657$, $P=0.001$). The RV Tei index in patients with CTD was useful for predicting EIPH with an area under the receiver operator curve value of 0.86. The receiver operating characteristics curve showed an optimal cutoff value for the RV Tei index of 0.41. Use of this cutoff value resulted in a sensitivity of 0.857 and specificity of 0.882. Furthermore, the IRT was significantly prolonged in the EIPH group compared with the non-EIPH group (87.0 ms [61.0, 106.0] vs 44.0 ms [33.0, 57.5], $P=0.008$). However, the ICT was not significantly different between the EIPH and non-EIPH groups (39.0 ms [37.0, 58.0] vs 32.0 ms [20.5, 47.0], $P=0.227$) (Fig. 4).

Subanalysis

The 6th (2018) World symposium on pulmonary hypertension proposed the mean $PAP>20$ mmHg, $PAWP\leq15$ mmHg, and $PVR\geq3$ WU as a hemodynamic definition of pre-capillary PH. Therefore, we performed subanalysis in patients with mean $PAP\leq20$ mmHg at rest. In subanalysis, patients were divided into the EIPH group ($n=5$) and non-EIPH group ($n=16$), and the RV Tei index in the EIPH group was significantly higher than that in the non-EIPH group (EIPH vs non-EIPH = 0.41 [0.32, 0.47] vs 0.25 [0.19, 0.30], $P=0.047$).

Table 2 Hemodynamics in EIPH and non-EIPH groups

	EIPH ($n=7$)	Non-EIPH ($n=17$)	P value
Hemodynamics at rest			
Arterial oxygen saturation, %	96.7 [95.6, 96.7]	96.8 [96.1, 97.2]	0.265
Mixed venous oxygen saturation, %	68.1 [65.3, 69.1]	72.5 [70.2, 75.0]	0.011
Heart rate, bpm	65.0 [63.0, 71.0]	73.0 [63.5, 83.0]	0.373
Systolic pulmonary artery pressure, mmHg	29.0 [29.0, 31.0]	25.0 [21.5, 27.5]	0.003
Diastolic pulmonary artery pressure, mmHg	11.0 [10.0, 14.0]	9.0 [7.0, 11.0]	0.084
Mean pulmonary artery pressure, mmHg	19.0 [18.0, 21.0]	15.0 [13.0, 17.0]	0.006
Pulmonary artery wedge pressure, mmHg	9.0 [9.0, 11.0]	8.0 [5.5, 10.0]	0.124
Right atrial pressure, mmHg	7.0 [6.0, 7.0]	5.0 [3.5, 6.0]	0.010
DPG, mmHg	2.0 [1.0, 3.0]	1.0 [0, 2.5]	0.437
Cardiac output, L/min	3.5 [3.1, 4.2]	4.0 [3.7, 4.9]	0.075
Cardiac index, L/min/m^2	2.2 [1.9, 2.5]	2.7 [2.4, 3.1]	0.031
Pulmonary vascular resistance, Wood Unit	2.5 [2.3, 3.4]	1.8 [1.4, 2.2]	0.006
Total pulmonary resistance, Wood Unit	3.4 [3.1, 4.0]	2.3 [2.2, 3.3]	0.013
Hemodynamics at exercise			
Arterial oxygen saturation, %	96.0 [93.1, 97.0]	96.0 [94.1, 96.9]	0.849
Mixed venous oxygen saturation, %	47.8 [46.6, 53.3]	50.7 [46.0, 55.9]	0.409
Heart rate, bpm	110.0 [101.0, 114.0]	117.0 [105.5, 144.0]	0.325
Systolic pulmonary artery pressure, mmHg	70.0 [58.0, 73.0]	45.0 [31.0, 47.5]	< 0.001
Diastolic pulmonary artery pressure, mmHg	27.0 [20.0, 32.0]	18.0 [14.0, 22.0]	0.017
Mean pulmonary artery pressure, mmHg	44.0 [40.0, 51.0]	29.0 [24.0, 36.0]	< 0.001
Pulmonary artery wedge pressure, mmHg	17.0 [14.0, 21.0]	11.0 [7.5, 15.5]	0.013
Right atrial pressure, mmHg	10.0 [8.0, 14.0]	6.0 [4.0, 8.5]	0.001
DPG, mmHg	8.0 [6.0, 10.0]	7.0 [4.0, 8.5]	0.338
Cardiac output, L/min	8.9 [6.6, 11.0]	10.5 [9.5, 14.6]	0.066
Cardiac index, L/min/m^2	5.4 [4.9, 6.3]	7.2 [6.3, 8.2]	0.007
Pulmonary vascular resistance, Wood Unit	3.4 [2.6, 3.7]	1.4 [1.1, 2.0]	< 0.001
Total pulmonary resistance, Wood Unit	3.9 [3.5, 4.1]	2.0 [1.7, 2.4]	< 0.001
Pressure–flow relationship			
ΔmeanPAP/ΔCO, mmHg/L/min	4.8 [4.4, 5.5]	1.6 [1.2, 2.4]	< 0.001

Values are median [25th, 75th percentiles] when appropriate

DPG diastolic pulmonary vascular pressure gradient, EIPH exercise-induced pulmonary hypertension, ΔmeanPAP exercise mean PAP-rest mean PAP, ΔCO exercise CO-rest CO

Discussion

The present study showed for the first time that the RV Tei index was correlated with EIPH in patients with CTD. The RV Tei index could be a noninvasive useful predictor of EIPH in patients with CTD. The 6MWD and peak VO_2/kg, which are indices of exercise tolerance, were lower in the EIPH group compared with the non-EIPH group. In hemodynamics at rest, systolic PAP, mean PAP, RAP, PVR and TPR in the EIPH group were significantly higher than those in the non-EIPH group. Furthermore, SvO_2 and the CI in the EIPH group were significantly lower than those in the non-EIPH group. These results suggested that resting hemodynamics were different between the EIPH and non-EIPH groups. In hemodynamics at exercise, PAP, PAWP, RAP, PVR, and TPR in the EIPH group were significantly higher than those in the non-EIPH group. These results are reasonable because patients were divided into two groups by hemodynamics at exercise. Although PAWP at exercise in EIPH group was elevated, DPG at exercise was elevated too. Consequently, we considered that EIPH group had impairment of pre-capillary.

The previous definition of EIPH was mean PAP ≥ 30 mmHg during exercise, and this criterion was used in the definition of "primary" pulmonary hypertension [8]. However, mean PAP during exercise was found to be significantly higher in older compared with young healthy subjects [9]. Consequently, defining a cutoff value of mean PAP for EIPH was difficult. Moreover, the previous definition of EIPH lacked level, type, and posture of exercise, a cutoff value for EIPH, and prognostic implications [10]. Therefore, the new criteria for definition of EIPH using RHC combined

Table 3 Echocardiographic data in EIPH and non-EIPH groups

	EIPH ($n=7$)	Non-EIPH ($n=17$)	P value
End-diastolic left ventricular dimension, mm	42.9 [42.3, 47.0]	43.6 [40.4, 46.9]	0.656
Left atrial dimension, mm	37.6 [31.8, 47.0]	33.2 [30.5, 38.4]	0.144
Left ventricular ejection fraction, %	77.1 [62.9, 79.4]	70.5 [63.9, 74.0]	0.112
Mitral E/e′	5.3 [5.0, 6.5]	8.4 [7.7, 10.2]	0.135
Left ventricular Tei index	0.44 [0.28, 0.58]	0.41 [0.36, 0.47]	0.680
Basal RVDd, mm	32.1 [31.0, 38.2]	33.0 [30.0, 36.7]	0.727
Mid RVDd, mm	25.9 [24.3, 32.0]	27.0 [24.8, 31.1]	0.799
Tricuspid regurgitation peak flow velocity, m/s	2.60 [2.33, 2.85]	2.45 [2.12, 2.69]	0.280
Tricuspid annular plane systolic excursion, cm	23.3 [19.7, 28.5]	21.7 [20.6, 24.3]	0.657
TDI S', cm/s	13.6 [11.6, 16.0]	13.5 [11.4, 14.7]	0.703
Tricuspid inflow			
E/A	0.97 [0.64, 1.22]	1.09 [0.91, 1.37]	0.374
Deceleration time, ms	252 [222, 379]	189 [151, 249]	0.133
Right ventricular Tei index	0.42 [0.41, 0.47]	0.25 [0.20, 0.32]	0.007
Isovolumic contraction time, ms	39.0 [37.0, 58.0]	32.0 [20.5, 47.0]	0.227
Isovolumic relaxation time, ms	87.0 [61.0, 106.0]	44.0 [33.0, 57.5]	0.008

Values are median [25th, 75th percentiles] when appropriate

EIPH exercise-induced pulmonary hypertension, mitral E/e′ ratio between early mitral inflow velocity and mitral annular early diastolic velocity, RVDd end-diastolic right ventricular dimension, TDI S' tissue Doppler-derived tricuspid lateral annular systolic velocity

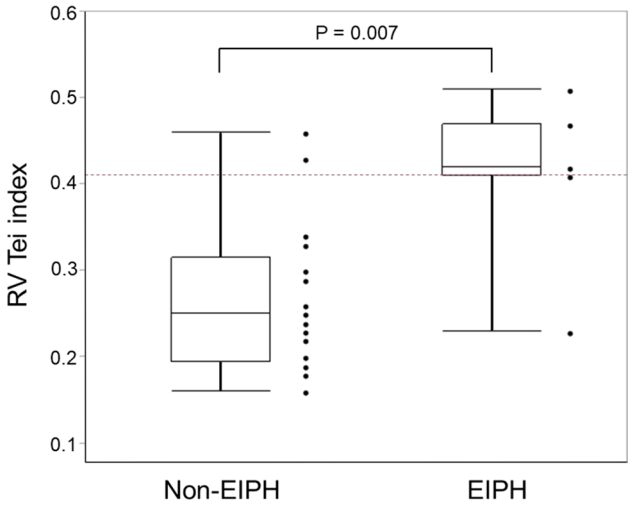

Fig. 3 Comparison of the RV Tei index between the EIPH and non-EIPH groups. RV Tei index in EIPH group was significantly higher than that in non-EIPH group (EIPH vs non-EIPH = 0.42 [0.41, 0.47] vs 0.25 [0.20, 0.32]; $P=0.007$). Values are shown as the median [25th, 75th percentiles] when appropriate. *EIPH* exercise-induced pulmonary hypertension, *RV* right ventricle

with maximum mean PAP and TPR during exercise were proposed. These criteria have a high diagnostic accuracy of pulmonary vascular disease with sufficient evidence [7, 11]. Loss of pulmonary vascular distensibility during exercise reflects early pulmonary vascular disease and might be associated with development of pulmonary vascular disease [12, 13]. Consequently, EIPH might occur by loss of pulmonary vascular distensibility.

Screening and early detection of PAH are currently recommended in patients with CTD because delayed diagnosis of CTD-PAH leads to an unfavorable outcome [3, 4, 14]. Stamm et al. [15] reported that EIPH using the new criteria in patients with SSc might have worse trans-free survival compared with those without EIPH. The effectiveness of PAH-targeted therapy in patients with SSc and EIPH is unclear. However, a pilot study reported that ambrisentan treatment in patients with SSc and EIPH demonstrated improvement in exercise hemodynamics and exercise capacity [16]. Furthermore, an open-label study of ambrisentan in patients with EIPH showed a significant improvement in hemodynamics, 6MWD, and symptoms after treatment [17]. These previous findings suggested that treatment for EIPH has a possibility to prevent progression of vascular remodeling and development of established PAH. Therefore, EIPH should be considered to a risk of PAH, and detecting EIPH in patients with CTD is important.

For echocardiographic assessment of the RV in adults, the guidelines of American Society of Echocardiography describe measuring RV chamber size, PAP, TAPSE, RV fractional area change, TDI S', the RV Tei index, and pulsed Doppler of tricuspid inflow [18]. These echocardiographic assessments of RV function are commonly used for patients with PH in clinical practice. Exercise echocardiography is used to detect and identify early-stage PH, even in patients without PH at rest [19]. Echocardiographic estimations of

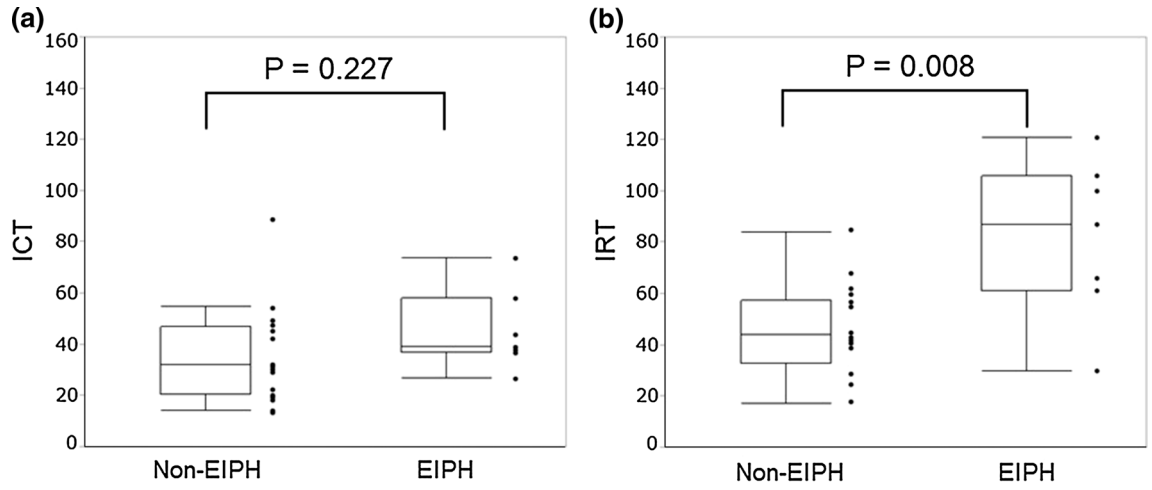

Fig. 4 Comparison of the ICT and IRT between the EIPH and non-EIPH groups. ICT was not significantly different between the groups (EIPH vs non-EIPH = 39.0 ms [37.0, 58.0] vs 32.0 ms [20.5, 47.0], $P = 0.227$) (**a**). However, IRT was significantly prolonged in the EIPH group compared with the non-EIPH group (EIPH vs non-EIPH = 87.0 ms [61.0, 106.0] vs 44.0 ms [33.0, 57.5], $P = 0.008$) (**b**). Values are shown as the median [25th, 75th percentiles] when appropriate. *EIPH* exercise-induced pulmonary hypertension, *ICT* isovolumic contraction time, *IRT* isovolumic relaxation time

RV and pulmonary vascular function during exercise are feasible with reasonable accuracy [20]. Although agreement between echocardiographic and invasive measures of pulmonary pressure during exercise is acceptable, the accuracy is highly dependent on the quality of the TR envelopes [21]. The RV Tei index is a global estimate of systolic and diastolic function of the RV, and this index can be measured without TR and is reproducible. The RV Tei index, which is obtainable only using pulsed-wave Doppler, appears to be relatively independent of preload, afterload, and heart rate [22]. Additionally, the findings about RV Tei index demonstrate usefulness in assessing patients with PH [23–25].

We showed that the Doppler-derived RV Tei index at rest was associated with EIPH in patients with CTD. Furthermore, the IRT which is the diastolic element of the RV Tei index, in the EIPH group was significantly prolonged compared with the non-EIPH group. However, there were no significant differences in RV systolic function, such as ICT, TAPSE, and TDI S' between the groups. Moreover, even in parameters of tricuspid inflow E/A ratio and deceleration time as diastolic function were not significantly differences. Hsu et al. [26] proved that RV sarcomere function in patients with SSc-PAH was depressed. Moreover, a previous study reported that patients with SSc had impaired RV diastolic function regardless of PH [27]. Patients with EIPH in CTD might have an RV diastolic dysfunction, and the RV Tei index may be able to be detected it. Additionally, RV Tei index may be sensitive more than tricuspid inflow as diastolic function in patients with CTD. An RV Tei index greater than 0.41 may predict EIPH and be useful for considering further invasive examinations, such as RHC during exercise in clinical practice.

Limitations

This study has some limitations. First, the number of cases was small, and we could not perform the multivariate analysis. A larger study is required to confirm our results in the future. Second, we evaluated hemodynamics during exercise by RHC. Therefore, we do not have echocardiographic data during exercise in this study. We should perform RHC, CPET, and echocardiography simultaneously during exercise in the next study. Third, we did not follow the prognosis of the study patients. Therefore, we should follow these patients to determine whether they develop resting PH.

Conclusion

The RV Tei index is a useful tool for predicting EIPH in patients with CTD. Additionally, the IRT which is the diastolic element included in the RV Tei index was significantly prolonged in EIPH. Patients with EIPH in CTD may have RV diastolic dysfunction. An RV Tei index greater than 0.41 may be helpful for considering further examinations in patients with CTD. A further large study is required to confirm that the RV Tei index is a predictor of EIPH in patients with CTD.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

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