Pulmonary hypertension (PH) is defined as high blood pressure in the pulmonary arteries and is an important cause of morbidity and mortality in connective tissue disease (CTD).\(^1\) In the REVEAL registry, the CTD patients with PH had a lower survival rate and freedom from hospitalization rate at 1 year compared with idiopathic PH patients.\(^2\) In recent years, however, survival rates in patients with CTD and PH have improved because of the early detection of PH and evidence-based treatment.\(^3\) Thus, early detection of PH and subsequent intervention in patients with CTD is imperative.

PH is a hemodynamic and pathophysiological state involving an elevation in mean pulmonary artery pressure (PAP) $\geq 25\text{mmHg}$ at rest on right heart catheterization (RHC).\(^5\)\(^,\)\(^6\) Despite RHC being a gold standard to diagnose PH, it is an invasive examination and is difficult to perform in all patients with CTD. Thus, echocardiography at rest is the leading modality for screening PH and is used to estimate the systemic PAP (SPAP) based on tricuspid regurgitation pressure gradient on echocardiography.\(^7\)\(^,\)\(^9\) Furthermore, PH might progress gradually, and echocardiography is non-invasive and appropriate to evaluate changes over time.

Recently, the topic of exercise-induced PH (EIPH) has garnered attention, due to being a marker for the risk of developing resting PH.\(^10\) EIPH on exercise echocardiography has recently been suggested as a potentially useful tool.\(^11\) A total of 40% of CTD patients with normal resting SPAP developed abnormally high values at peak exercise,\(^12\) and mean PAP after exercise (but not mean PAP at rest) correlated with the development time of PH.\(^13\) CTD is not only characterized by the presence of cardiopulmonary functional disorder but also various organ failures. Furthermore, lung disease or left cardiac dysfunction is also a complication of CTD, and these functional disorders are related to PH, thereby necessitating the establishment of a multidisciplinary approach to evaluate PH in patients with CTD.\(^5\) To date, however, factors associated with EIPH remain undetermined. Thus, this study investigated the factors related to EIPH in patients with CTD.
Methods

In this study, we enrolled 63 consecutive patients with CTD who did not have PH at rest at Japanese Red Cross Kagoshima Hospital (Kagoshima, Japan). All patients were diagnosed with CTD in accordance with the diagnostic criteria of the American College of Rheumatology. While PH at rest was defined as estimated right ventricular systolic pressure ≥40 mmHg on echocardiography, right ventricular systolic pressure was considered equivalent to SPAP. In the present study cohort, no patient had left ventricular (LV) dysfunction, moderate or severe valvular disease at rest, or atrial fibrillation.

All patients underwent 6-min walk test (6MWT) to assess exercise capacity and also underwent echocardiography before and immediately after 6MWT to detect EIPH. They underwent blood sampling and pulmonary function test before the 6MWT. We measured brain natriuretic peptide (BNP) using a completely automated sample selective analyzer with a commercially available assay (AIA-360; TOSOH Bioscience, San Francisco, CA, USA). Then, we evaluated pulmonary function using FUDAC-77 (Fukuda Denshi, Tokyo, Japan).

This study was approved by the Institutional Ethics Committee of the Graduate School of Medical and Dental Sciences, Kagoshima University and Japanese Red Cross Kagoshima Hospital, and conformed to the guidelines of the Declaration of Helsinki. We obtained written informed consent from all patients for the use and publication of their data.

Echocardiography

We performed transthoracic echocardiography using conventional methods with an ultrasound machine (Vivid E9 pro; GE Healthcare, Horten, Norway), equipped with a 1.5–4.6-MHz transducer at rest and immediately after 6MWT. We then evaluated LV end-diastolic dimension (LVDd), LV end-systolic dimension, interventricular septum thickness (IVSth), and posterior LV wall thickness (PWth) on parasternal long-axis view. LV mass was obtained using the Devereux formula: 0.8 × [(IVSth + LVDd + PWth)3 − (LVDd)3] + 0.6.16 Next, pulse Doppler recording of the mitral flow velocity was obtained on apical 4-chamber view by placing the sample volume between the tips of the mitral leaflets. We then measured the peak early (E) and late diastolic (A) transmitral flow velocities, E/A ratio, and

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### Table 1. CTD Patient Characteristics According to EIPH Status

|               | EIPH (n=35) | Non-EIPH (n=28) | P-value |
|---------------|-------------|-----------------|---------|
| Female (%)    | 94          | 89              | 0.6480  |
| Age (years)   | 61±15       | 55±12           | 0.1057  |
| Height (cm)   | 153±9       | 157±8           | 0.0786  |
| Weight (kg)   | 52±12       | 54±11           | 0.5094  |
| BMI (kg/m²)   | 22.1±3.8    | 22.0±4.1        | 0.9350  |
| BSA (m²)      | 1.47±0.20   | 1.52±0.16       | 0.2539  |
| SBP at rest (mmHg) | 129±17     | 117±13          | 0.0035  |
| HR at rest (beats/min) | 72±11      | 68±10           | 0.1230  |
| PaO₂ at rest (mmHg) | 89±13      | 89±11           | 0.9514  |
| SpO₂ at rest (%) | 98±1       | 98±1            | 0.8897  |
| SpO₂ after 6MWT (%) | 94±6       | 97±2            | 0.0201  |
| 6MWD (m)      | 442±151     | 478±96          | 0.2805  |
| Hypertension (%) | 60         | 25              | 0.0101  |
| Dyslipidemia (%) | 54         | 50              | 0.8026  |
| Diabetes mellitus (%) | 14       | 18              | 0.7400  |
| IP (%)        | 17          | 7               | 0.2825  |
| Medication    |             |                 |         |
| Prednisolone (%) | 66        | 50              | 0.3032  |
| Ca blocker (%) | 34         | 29              | 0.7864  |
| ARB/ACEI (%)  | 31          | 7               | 0.0270  |
| Statin (%)    | 17          | 14              | 0.4023  |
| PGI2 (%)      | 14          | 7               | 0.4478  |

Data given as mean±SD or %. 6MWD, 6-min walking distance; 6MWT, 6-min walk test; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BSA, body surface area; CTD, connective tissue disease; EIPH, exercise-induced pulmonary hypertension; HR, heart rate; IP, interstitial pneumonia; PaO₂, partial pressure of arterial oxygen; PGI₂, prostaglandin I₂; SBP, systolic blood pressure; SpO₂, oxygen saturation of peripheral artery.
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and categorical variables were assessed using the Student’s unpaired t-test and the chi-squared test, respectively. We performed the univariate logistic regression analysis to evaluate the correlation between EIPH and clinical variables, including systolic BP (SBP) at rest, HR at rest, SPAP at rest, BNP, vital capacity (VC), forced expiratory volume in 1 s (FEV1.0) and diffusing capacity of the lung carbon monoxide (DLCO). In addition, the independence of the association between variables was tested on multiple logistic regression analysis, and receiver operating characteristics (ROC) analysis was used to test the ability of the variable to discriminate between the presence and absence of EIPH. Finally, P<0.05 was considered statistically significant. All comparisons in this study were performed using JMP Pro version 14 (SAS Institute, Cary, NC, USA).

Table 2. Blood Parameters According to EIPH Status in CTD Patients

|                      | EIPH (n=35) | Non-EIPH (n=28) | P-value |
|----------------------|------------|-----------------|---------|
| WBC (μ/L)            | 5,727±1,921| 5,052±1,553     | 0.1374  |
| Hb (g/dL)            | 12.2±1.6   | 12.1±1.5        | 0.8835  |
| BUN (mg/dL)          | 17.4±7.5   | 12.9±3.9        | 0.0055  |
| Cr (mg/dL)           | 0.77±0.25  | 0.68±0.14       | 0.0968  |
| BNP (pg/mL)          | 47.4±45.3  | 25.4±16.4       | 0.0174  |
| Log BNP              | 1.53±0.36  | 1.31±0.30       | 0.0118  |
| FBS (mg/dL)          | 102±21     | 94±13           | 0.1222  |
| HbA1C (%)            | 5.8±0.5    | 5.7±0.5         | 0.6941  |
| LDL-C (mg/dL)        | 115±33     | 118±30          | 0.7541  |
| CRP (mg/dL)          | 0.25±0.56  | 0.11±0.10       | 0.1969  |
| ESR (mm)             | 27±29      | 23±25           | 0.5333  |

Data given as mean±SD. BNP, brain natriuretic peptide; BUN, blood urea nitrogen; Cr, creatinine; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FBS, fasting blood sugar; Hb, hemoglobin; HbA1C, glycosylated hemoglobin A; LDL-C, low-density lipoprotein cholesterol; WBC, white blood cells. Other abbreviations as in Table 1.

Table 3. CTD Patient Cardiac and Pulmonary Functions According to EIPH Status

|                      | EIPH (n=35) | Non-EIPH (n=28) | P-value |
|----------------------|------------|-----------------|---------|
| Echocardiography     |            |                 |         |
| LVDd (mm)            | 42.6±5.3   | 43.3±5.0        | 0.5901  |
| LVDs (mm)            | 25.4±3.7   | 26.3±4.2        | 0.4080  |
| LVM (g)              | 167.7±55.3 | 150.6±37.6      | 0.1674  |
| LAD (mm)             | 32.7±5.1   | 32.0±4.4        | 0.5528  |
| LVEF (%)             | 70.0±5.5   | 70.0±6.1        | 0.9615  |
| E/A ratio            | 0.98±0.31  | 1.17±0.42       | 0.0396  |
| Deceleration time (ms)| 209±53    | 212±38          | 0.8239  |
| E/e’                 | 11.7±5.2   | 9.4±3.3         | 0.1131  |
| Pericardial effusion (%) | 14      | 21              | 0.5174  |
| SPAP at rest (mmHg)  | 32.6±4.6   | 27.9±4.4        | <0.0001 |
| SPAP after 6MWT (mmHg) | 51.9±7.9  | 33.1±4.8        | <0.0001 |
| Pulmonary function   |            |                 |         |
| VC (L)               | 2.29±0.75  | 2.88±0.54       | 0.0008  |
| FEV1.0 (L)           | 1.80±0.59  | 2.30±0.51       | 0.0008  |
| DLCO (%)             | 90.4±27.0  | 87.9±18.0       | 0.6740  |

Data given as mean±SD or %. A, peak atrial-systolic transmural flow velocity; DLCO, diffusing capacity of the lung carbon monoxide; E, peak early diastolic transmural flow velocity; e’, early diastolic mitral annular velocity; FEV1.0, forced expiratory volume in 1 s; LAD, left atrial diameter; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; SPAP, systolic pulmonary artery pressure; VC, vital capacity. Other abbreviations as in Table 1.

deceleration time of the E wave, and we measured e’, the early diastolic mitral annular velocity on the septal side. In addition, the tricuspid regurgitation peak velocity (TRV) was evaluated and SPAP was calculated using the modified Bernoulli equation: SPAP=4×TRV²+right atrial (RA) pressure. The RA pressure was evaluated from the inferior vena cava diameter and collapsibility, according to the guidelines of the American Society of Echocardiography.17 Furthermore, SPAP was measured to assess EIPH at rest and immediately after 6MWT. We defined EIPH as SPAP at rest <40 mmHg and SPAP after 6MWT ≥40 mmHg.

Statistical Analysis

All continuous variables are expressed as mean±SD, and categorical variables are expressed as percentages. In addition, differences between the 2 groups for continuous
Results

Table 1 lists the baseline patient characteristics. In this study, EIPH was diagnosed in 35 patients (EIPH group), and 28 were non-EIPH patients (non-EIPH group). No significant difference was observed in gender or mean age between the 2 groups. In the EIPH group, SBP at rest was significantly higher than in the non-EIPH group (SBP, 129±17 mmHg vs. 117±13 mmHg, \( P=0.0035 \)). Although SpO\(_2\) at rest was not significantly different between the 2 groups, SpO\(_2\) after 6MWT in the EIPH group was significantly lower than in the non-EIPH group. We observed no significant differences in 6-min walk distance between the 2 groups (EIPH group vs. non-EIPH group, 442±151 m vs. 478±96 m, \( P=0.2805 \)). In the EIPH group, log BNP was significantly higher than in the non-EIPH group (Table 2; \( P=0.0118 \)). In addition, C-reactive protein and erythrocyte sedimentation rate were not significantly different between the 2 groups.

Table 3 lists the cardiac and pulmonary function according to EIPH status. In the EIPH group, SPAP at rest and also after 6MWT were significantly higher than in the non-EIPH group (SPAP at rest, 32.6±4.6 mmHg vs. 27.9±4.4 mmHg, \( P<0.0001 \); SPAP after 6MWT, 51.9±7.9 mmHg vs. 33.1±4.8 mmHg, \( P=0.0001 \)). We observed no significant differences in LV diameter, LV mass, left atrial diameter, ejection fraction or E/e' between the 2 groups. In addition, VC and FEV1.0 in the EIPH group were significantly lower than in the non-EIPH group. We observed no significant differences in 6-min walk distance between the 2 groups (EIPH group vs. non-EIPH group, 442±151 m vs. 478±96 m, \( P=0.2805 \)). In the EIPH group, log BNP was significantly higher than in the non-EIPH group (Table 2; \( P=0.0118 \)). In addition, C-reactive protein and erythrocyte sedimentation rate were not significantly different between the 2 groups.

EIPH and Clinical Variables

Table 4 lists the univariate logistic regression analysis between EIPH and clinical variables. SBP at rest, SPAP at rest, log BNP, VC, and FEV1.0 were significantly correlated with EIPH, but DLCO was not.

Multiple logistic regression analysis of EIPH is given in Table 5. In model 1, SPAP at rest and VC were independent predictors of EIPH, whereas log BNP was not significant. In model 2, SPAP at rest was an independent predictor of EIPH. Although FEV1.0 and log BNP were not significantly associated with EIPH, FEV1.0 had a tendency towards being a predictor of EIPH.

ROC Curve Analysis

We performed ROC curve analysis on the ability of BNP, SPAP at rest, VC and FEV1.0 to predict EIPH (Figure). The area under the ROC curve (AUC) for BNP (Figure A) was 0.67, with the highest discriminating sensitivity and specificity at 0.40 and 0.93, respectively, at BNP=49.3 pg/mL.

Discussion

This study investigated the correlation between EIPH and various clinical parameters inducing cardiac and pulmonary functions in patients with CTD, and identified the predictors of EIPH. SPAP at rest and the parameter of respiratory function, VC, were significant predictors of EIPH, although BNP and FEV1.0 were not. Furthermore, the cut-offs of BNP, SPAP at rest, VC, and FEV1.0 to predict EIPH were also calculated. Thus, SPAP at rest, VC, and FEV1.0 might be better predictors for EIPH than BNP.

PH is a predictor of outcome in CTD that warrants early intervention. Given that EIPH is considered a preliminary stage of PH, screening of EIPH is crucial. EIPH has also been reported to be a predictor of future PH in patients with systemic sclerosis (SSc). Although PH is diagnosed on RHC in clinical practice, we performed a simple screening test for EIPH on stress echocardiography in 63 patients with CTD, and diagnosed 38 patients (56%) with EIPH. The EIPH screening test should be simple, non-invasive, with no need for specialized and expensive equipment. Moreover, EIPH screening should be available not only at large hospitals but also at various facilities, including clinics.

We believe that the present results could be critical and useful in the screening of EIPH in patients with CTD because the methods are simple, and non-invasive, and require no specialized equipment.

Several studies have established a correlation between EIPH and other factors. DLCO was found to correlate significantly with exercise SPAP, and lower DLCO was found to be associated with a higher risk of developing higher SPAP. In the present study, however, VC, but not DLCO, was a significant predictor of EIPH. We speculate that DLCO had not decreased in the present patients at the time of the study because all of the patients were in the early stage of PH. To the best of our knowledge, this is the first study to demonstrate a significant correlation between...
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EIPH and VC. Given that the respiratory function parameter VC can be evaluated using a simple and non-invasive method, it is useful for detecting EIPH. There are several reports on the impairment of respiratory function in CTD patients. CTD patients often have respiratory diseases, such as airway disease, parenchymal lung disease and pleurisy. Airway disease causes a decrease in %FEV1.0, while parenchymal lung disease and pleurisy cause a decrease in VC. Also, prevalence of bronchitis in patients with RA was higher than that in patients without RA.20 VC and FEV1.0 in RA patients was significantly lower than in the control group.21,22 Pulmonary function is associated with SPAP at rest in the general population23,24 and there may be a significant relationship between pulmonary function and SPAP in CTD patients. In contrast, the prevalence of interstitial pneumonia (IP) with RA is 0.86–6.9%.25 IP is considered an important factor for prognosis, and IP is caused by sustained RA activity. Although DLCO was reported to be significantly related to EIPH in CTD patients,26 this significant relationship between DLCO and EIPH was not seen in the present study. The present patients were at an early stage of CTD, and hence DLCO had not declined because IP had not developed, but VC and FEV1.0 may have declined due to bronchitis and pleurisy even in the early stage. It is not clear, however, why VC and EIPH were related, and further study is needed.

In addition, a correlation between EIPH and LV function has been reported in CTD. EIPH was found to be associated with both increased exercise LV filling pressure and exercise pulmonary vascular resistance (PVR) in patients with SSc.11 Peak exercise SPAP has also been found to be affected by age, interstitial lung disease, and right ventricular and LV diastolic dysfunction, and, in only 5% of patients, it was associated with an increase in PVR during exercise.12 The heterogeneity of the EIPH mechanisms in CTD, such as pulmonary vascular dysfunction, respiratory dysfunction,
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