Latent left ventricular dysfunction in patients with pulmonary arterial hypertension associated with systemic sclerosis

Sumiaki Tanaka, Yu Matsueda, Junichi Kondo, Kunihiro Yamaoka

Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine

Objective: To investigate latent left ventricular dysfunction in patients with pulmonary arterial hypertension associated with systemic sclerosis (PAH-SSc).

Patients and Methods: A total of 83 patients diagnosed as having PAH associated with connective tissue disease (CTD) at our facility from April 2001 through March 2013 comprised the patient population of this study. We compared serum levels of B-type natriuretic peptide (BNP) and hemodynamics between a PAH-SSc patient group (PAH-SSc(+)) and a group including PAH patients with CTD other than SSc (PAH-SSc(-)).

Results: The PAH-SSc(+) included 41 patients. The PAH-SSc(-) included 42 patients: SLE (20), MCTD (16), and others (6). Serum BNP levels were analyzed at each of 2,786 patient visits. In a holistic comparison, the median serum BNP level was higher in the PAH-SSc(+) group than that in the PAH-SSc(-) group (104 pg/ml vs. 48.9 pg/ml, respectively) (P = 0.01). In a mixed model investigation, serum BNP levels were higher (P < 0.0001) in the same sequence as the WHO functional classification (WHO-FC) and were also higher within each WHO-FC (P = 0.013) in PAH-SSc(+) than those in PAH-SSc(-). In a full cardiac catheterization data analysis of the treatment phase (n = 173), pulmonary arterial wedge pressure was higher in the PAH-SSc(+) than that in the PAH-SSc(-) (8.7 ± 3.9 mmHg vs. 7.0 ± 2.7 mmHg, respectively) (P = 0.035).

Conclusion: These results indicate that the pathology of PAH-SSc includes a high incidence of latent left ventricular dysfunction.

Key words: pulmonary arterial hypertension, connective tissue disease, systemic sclerosis, B-type natriuretic peptide

Introduction

Pulmonary arterial hypertension (PAH) is a chronic disease which obliterates the pulmonary vascular bed through the medial thickening of pulmonary arterioles, intimal thickening, plexiform lesions, and other modes of vascular remodeling. This obliteration increases pulmonary arterial pressure, causing chronic right heart failure. PAH is classified into forms including PAH associated with various diseases, familial PAH, and idiopathic PAH (IPAH) seen sporadically. Connective tissue disease (CTD) is representative of the various diseases with which PAH is associated, with frequent manifestations in systemic sclerosis (SSc), mixed connective tissue disease (MCTD), and systemic lupus erythematosus (SLE). In the past 20 years, the increased use of PAH-specific drugs, which have a potent pulmonary vasodilating effect, has greatly improved the survival of patients with PAH. However, survival has been worse in PAH associated with CTD (PAH-CTD) than in IPAH. Among the PAH-CTD patients, survival of those with PAH associated with SSc (PAH-SSc) remains the worst. SSc is a multiorgan disease characterized by fibrosis of the visceral organs, peripheral vascular disorders, and immunopathy. Affected organs include the lungs and the heart in cases of interstitial pneumonia and cardiomyopathy, each of which contributes to the onset of pulmonary hypertension. The co-presence of either or both of these diseases with PAH complicates the pathology of PAH-SSc. Myocardial involvement in SSc is often revealed as asymptomatic left ventricular diastolic dysfunction, the evaluation of
which requires a comprehensive assessment of hemodynamics through bilateral cardiac catheterization studies including a fluid volume challenge test. Consequently, to our knowledge, there are no reported investigations in the literature that include long-term observation of the effects of left ventricular dysfunction on PAH-SSc. Diagnostic guidelines also discuss the serum B-type natriuretic peptide (BNP) level, a useful biomarker commonly used in the diagnoses of heart failure, risk assessment, and determining treatment goals. Serum BNP level is also used as part of the treatment goal in therapies using PAH-specific drugs and is measured periodically. Consequently, we devised a study that analyzes the serum BNP level to diagnose left ventricular dysfunction in PAH-SSc.

Materials and Methods

Patients
The patients for this study were chosen from the PAH-CTD patient registration which was begun at our facility in January 1980 and consisted of 83 individuals whose serum BNP levels were measured for use in treatments provided from April 2001 through March 2013. Treatment using PAH-specific drugs followed the commonly used guidelines, specifically, for goal-oriented combination therapy, and treatment strategies were not varied according to the CTD type.

Diagnosis of PAH
PAH was diagnosed in patients with the mean pulmonary arterial pressure of ≥25 mmHg and pulmonary arterial wedge pressure (PAWP) of <15 mmHg in right heart catheterization (RHC) measured at rest.

Study design
Retrospective observational research of 83 patients was conducted on information from medical records including serum BNP levels from 2,786 measurements, WHO functional classification (WHO-FC) levels, results from 173 RHC procedures, types of CTD, and other clinical information. A PAH-SSc patient group (PAH-SSc[+]) and a PAH patient group with a CTD but without SSc (PAH-SSc[-]) were compared using their serum BNP levels and hemodynamics measured by RHC including mean pulmonary arterial pressure (mPAP), PAWP, cardiac output (CO), and pulmonary vascular resistance (PVR). The research had the approval of an ethics committee of Kitasato University School of Medicine (B16-178).

Statistical analysis
Results are shown as mean ± standard deviation and median (for quartiles). The Student t-test, Mann-Whitney U-test, and the chi-square test were used to compare the groups as appropriate, depending on the type of variable. P values of <0.05 were considered to be statistically significant. In analyses of serum BNP levels, a mixed effects model was used to estimate predicted mean values of serum BNP levels according to their PAH-SSc(+) or PAH-SSc(-) status and WHO-FC levels. Patients were designated according to their individual patient characteristics to the model, and assigned to either the PAH-SSc(+) or the PAH-SSc(-) group; their WHO-FC levels of I, II, III, or IV at the measurements; and their ages at each measurement were designated as fixed effects. The results are shown as means (95% confidence interval). The PAH-SSc(+) or PAH-SSc(-) groups were also compared according to the RHC results at the time of the PAH diagnoses and their complete histories. These analyses were performed using JMP v10 (SAS Institute Inc., NC, USA) and IBM SPSS Statics v22 (IBM Inc., NY, USA).

Results

Patient profile at the PAH diagnosis
The PAH-SSc(+) group was comprised of 42 individuals (35 women) and the PAH-SSc(-) group of 41 individuals (38 women), 20 with SLE and 16 with mixed CTD (Table 1). Age at PAH diagnosis was higher in the PAH-SSc(+) group, at 57.0 ± 11.6 years vs. 43.4 ± 15.5 in the PAH-SSc(-) group (P < 0.0001). No intergroup differences were noted in the WHO-FC distribution, and no intergroup differences were noted in the hemodynamic parameters of mPAP, CO, PVR, or PAWP, even though PAWP in the PAH-SSc(+) group was 7.8 ± 4.2 mmHg vs. 7.0 ± 2.9 mmHg in the PAH-SSc(-) group (P = 0.0614).

Serum BNP level analysis
The duration of patient observations in the research period ranged from 0.5 to 12 years, with a median of 6 years, and the median number of serum BNP level measurements was 27 (interquartile range [IQR]: 4–55). Measurement of serum BNP levels was performed as one goal, and the total number of observations was 2,786, including 1,225 in the PAH-SSc(+) group and 1,561 in the PAH-SSc(-) group. Figure 1 presents histograms for serum BNP levels in the PAH-SSc(+) and PAH-SSc(-) groups, respectively. The median serum BNP level in the PAH-SSc(+) group was 104 (IQR: 52.5–214) pg/ml.
Latent left ventricular dysfunction of SSc-PAH

**Table 1.** Patient background at diagnosis of PAH

<table>
<thead>
<tr>
<th>Group</th>
<th>PAH-SSc(+) (n = 41)</th>
<th>PAH-SSc(-) (n = 42)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>57 ± 11.6</td>
<td>43.4 ± 15.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Women</td>
<td>35</td>
<td>38</td>
<td>0.5195</td>
</tr>
<tr>
<td>CTDs</td>
<td>SSc (41)</td>
<td>SLE (20), MCTD (16), Other (6)</td>
<td>0.3845</td>
</tr>
<tr>
<td>WHO-FC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>12</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>22</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Hemodynamics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>36.0 ± 9.5</td>
<td>39.6 ± 13.0</td>
<td>0.3357</td>
</tr>
<tr>
<td>PAWP (mmHg)</td>
<td>7.8 ± 4.2</td>
<td>7.0 ± 2.9</td>
<td>0.5675</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>4.3 ± 1.0</td>
<td>5.2 ± 1.0</td>
<td>0.0614</td>
</tr>
<tr>
<td>PVR</td>
<td>7.2 ± 3.9</td>
<td>6.9 ± 3.7</td>
<td>0.8169</td>
</tr>
</tbody>
</table>

CTD, connective tissue disease; SSc, systemic sclerosis; SLE, systemic lupus erythematosus; MCTD, mixed connective tissue disease; WHO-FC, WHO functional class; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; CO, cardiac output; PVR, pulmonary vascular resistance

**Figure 1.** Histograms of serum BNP levels in PAH-SSc(+) and PAH-SSc(-) groups (N = 2,786)
The lines show normal distribution curves. BNP, B-type natriuretic peptide
significantly higher than that of 48.8 (IQR: 19.9−149.4) pg/ml in the PAH-SSc(-) group. Estimated serum BNP levels for each WHO-FC level were also higher in the PAH-SSc(+) group vs. those in the PAH-SSc(-) group in each case (Table 2).

Hemodynamics analysis
Table 1 shows the hemodynamics at the time of the PAH diagnoses and that mPAP, PAWP, and PVR were equivalent. CO in the PAH-SSc(+) group was 4.3 ± 1.0 l/min, slightly lower than the 5.2 ± 4.3 l/min level in the PAH-SSc(-) group (P = 0.062).

RHC procedures (n = 173) were performed during the whole period: 77 in the PAH-SSc(+) group, and 96 in the PAH-SSc(-) group. The duration of patient observation ranged from 0.5 to 12 years, and the median number of RHCs was 3 (IQR: 1−4). RHCs carried out during the whole period were performed at the time of admission to our facility due to aggravation of CTD (WHO-FC III or IV). Hemodynamics were compared between the PAH-SSc(+) and PAH-SSc(-) groups (Figure 2) and were equivalent for mPAP (36.8 ± 10.6 mmHg vs. 38.4 ± 12.2 mmHg, respectively) (P = 0.629); for CO (4.6 ± 1.3 mmHg vs. 4.8 ± 1.2 mmHg, respectively) (P = 0.223); and for PV (6.8 ± 3.9 WU vs. 7.0 ± 4.3 WU, respectively) (P = 0.883). PAWP was higher in the PAH-SSc(+) group than that in the PAH-SSc(-) group (8.7 ± 3.9 mmHg vs. 7.0 ± 2.7 mmHg, respectively) (P = 0.035).

Discussion
The results of the present study showed that serum BNP levels in the PAH-SSc(+) group were higher than those in the PAH-SSc(-) group, and throughout the observational period, serum BNP levels were higher in the PAH-SSc(+) group at all the WHO-FC levels, as well. Regarding hemodynamics, the results also showed that PAWP was higher in the PAH-SSc(+) group than the PAH-SSc(-) group.

BNP was isolated from porcine brain by Sudoh et al. in 1988 and later found to be secreted by the human heart. As soon as a pressure overload is applied to the ventricles, precursor synthesis begins; and three different substances are released into the blood: proBNP, its catabolite NT-proBNP, and BNP. BNP has a vasodilating effect, a natriuretic effect, and an antagonist effect on the

---

Table 2. Estimated Serum BNP levels in PAH-SSc(+) and PAH-SSc(-) groups

<table>
<thead>
<tr>
<th>WHO-FC</th>
<th>PAH-SSc(+)</th>
<th>PAH-SSc(-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>54.0 (41.5−70)</td>
<td>35.0 (27.2−44.8)</td>
</tr>
<tr>
<td>II</td>
<td>103.5 (80.3−133.3)</td>
<td>67.1 (52.3−85.9)</td>
</tr>
<tr>
<td>III</td>
<td>167.1 (128.9−216.8)</td>
<td>108.3 (83.9−139.7)</td>
</tr>
<tr>
<td>IV</td>
<td>346.4 (261.6−458.6)</td>
<td>224.4 (170.0−297.9)</td>
</tr>
</tbody>
</table>

*Means (95% CI) estimated with mixed effects model (fixed effects: SSc, WHO-FC; random effect: patient). SSc, P = 0.013; WHO-FC, P < 0.0001; BNP, B-type natriuretic peptide
sympathetic nervous system and the renin-angiotensin system. Based on these characteristics, assay of the serum BNP level is used widely for the diagnosis of acute and chronic left ventricular dysfunction, risk analysis, and as a treatment goal. And as right ventricular dysfunction also occurs in PAH, serum BNP level is used there as well as for risk assessment, evaluation of treatment, and as a treatment goal.

We used a mixed effects model in our analysis. Individual patient characteristics were incorporated into the model by repeated measures as random effects in order to allow appropriate evaluation of the influence of those fixed effects on the serum BNP level. This analysis produced consistently higher serum BNP levels in the PAH-SSc(+) group than those in the PAH-SSc(-) group, indicating that ventricular dysfunction is severe in PAH-SSc patients. Additionally, in the hemodynamics evaluation, only PAWP was significantly lower in the PAH-SSc(+) group. These analytical results confirm that left ventricular dysfunction is a frequent, latent comorbidity in PAH-SSc patients. Though myocardial fibrosis is reported as a frequent observation in autopsied cases of SSc, comorbid symptoms such as arrhythmia and heart failure are uncommon. Recent reports describe that myocardial involvement in SSc often takes the form of asymptomatic left ventricular diastolic dysfunction, and that the evaluation of a fluid volume challenge test in bilateral heart catheterization studies revealed concomitant left ventricular diastolic dysfunction in PAH-SSc. The results of the present study are also consistent with these reports.

Recent treatment strategies for PAH have increasingly sought to restore normal hemodynamics through upfront combination therapy with aggressive incorporation of PAH-specific drugs. But when there is left ventricular dysfunction, many experts fear that the dosage step-up process for PAH-specific drugs may temporarily aggravate the left ventricular dysfunction. Hassoun et al. reported improvement in hemodynamics after pursuit of upfront combination therapy for PAH-SSc in cases where pulmonary hypertension associated with left ventricular dysfunction was prudently excluded. However, we re-emphasize that the safe pursuit of treatments using PAH-specific drugs demands a crucial recognition that left ventricular dysfunction is a frequent, asymptomatic comorbidity in PAH-SSc. Further improvement of quality of life (QOL) and survival prognosis for PAH-SSc patients may require other treatment goal weighted serum BNP levels, for example.

As retrospective, observational research, the present study has a number of limitations. First, analysis of cardiac involvement was precluded by factors such as echocardiography parameters in current use and an insufficient number of evaluations by methods such as myocardial MRI and myocardial biopsy. We were unable to qualitatively evaluate heart failure and were, therefore, unable to fully evaluate myocardial involvement as an aspect of SSc. Moreover, because these patients were from a PAH-CTD patient registration, we were unable to comparatively study patients with cardiac involvement in SSc. Further research is warranted in the forms of either a prospective cohort and/or interventional studies supplemented by patient registries from additional centers.

These results indicate that PAH-SSc includes a high incidence of latent left ventricular dysfunction. Further improvement of QOL and survival prognosis for not only PAH-SSc patients but for all SSc patients requires new diagnostic and assessment techniques for latent myocardial involvement in SSc and development of comprehensive treatment management strategies incorporating these innovations in treatment goals.

Acknowledgment

We thank the laboratory technicians at Kitasato University Hospital for their support in performing the echocardiographic studies. We also thank Hirobumi Kondo, M.D., Ph.D., and Jun Okada, M.D., Ph.D., for their support in this long-term study.

Conflicts of Interest: None

References


