Prevalence of Pulmonary Arterial Hypertension in Korean Adult Patients with Systemic Sclerosis: Result of a Pilot Echocardiographic Screening Study

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BACKGROUND: Pulmonary arterial hypertension (PAH) is a major cause of morbidity and mortality among patients with systemic sclerosis (SSc). Early detection and prompt treatment of PAH associated with SSc (SSc-PAH) result in better prognosis. We conducted echocardiographic study to presume the prevalence of PAH in Korean adult SSc patients and to diagnose SSc-PAH in their early stages with right heart catheterization (RHC).

METHODS: We performed free of charge echocardiographic study including 37 adult SSc patients at the Chungnam National University Hospital. The possibility of PAH is determined by the estimation of pulmonary arterial pressure by peak tricuspid regurgitation velocity of > 3.0 m/s. Patients with possible PAH were recommended to undergo RHC to confirm the diagnosis.

RESULTS: In 37 patients, 8 patients were suspected with PAH. Among them, 6 patients agreed to be examined with RHC, and 4 were confirmed with PAH. The prevalence of possible PAH was 21.6% (8 of 37 patients), and that of confirmed PAH was 10.8% (4 of 37 patients). Four patients who were confirmed with SSc-PAH through RHC have been treated with specific pulmonary vasodilators and maintained stable.

CONCLUSION: Eight patients (21.6%) were possible PAH and 4 (10.8%) were diagnosed as SSc-PAH by RHC after the echocardiographic screening study of 37 adult SSc patients.

KEY WORDS: Systemic sclerosis · Pulmonary arterial hypertension · Echocardiography · Right heart catheterization · Screening.
the pulmonary arterial pressure and is useful for screening in early stages, all patients with SSc are recommended to take an echocardiographic survey to find SSc-PAH.9 Because there have been several obstacles to performing annual echocardiographic screening in adult SSc patients in Korea, the precise prevalence of SSc-PAH is unknown. In this study, we planned to presume the prevalence of SSc-PAH in Korean adult patients with SSc through the echocardiography. If patients had the possibility of SSc-PAH without other causes of elevated pulmonary arterial pressure, they were recommended to receive a right heart catheterization (RHC) to confirm the diagnosis. Through this screening process, we hoped to give patients the opportunity to treat SSc-PAH in early stages.

METHODS

PATIENTS

All consecutive patients who had been diagnosed and managed with SSc were enrolled in this screening program from April 2013 to December 2015. The diagnosis of SSc was made following the 1980 American College of Rheumatology (ACR) preliminary criteria for the classification of SSc and the 2013 ACR/European league against rheumatism classification criteria for SSc.1011 Patients who already had been diagnosed with PAH were excluded.

METHOD

Patients had more than one echocardiographic examination by two experienced cardiologists and a sonographer in this echocardiographic screening.

All participants underwent comprehensive 2-dimensional and Doppler echocardiography using an E9 echocardiographic machine with an M4S probe (GE Vingmed, Horten, Norway) and all echocardiographic images were stored digitally.

Echocardiographic dimensions were measured using M-mode echocardiography was performed on parasternal views. Left ventricular (LV) end-diastolic volume (LVEDV) and LV end-systolic volume values were measured using the biplane Simpson’s method on apical 4-chamber and 2-chamber views. LV ejection fraction was calculated as the division of stroke volume by LVEDV multiplied by 100. All conventional echocardiographic parameters were measured and averaged from 3 cardiac cycles.

The estimation of pulmonary artery systolic pressure was estimated from the maximal continuous-wave Doppler velocity of the tricuspid regurgitation (TR) jet plus estimated right atrial pressure with size of inferior vena cava and degree of change in caval diameter during respiration.12 TR Vmax value were averaged more than 3 beats and value more than 3.0 m/s (pulmonary arterial systolic pressure more than 41 mm Hg) was regarded as the possible PAH.

After the screening, the patients with possible PAH were recommended to undergo RHC to confirm the diagnosis. However, if patients had other causes of elevating pulmonary arterial pressure, the RHC was postponed after the correction of the causes. The PAH is defined as a mean pulmonary arterial pressure of ≥ 25 mm Hg at rest with a pulmonary capillary wedge pressure of < 15 mm Hg, and a pulmonary vascular resistance (PVR) > 3.0 Wood units in the absence of other causes of precapillary pulmonary hypertension (PH) such as PH due to lung diseases, chronic thromboembolic PH or other rare diseases.13 The study protocol had been reviewed and approved by the Institutional Review Board of Chungnam National University Hospital (IRB number is 2016-08-018). All participants gave their consent to collect and use their personal information.

Statistical analysis

Differences between non-PAH and confirmed PAH by RHC groups were analyzed. Statistical analysis was done with a commercial program (IBM SPSS Statistics for Windows, version 20.0, IBM Corp., Armonk, NY, USA). Data was expressed as mean standard deviation for continuous variables and as frequencies (percentages) for categorical variables. Statistical differences between groups were assessed using Fisher’s exact tests for categorical variables and Mann-Whitney U test for continuous variables. p < 0.05 was considered statistically significant.

RESULTS

We enrolled 37 patents in screening program with echocardiography. All patients underwent more than one echocardiographic examination, and 7 patients received echocardiographic studies 2 times for their follow-up evaluation. Patients’ baseline characteristics are summarized in Table 1. Of the total 37 adult patients with SSc, 9 were suspected to have PAH. Out of the 9 patients, 1 was found to have increased pulmonary arterial pressure due to another cause, 2 refused to go through with the RHC, and 6 agreed to be examined through RHC. Four of the 6 patients who underwent the RHC were confirmed with PAH. The process and result of this study was summarized in the Fig. 1. The comparison of clinical and laboratory parameters according to the presence of PAH was summarized in the Supplementary Table 1. The characteristics of patients who underwent the RHC and their results of RHC are presented in Table 2 and 3. The percentage of possible PAH was 21.6 (8 of 37 patients). And that of confirmed PAH was 10.8 (4 of 37 patients). SSc-PAH patients seemed to be older than control patients. Three among 4 patients with confirmed SSc-PAH had limited type of SSc. Patients with confirmed SSc-PAH complained more severe grade of dyspnea. Two of 6 patients who underwent RHC were not diagnosed as PAH. One patient who was diagnosed as mildly elevated PH (mean PA pressure was 26 mm Hg) without elevated PVR (PVR was 231 dynes-sec-cm⁻²) had been diagnosed as PAH about 11 months after the first RHC. She had been managed with oral
sildenafil treatment. However, the patient expired from renal crisis about 14 months after the RHC.

One patient who refused RHC had no pulmonary symptom and her initial TR Vmax was 3.1 m/sec. In the follow-up echocardiography after 32 months, her TR Vmax was decreased to 3.1 to 2.8 m/sec. The other patient complained of dyspnea with World Health Organization grade 1 with an initial TR Vmax of 3.6 m/sec.

Another patient, who was suspected to have PAH, had anemia and hypertension which can cause reactive PH. In this patient, the elevated TR Vmax was normalized with iron supply and antihypertensive medications within about 6 months.

The patients who were confirmed with PAH have been treated with specific pulmonary vasodilator medications including bosentan and conventional therapy. With these medications 2 patients have been improving and other 2 patients have maintained stable disease activity.

**Discussion**

In this pilot echocardiographic study among 37 Korean adult patients with SSc, we found 8 possible patients (21.6%) and 4 confirmed patients (10.8%) with SSc-PAH.

PH is one of the major causes of death in patients with CTD. In recently published data of Korean PAH registry including 625 patients, CTD was the most common etiology (49.8%). In CTD-associated PAH, SSc was the second common etiology of PAH secondary to systemic lupus erythematosus in Korea. CTD-associated PAH showed poor progno-

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### Table 1. Baseline characteristics

| Characteristics | Total (n = 37) |
|-----------------|---------------|
| **Demographics** |               |
| Female, n (%)   | 28 (75.6)     |
| Age (years)     | 54.0 ± 9.9    |
| Body mass index (kg/m²) | 22.6 ± 3.1 |
| **SSc characteristics** |   |
| Disease duration (month) | 79.9 ± 73.8 |
| Subtype, n (%)  |               |
| Diffuse         | 12 (32.4)     |
| Limited         | 25 (67.6)     |
| Raynaud’s phenomenon, n (%) | 37 (100) |
| Sclerodactyly, n (%) | 29 (78.4) |
| Telangiectasia, n (%) | 2 (5.4) |
| Digital ulcer, n (%) | 8 (21.6) |
| Interstitial lung disease, n (%) | 17 (45.9) |
| Reflux symptom, n (%) | 27 (73.0) |
| Dyspnea (WHO functional class), n (%) |             |
| 0               | 19 (51.4)     |
| 1               | 7 (18.9)      |
| 2               | 6 (16.2)      |
| 3               | 5 (13.5)      |
| 4               | 0 (0)         |
| **Serum markers** |               |
| ANA titer       | 948 ± 488.3   |
| Anti-Scl-70 Ab positivity, n (%) | 17/26 (65.4) |
| Anti-centromere Ab positivity, n (%) | 2/11 (18.2) |
| **Echocardiography** |       |
| LVEF (%)        | 61.2 ± 0.7    |
| TR Vmax (m/s)   | 2.87 ± 0.40   |
| TR Vmax (m/s), n (%) |             |
| ≤ 2.8           | 24 (64.9)     |
| > 2.8 to ≤ 3.4  | 11 (29.7)     |
| > 3.4           | 2 (5.4)       |

SSc: systemic sclerosis, WHO: World Health Organization, ANA: antinuclear antibody, LVEF: left ventricular ejection fraction, TR Vmax: maximal velocity of tricuspid regurgitation

### Table 2. The characteristics of patients with pulmonary arterial hypertension associated with SSc

| Patient | Age (years) | Gender | BMI (kg/m²) | Duration of disease (months) | Dyspnea (WHO FC) | Type of SSc | ANA titer | PFT DLCO (%) | FVC (%) | Pro-BNP (pg/mL) |
|---------|-------------|--------|-------------|-----------------------------|-------------------|-------------|-----------|--------------|----------|----------------|
| 1       | 61          | Female | 22.9        | 153                         | III               | Diffuse     | NC        | 81           | 77       | 181            |
| 2       | 40          | Female | 20.5        | 120                         | II                | Diffuse     | 1:1280    | NC           | NC       | NC             |
| 3       | 73          | Female | 16.8        | 120                         | III               | Limited     | 1:640     | NC           | NC       | NC             |
| 4       | 60          | Female | 19.1        | 192                         | III               | Diffuse     | 1:640     | 68           | 42       | 348            |

BMI: body mass index; WHO FC: World Health Organization-functional class; SSc: systemic sclerosis; ANA: antinuclear antibody; PFT: pulmonary function test; DLCO: diffusing capacity of the lungs for carbon monoxide; FVC: forced vital capacity; Pro-BNP: pro-b type natriuretic peptide, NC: not checked

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**Fig. 1.** The flow chart of this study. TR Vmax: maximal velocity of tricuspid regurgitation, PAH: pulmonary arterial hypertension, RHC: right heart catheterization, SSc-PAH: pulmonary arterial hypertension associated with systemic sclerosis.
cardiographic screening in high-risk patients of PAH. Recent guidelines recommend yearly echocardiographic screening of PAH. However, large screening programs should be needed in order for this data to be generalized. Second, we can’t perform the RHC in 2 patients with suspected PAH.

In conclusion, we performed an echocardiographic study to determine precise prevalence rate in Korea. However, we tried to include all patients with SSc in our institution. Further studies with a larger study population will be needed in order for this data to be generalized. Second, we can’t perform the RHC in 2 patients with suspected PAH.

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